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EDITORS

The ASCRS Textbook of Colon and Rectal Surgery

Fourth Edition

Springer

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Thomas E. Read • Charles B. Whitlow
Editors

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ASCRS
American Society of Colon & Rectal Surgeons

Springer

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Foreword

Drs. Steele, Hull, Hyman, Maykel, Read, and Whitlow and their respective chapter authors are to be congratulated on the successful completion of the fourth edition of *The ASCRS Textbook of Colon and Rectal Surgery*. This edition is greatly enhanced with new authors for each chapter reflecting international experts in the treatment of colorectal disease, expansion of online videos, and a continued emphasis on algorithms and evidence-based recommendations. This edition also serves as the first step in expansion to an online modular platform, facilitating dynamic updates of content.

The ASCRS Textbook of Colon and Rectal Surgery is unique. The concept of a definitive text for state-of-the-art information for all health professional learners and practitioners, including residents in training in colon and rectal surgery as well as fully trained surgeons in practice, was conceived, implemented, and supported by the American Society of Colon and Rectal Surgeons in 2007. It was the recognition of an idea initially conceived by Bruce Wolf, co-implemented by Jim Fleshman, and fully supported by the ASCRS Executive Council. All chapters have been extensively referenced, authoritatively written and illustrated, and have included ASCRS clinical practice guidelines. The success of the first edition led to second and third editions in 2011 and 2016. With the rapid expansion of knowledge, technology, and techniques, each edition has been meticulously and thoroughly updated to reflect state-of-the-art, evidence-based practice. The editors have been continuously refreshed just like the content to keep the book fresh and contemporary. With the fourth edition, the torch has been picked up and carried by each group of editors since the inception.

The textbook remains fully supported and endorsed by the American Society of Colon and Rectal Surgeons: the work is a product of and for the Society, owned by our society with all proceeds flowing back to the Education Fund of the society to continue to support a long-term commitment of the organization to the lifelong education not just of colon and rectal surgery trainees but all clinicians.

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Preface

One given definition of the word *textbook* is "a book used as *a standard* work for the study of a particular subject." Our collective goal for the fourth edition of *The ASCRS Textbook of Colon and Rectal Surgery* was to make this volume *the standard* for the study of colon and rectal surgery, providing a valuable resource for surgeons and health care providers at all stages of their career caring for patients with colorectal disease. This edition provides all newly written chapters, organized around the "pillars" of colorectal disease: perioperative (including endoscopy); anorectal disease; benign disease (including inflammatory bowel disease); malignancy; pelvic floor disorders; and a "miscellaneous" section that covers aspects both inside and beyond the operating room.

Colon and rectal surgery is in a golden age; our special skills and expertise are highly valued by patients and colleagues alike. Colon and rectal training programs continue to thrive, attracting the very best and brightest surgery residents – they are the rock stars of their generation! We hope this textbook will also expose the many critical gaps in our knowledge base and inspire the next generation to answer them through thoughtful and high-level scientific inquiry.

Finally, we would like to thank our Developmental Editor Elektra McDermott for her extraordinary efforts and thoroughness in overseeing and ensuring its timely completion, along with each chapter author and coauthor(s) for their devotion to this task and to the mission of the ASCRS. We are deeply indebted to our teachers and mentors, who have been our heroes and generously shared their knowledge, experience, and enthusiasm over the years. We devote this edition to our trainees, whose energy, intellectual curiosity, and commitment to excellence drive us every day to be better. Pass it forward!

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Part I

Perioperative/Endoscopy

Anatomy and Embryology of the Colon, Rectum, and Anus

1

Joseph C. Carmichael and Steven Mills

Key Concepts

- The dentate line represents a true division between embryonic endoderm and ectoderm.
- The location of the anterior peritoneal reflection is highly variable and can be significantly altered by disease such as rectal prolapse.
- The right and left ischioanal space communicate posteriorly through the deep postanal space between the levator ani muscle and anococcygeal ligament.
- The junction between the midgut (superior mesenteric artery) and the hindgut (inferior mesenteric artery) leads to a potential watershed area in the area of the splenic flexure.
- There is a normal, three-stage process by which the intestinal tract rotates during development beginning with herniation of the midgut followed by return of the midgut to the abdominal cavity and ending with its fixation.

Anatomy of the Anal Canal and Pelvic Floor

Textbooks of anatomy would define the "anatomic" anal canal as beginning at the dentate (pectinate) line and extending to the anal verge. This definition is one defined truly by the embryology and mucosal histology. However, the "surgical" anal canal, as first defined by Milligan and Morgan [1], extends from the anorectal ring to the anal verge. The surgical definition of the anal canal takes into account the surrounding musculature that is critical to consider during the conduct of operations from low anterior resection to anal fistulotomy. The surgical anal canal is formed by the internal anal sphincter, external anal sphincter, and puborectalis (Fig. 1.1) and is easily identified on digital examination, ultrasound imaging [2], and magnetic resonance imaging (MRI) [3].

On average, the surgical anal canal is estimated to be longer in males than in females. Intraoperative measurements of the posterior anal canal have estimated the surgical anal canal to be 4.4 cm in men compared with 4.0 cm in women [4]. In addition, the anal canal was shown to be a unique muscular unit in that its length did not change with age. However, when using MRI, the anatomy of the anal canal has been characterized differently. MR imaging did not show a difference in the length of the posterior anal canal in men and women but did show that the anterior and posterior external anal sphincter length (not including puborectalis) was significantly shorter in women [5].

The anal canal forms proximally where the rectum passes through the pelvic hiatus and joins with the puborectalis muscle. Starting at this location, the muscular anal canal can be thought of as a "tube within a tube." The inner tube is the visceral smooth muscle of the internal anal sphincter and longitudinal layer that is innervated by the autonomic nervous system. The outer muscular tube consists of somatic muscles including the components of the puborectalis and external anal sphincter [6]. It is the outer muscular tube that provides conscious control over continence and is strengthened during Kegel exercises. The external anal sphincter extends distal to the internal anal sphincter, and the anal canal terminates at the anal verge where the superficial and subcutaneous portions of the external anal sphincter join the dermis.

Anal Canal Epithelium

The proximal anal canal has a pink appearance and is lined by the columnar epithelium of the rectal mucosa. Six to 12 mm proximal to the dentate line, the anal transition zone (ATZ) begins. The ATZ appears purple in color and represents an area of gradual transition of columnar epithelium to squamous epithelium. In a parallel to cervical anatomy, the

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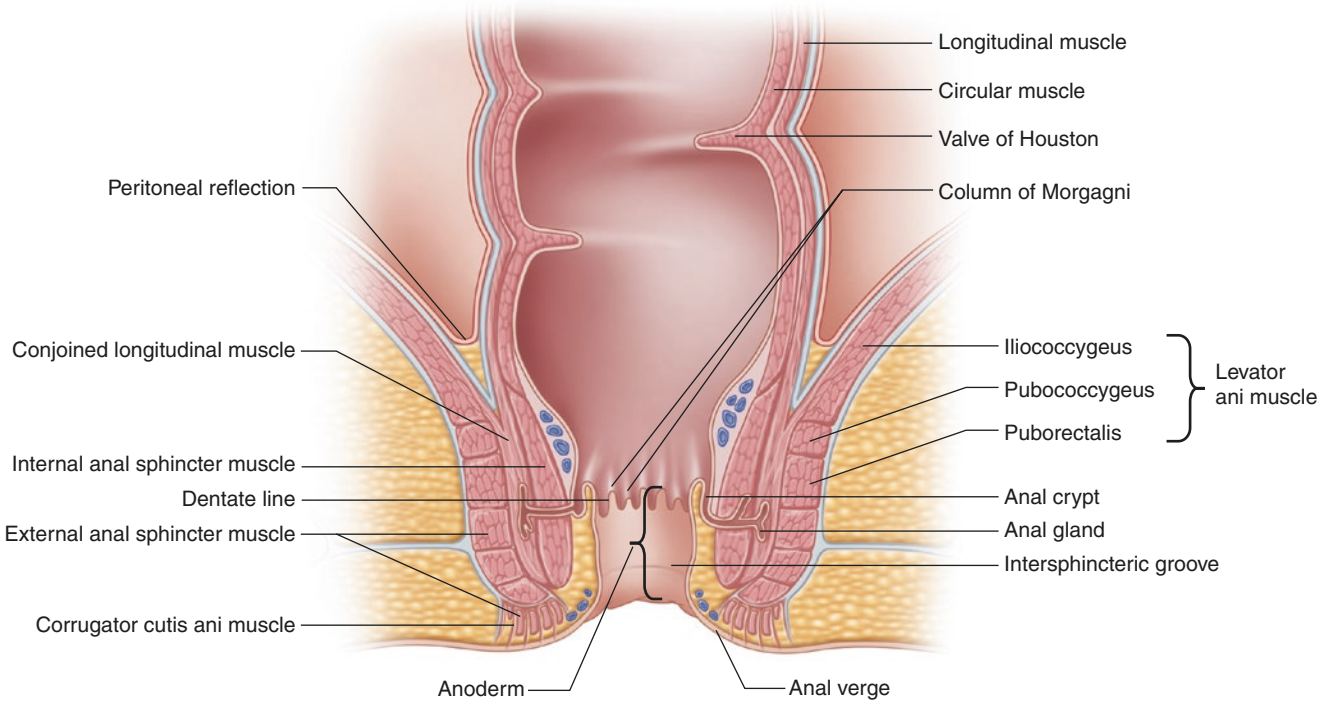


Fig. 1.1 Anal canal

ATZ is the area in which the majority of human papillomavirus-related dysplastic lesions are found in the anal canal [7]. The columns of Morgagni are noted in this area where redundant columns of tissue are noted with anal crypts at their base. This forms the rippled dentate line (or pectinate line) which can be most easily identified by locating the anal crypts at the base of the anal columns (columns of Morgagni). Anal crypts are connected to underlying anal glands which are the presumed source of sepsis in the majority of anorectal abscesses and fistula. On average, there are six anal glands surrounding the anal canal (range, 3–12) [6, 8, 9], and they tend to be more concentrated in the posterior quadrants. More than one gland may open into the same crypt, and some crypts may not be connected to anal glands. The anal gland ducts proceed inferior and lateral from the anal canal and enter the submucosa where two-thirds enter the internal anal sphincter and half terminate in the intersphincteric plane [8]. It is theorized that obstruction of these ducts leads to anal abscess and fistula [6]. Knowledge of the anatomy also explains why the internal opening of a "cryptoglandular" anal fistula should typically be at the dentate line.

Distal to the dentate line, the anoderm begins and extends for approximately 1.5 cm. According to Milligan and Morgan, anoderm or "anal canal skin… has the structure of skin, but there are no hairs and sweat glands and it consists of modified squamous transitional epithelium" [10]. In other words, anoderm has squamous histology and is devoid of hair, sebaceous glands, and sweat glands. At the anal verge, the anal canal lining becomes thickened and pigmented and contains hair follicles – this represents normal skin.

The dentate line represents a true division between embryonic endoderm and ectoderm. Proximal to the dentate line, the innervation is via the sympathetic and parasympathetic systems, with venous, arterial, and lymphatic drainage associated with the hypogastric vessels. Distal to the dentate line, the innervation is via somatic nerves with blood supply and drainage from the inferior hemorrhoidal system.

Internal Anal Sphincter

The internal anal sphincter (IAS) is the downward continuation of the circular smooth muscle of the rectum and terminates with a rounded edge approximately 1 cm proximal to the distal aspect of the external anal sphincter. 3D imaging studies of this muscle demonstrate the overall volume does not vary according to gender, but the distribution is different with women tending to have a thicker medial/distal internal anal sphincter [11]. Overall, the IAS was found to be approximately 2 mm in thickness and 35 mm in length. The authors note that on any study, it is difficult to identify the proximal portion of the IAS as it is a continuation of the wall of the lower rectum.

Conjoined Longitudinal Muscle

The anatomy and function of the perianal connective tissue is often overlooked but plays a significant role in normal anorectal function. Measuring approximately 0.5 mm to 2.0 mm in thickness, the conjoined longitudinal muscle (or conjoined longitudinal coat) lies in between the internal and external anal sphincters. It begins at the anorectal ring as an extension of the longitudinal rectal muscle fibers and descends caudally joined by fibers of the puborectalis muscle [12]. At its most caudal aspect, some of the conjoined longitudinal muscle fibers (referred to as *corrugator cutis ani muscle*) traverse the distal external anal sphincter and insert into the perianal skin, and some enter the fat of the ischiorectal fossa. Fibers of the conjoined longitudinal muscle also pass obliquely and caudally through the internal anal sphincter to interlace in a network within the subepithelial space. These subepithelial smooth muscle fibers were originally described by Treitz in 1853 [13] and have been referred to as Treitz's muscle. They have also been referred to as *corrugator cutis ani*, *musculus submucosae ani*, *mucosal suspensory ligament*, and *musculus canalis ani* [14]. It has been hypothesized by Thomson that disruption of Treitz's muscles results in anal cushion prolapse, vascular outflow obstruction, and hemorrhoidal bleeding and thrombosis [15]. Haas and Fox have hypothesized that the conjoined longitudinal muscle, and the network of connective tissue that it supports, plays a role in minimizing anal incontinence after sphincterotomy [12].

External Anal Sphincter

The external anal sphincter (EAS) is composed of striated muscle that forms an elliptical tube around the internal anal sphincter and conjoined longitudinal muscle. As it extends beyond the distal most aspect of the internal anal sphincter, the intersphincteric groove is formed. At its distal most aspect, *corrugator cutis ani muscle* fibers from the conjoined longitudinal muscle traverse the external anal sphincter and insert into the perianal skin. Milligan and Morgan described the external anal sphincter as having three distinct divisions from proximal to distal that were termed sphincter ani externus profundus, superficialis, and subcutaneous [1]. With time, this theory of three distinct divisions was proven invalid by Goligher who demonstrated that the external anal sphincter was truly a continuous sheet of skeletal muscle extending up to the puborectalis and levator ani muscles [16]. While the external anal sphincter does not have three distinct anatomic layers, it is common to see the proximal portion of the EAS referred to as deep EAS, the midportion as the superficial EAS, and the most distal aspect as the subcutaneous EAS. The mid EAS has posterior attachment to the coccyx via the anococcygeal ligament, and the proximal EAS becomes continuous with the puborectalis muscle. Anteriorly, the proximal EAS forms a portion of the perineal body with the transverse perineal muscle. There are clear differences in the morphology of the anterior external anal sphincter that have been demonstrated on both MRI and three-dimensional endoanal ultrasound studies in normal male and female volunteers [17, 18]. The normal female external anal sphincter has a variable natural defect occurring along its proximal anterior length below the level of the puborectalis sling that was demonstrated in 75 percent of nulliparous volunteers. This defect correlated with findings on anal manometry, and the authors noted that it can make interpretation of an isolated endoanal ultrasound difficult resulting in overreporting of obstetric sphincter defects [17]. This natural defect of the anterior anal sphincter provides some justification as to why anterior anal sphincterotomy is not routinely recommended in women.

The external anal sphincter is innervated on each side by the inferior rectal branch of the pudendal nerve (S2 and S3) and by the perineal branch of S4. There is substantial overlap in the pudendal innervation of the external anal sphincter muscle on the two sides which enables reinnervation to be partially accomplished from the contralateral side following nerve injury [19].

Hemorrhoids

Hemorrhoids are a normal feature of human anatomy and have been identified as present in the embryonic stage of development [20]. While many perceive hemorrhoids as a pathologic phenomenon, they are present in all humans and function to improve anal continence. The pathogenesis and treatment of hemorrhoids will be discussed elsewhere in this book, but here we will review the features of non-pathologic hemorrhoids.

Hemorrhoids are blood-filled cushions that line the anal canal. Hemorrhoids are located above and below the dentate line and have three important components: (1) the lining (mucosa or anoderm), (2) the stroma (blood vessels surrounded by connective tissue), and (3) anchoring connective tissue that secures the hemorrhoid to the internal sphincter and conjoined longitudinal muscle [20]. Hemorrhoids receive their blood supply from terminal branches of the superior hemorrhoidal artery [21]. While it has been previously stated that the terminal branches of the superior hemorrhoidal artery end in the right anterior, right posterior, and left lateral positions of the anal canal [20], this has been disputed [21]. At the level of the hemorrhoidal cushion, arteriovenous anastomosis (A-V shunts) exists in a complex vascular network termed the "corpus cavernosum recti" by Steltzner [22]. This vascular network with an arterial blood

supply is why pulsatile bleeding can be seen at the time of hemorrhoidectomy.

Perineal Body

The perineal body represents the intersection of the external anal sphincter, superficial transverse perinei, deep transverse perinei, and bulbospongiosus (also referred to as bulbocavernosus) muscles (Fig. 1.2). Recent research, based on advanced magnetic resonance imaging and ultrasound, has suggested that the transverse perinei (TP) and bulbospongiosus (BS) muscles contribute significantly to anal incontinence [23]. It has been proposed that the EAS, TP, and BS muscles be collectively referred to as the "EAS complex muscles." In this theory, the EAS complex morphology is "purse string" shaped rather than the typical "donut" shape previously considered. When these muscles are considered as a functional unit, it lends further support to the idea that it is critical to attempt to repair the perineal body during overlapping sphincter reconstructions.

Pelvic Floor Muscles

In addition to the anal sphincter and perineal body, the levator ani (LA) muscles contribute to pelvic organ support. For example, injury to the LA is seen in 55% of women with pelvic organ prolapse but in only 16% without prolapse [24]. The LA has three subdivisions including the pubococcygeus (aka pubovisceral), puborectalis, and iliococcygeus. Some authors had previously suggested that the puborectalis was part of the deep portion of the EAS [25] or that the LA did not actually have three definable divisions [26]; however, a significant amount of evidence has been presented to the contrary. In vivo MRI measurements in women have shown distinct, visible muscle fascicle directions for each of the three LA component muscles [27]. Embryology studies have also demonstrated that the puborectalis muscle is a portion of the LA muscle and shares a common primordium with the iliococcygeus and pubococcygeus muscles [28].

Innervation of the levator ani muscles has been described in detailed cadaveric studies [29]. The contemporary cadaveric studies suggest that the LA muscles are innervated by the pudendal nerve branches: perineal nerve and inferior rectal nerve as well as direct sacral nerves S3 and/or S4 (aka levator ani nerve) [30]. The pubococcygeus muscle and puborectalis muscle are primarily innervated by the pudendal nerve branches, while the iliococcygeus muscle is primarily innervated by the direct sacral nerves S3 and/or S4 (Fig. 1.3).

Puborectalis Muscle

The puborectalis muscle (PRM) fibers arise from the lower part of the symphysis pubis and from the superior fascia of the urogenital diaphragm and run alongside the anorectal junction. Posterior to the rectum, the fibers join forming a sling. The "anorectal ring" is composed of the upper borders of the internal anal sphincter and puborectalis muscle [1]. Contraction of the PRM sling causes a horizontal force [27] that closes the pelvic diaphragm and decreases the anorectal angle during squeeze. This is widely considered the most important contributing factor to gross fecal continence.

Iliococcygeus Muscle

Iliococcygeus muscle (ICM) fibers arise from the ischial spines and posterior obturator fascia, pass inferior/posterior and medially, and insert into the distal sacrum, coccyx, and anococcygeal raphe. The ICM, along with the pubococcygeus muscle, contributes to "lifting" of the pelvic floor [27].

Pubococcygeus Muscle

The pubococcygeus (PCM) muscle lies medial to the PRM. PCM fibers arise from the anterior half of the obturator fascia and the high posterior pubis. The PCM fibers are directed posterior/inferior and medially, where they intersect with fibers from the opposite side and form the anococcygeal raphe (or anococcygeal ligament). PCM muscle fibers insert in the distal sacrum and tip of the coccyx. Portions of the PCM contribute to the conjoined longitudinal muscle. The PCM forms the "levator hiatus" as it ellipses the lower rectum, urethra, and either the vagina in women or the dorsal vein of the penis in men. The levator hiatus is connected to the intrahiatal organs by a fascial condensation called the "hiatal ligament" (Fig. 1.4). The hiatal ligament arises circumferentially around the hiatal margin as a continuation of the fascia on the pelvic surface of the levator muscle [31]. Enlargement of the levator hiatus has been implicated as a cause of female pelvic organ prolapse [32]. The PCM is the portion of the levator ani that is typically injured during traumatic vaginal delivery [33].

Anatomy of the Rectum

The rectum is arbitrarily considered to have three distinct parts: the upper, middle, and lower rectum. Although not anatomically distinct, the upper, mid, and lower rectal divisions are important when considering surgical treatment of rectal cancer. From the anal verge, the lower rectum is 0–7 cm; middle rectum, 7–12 cm; and upper rectum, 12–15 cm [34]. However, the rectum is actually variable in length and may

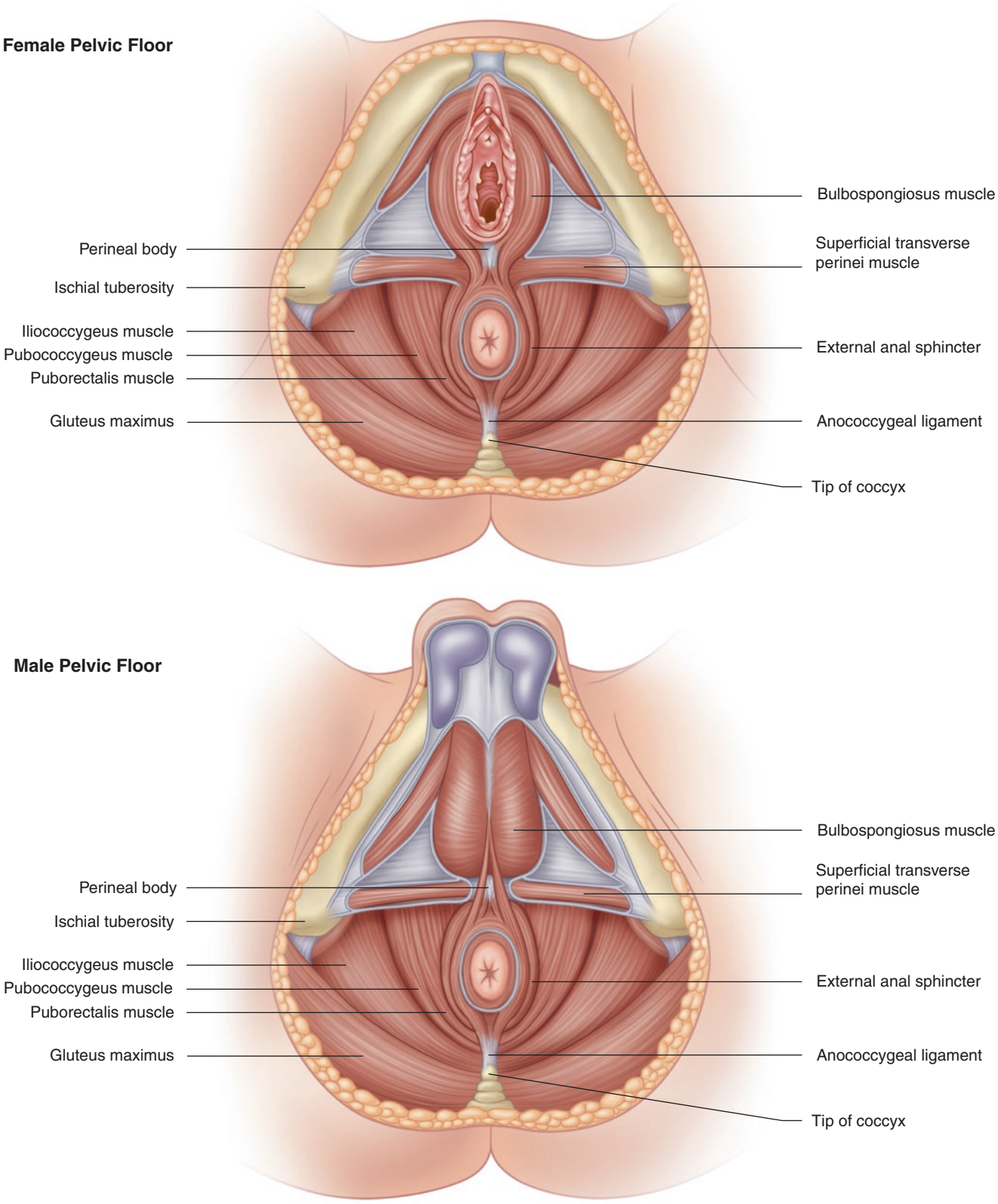


Fig. 1.2 Pelvic floor muscles

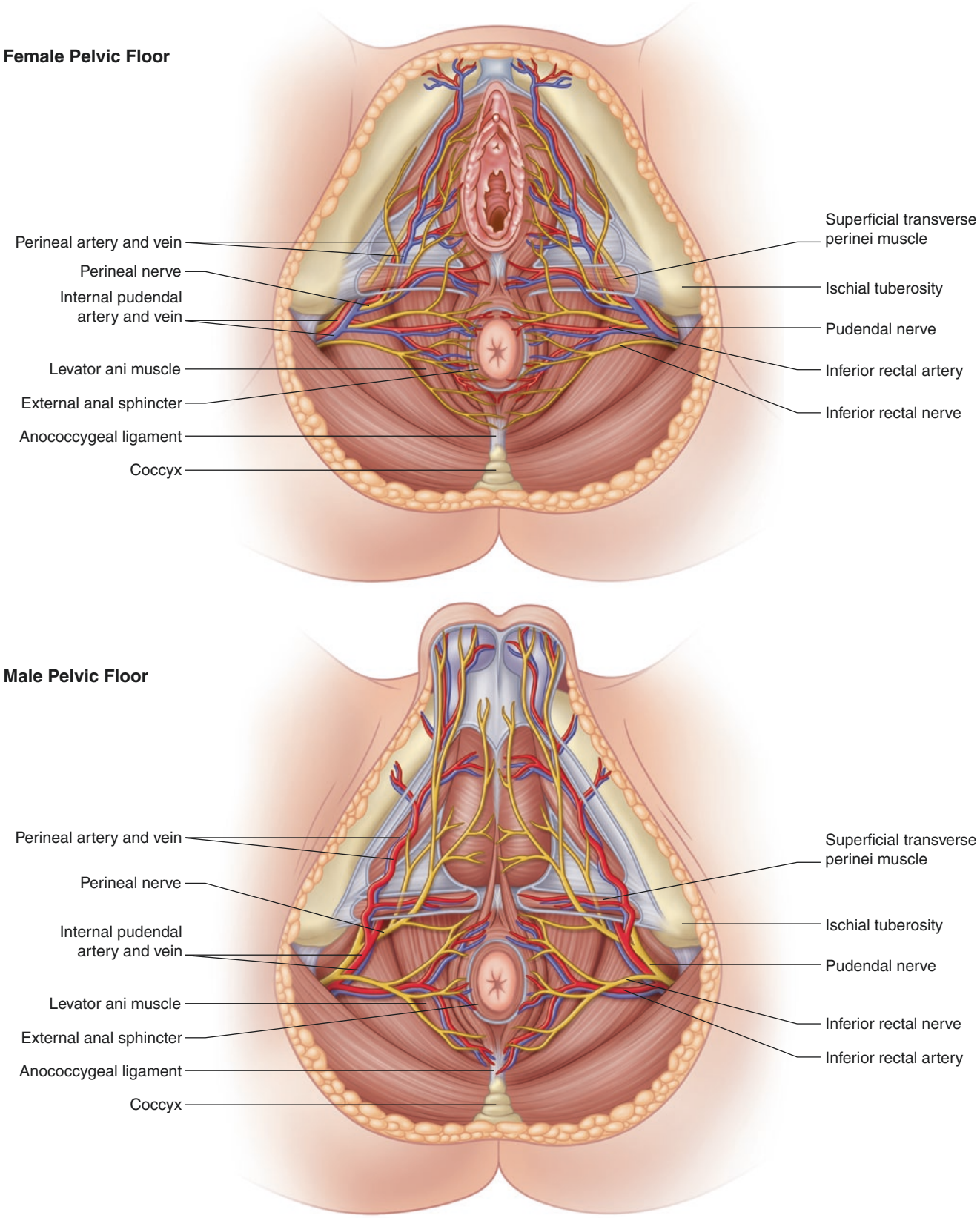


Fig. 1.3 Pelvic floor nerves and blood supply

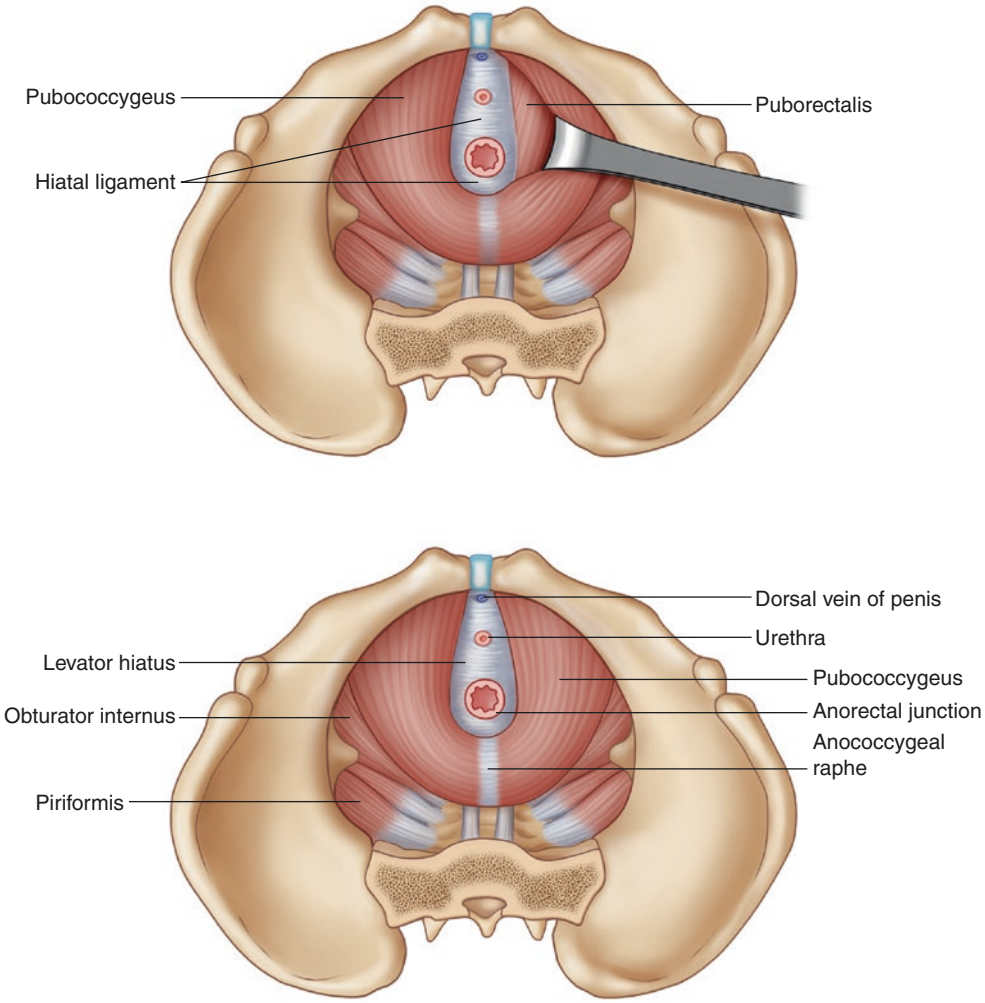


Fig. 1.4 Pelvic floor anatomy, abdominal view

extend beyond 15 cm from the anal verge. The upper rectum can be distinguished from the sigmoid colon by the absence of taenia coli and epiploic appendages.

The majority of the rectum lies outside of the peritoneal cavity, although anteriorly and laterally the upper rectum is covered by a layer of visceral peritoneum down to the peritoneal reflection. The location of the anterior peritoneal reflection is highly variable and can be significantly altered by disease such as rectal prolapse. Given the importance of the location of the peritoneal reflection with respect to transanal excision of rectal tumors, one study sought to identify the location of the anterior peritoneal reflection in 50 patients who were undergoing laparotomy [35]. It was found that the anterior peritoneal reflection was located on average 9 cm from the anal verge in females and 9.7 cm from the anal verge in males – there was no statistically significant difference based on gender.

Mesorectum

The origin of the word "mesorectum" is difficult to identify and may be attributed to Maunsell in 1892 [36] but was certainly later popularized by Heald [37]. Unfortunately, the term mesorectum is a misnomer that is not generally acknowledged in classic texts of anatomy such as the *Nomina Anatomica* [38]. In anatomic terms, the prefix "meso" refers to two layers of peritoneum that suspend an organ, and the suffix applied indicates the target organ (e.g., mesocolon). The term "meso" cannot be assigned to the rectum, as it implies a mobile, suspended rectum, which may only be the case in patients with rectal prolapse.

The mesorectum is a term employed by surgeons to describe the fascial envelope of the rectum that is excised during surgical treatment of rectal cancer. Indeed, failure to completely excise this envelope intact has been associated with an increased

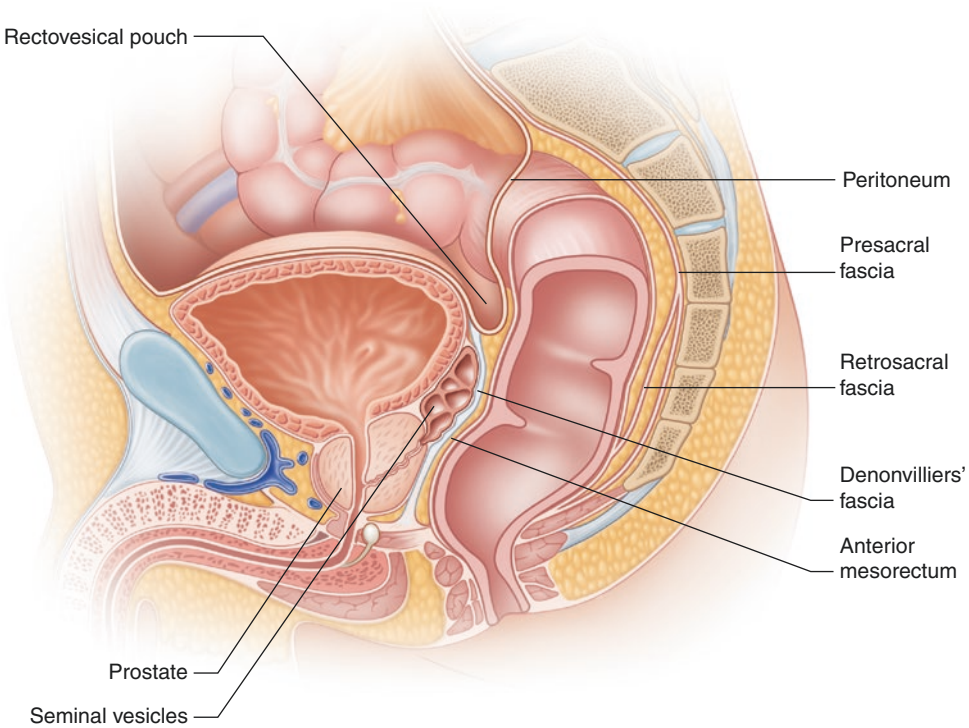


Fig. 1.5 Fascial relationships of the rectum

incidence of local recurrence of rectal cancer [39]. The mesorectum is contained within the fascia propria. The fascia propria is an upward projection of the parietal endopelvic fascia that lines the walls and floor of the pelvis. The fascia propria encloses the perirectal fat, lymphatics, blood vessels, and nerves and is not considered a barrier strong enough to prevent the spread of infection or malignancy [40].

Presacral Fascia

The presacral fascia is a thickened portion of the parietal endopelvic fascia overlying the sacrum that covers the presacral veins and hypogastric nerves (Fig. 1.5). It extends laterally to cover the piriformis and upper coccyx. As the presacral fascia extends laterally, it becomes continuous with the fascia propria and contributes to the lateral ligaments of the rectum. Caudally, this fascia extends to the anorectal junction covering the anococcygeal ligament. During total mesorectal excision, the fascia propria is elevated sharply off the presacral fascia. Leaving the presacral fascia intact eliminates the possibility of causing presacral bleeding.

Retrosacral Fascia

The retrosacral fascia originates at the third and fourth portion [41] of the sacrum and extends anteriorly to the posterior layer of the fascia propria 3–5 cm proximal to the anorectal junction [42]. This tough fascia layer is surgically relevant as it must be sharply incised during total mesorectal excision [40]. The space posterior to the retrosacral fascia is referred to as the supralevator or retrorectal space.

Waldeyer's Fascia

There is significant confusion about what Waldeyer's fascia represents as the eponym has been used to describe the presacral fascia, the retrosacral fascia, or all fascia posterior to the rectum. In Waldeyer's original description of pelvic fascia, there was no particular emphasis on the presacral component [40, 42]. While the debate continues regarding "Waldeyer's fascia," it is important to simply understand that the phrase can have the potential to mean presacral fascia, retrorectal fascia, or both [43].

Denonvilliers' Fascia

Denonvilliers' fascia arises from the fusion of the two walls of the embryological peritoneal cul-de-sac and extends from the deepest point of the rectovesical pouch to the pelvic floor [44]. Originally described by Denonvilliers in 1836 as a "prostatoperitoneal" membranous layer between the rectum and seminal vesicles, Denonvilliers fascia is also pres-

ent in females as part of the rectovaginal septum and is sometimes referred to as rectovaginal fascia. It is found immediately beneath the vaginal mucosa and is clearly what most would consider as part of the vaginal wall. It merges superiorly with the cardinal/uterosacral complex in females or the rectovesical pouch in males. It merges laterally with the endopelvic fascia overlying the levator muscle and distally with the perineal body. It contains collagen, some strands of smooth muscle, and heavy elastin fibers. Rectoceles represent a defect in this layer that allows the rectum to bulge anteriorly [45].

Microscopically, the Denonvilliers' fascia has two layers; however, it is not possible to discern two layers during pelvic dissection [44]. In the anterior rectal plane, the mesorectum is contained by the fascia propria which lies dorsal to Denonvilliers' fascia. The cavernous nerves run in neurovascular bundles at the anterolateral border of Denonvilliers' fascia.

Lateral Ligaments

While frequently referred to by surgeons, there are two controversial points regarding the lateral ligaments of the rectum. First, do the lateral ligaments exist? Second, what do they contain? Miles refers to division of the lateral ligaments of the rectum in his seminal description of abdominoperineal resection in 1908. Specifically, he notes "In these structures the middle haemorrhoidal arteries are found but seldom require a ligature" [46]. It is interesting to note that at least one modern cadaveric dissection study identified the presence of a middle rectal artery in only 22% of specimens [41] which could be a contributing factor as to why Miles saw no significant bleeding in this area.

Total mesorectal excision, as popularized and described by Heald, involves sharp dissection along the fascia propria circumferentially to the pelvic floor. While acknowledging that the middle rectal vessels are "divided as far from the carcinoma as possible," Heald does not mention "lateral ligaments" of the rectum at all [47].

In an extensive review of the anatomy of the lateral ligament, Church notes that it is a common misconception that the lateral ligaments contain the middle rectal artery at all. It appears that the lateral ligaments comprise "primarily nerves and connective tissue" and their division without bleeding attests to the absence of a "significant accessory rectal artery in this location in the majority of patients" [40].

In a separate cadaveric study, the lateral ligaments of the rectum were identified as trapezoid structures originating from mesorectum and anchored to the endopelvic fascia at the level of the midrectum. It was recommended that, as lateral extensions of the mesorectum, the ligaments must be cut and included in the total mesorectal excision (TME) specimen. It was further noted that the lateral ligaments did not contain middle rectal arteries or nerve structures of importance. The urogenital bundle runs just above the lateral ligament at its point of insertion on the endopelvic fascia, the middle rectal artery (if present) runs posterior to the lateral ligament, and the nervi recti fibers (which originate from the inferior hypogastric plexus) course transversely under the lateral ligament to the rectal wall [48]. Other modern cadaveric investigations note the rarity of middle rectal arteries and the absence of clinically relevant neurovascular structures in the lateral ligaments [49].

Rectal Valves: The Spiral Valves of Houston and Kohlrausch's Valve

The first anatomic description of rectal valves is credited to Giovanni Morgagni [50]; however, it was John Houston, an Irish anatomist and surgeon, who presented the first seminal work on the structures [51, 52]. Houston described an average of three oblique valves with an upward orientation and concave surface that were located successively on opposite sides of the rectum that formed "a sort of spiral tract down its cavity." Houston theorized that these valves might aid in continence by supporting "the weight of fecal matter"; however, this has not been substantiated elsewhere.

Modern anatomy texts usually also describe three rectal valves (Fig. 1.1) with the superior and inferior valves located on the left side of the rectum and the more prominent middle rectal valve on the right; however, this is not uniformly the case [53]. Only 45.5% of patients will have the classic three valve rectal anatomy; 32.5% will have only two valves; and 10.25% may have four valves.

After Houston's definitive description of rectal valves in 1830, Otto Kohlrausch, a physician and scientist in Germany, described a single mid-rectal valve in 1854 [54]. When there are three valves, current anatomists identify Kohlrausch's valve as the middle one [51]. This valve is usually the largest, located on the right and approximately 9–11 cm from the anal verge, and some authors have suggested this valve could serve as an intraluminal marker for the area of the anterior peritoneal reflection [55].

Anorectal Spaces

It is important to acknowledge and understand the anorectal spaces created by the various myofascial relationships in the pelvis as these spaces help us understand how anorectal sepsis can spread throughout the pelvis.

Perianal Space

The perianal space contains external hemorrhoid cushions, the subcutaneous external anal sphincter and the distal internal anal sphincter. The perianal space is in communication

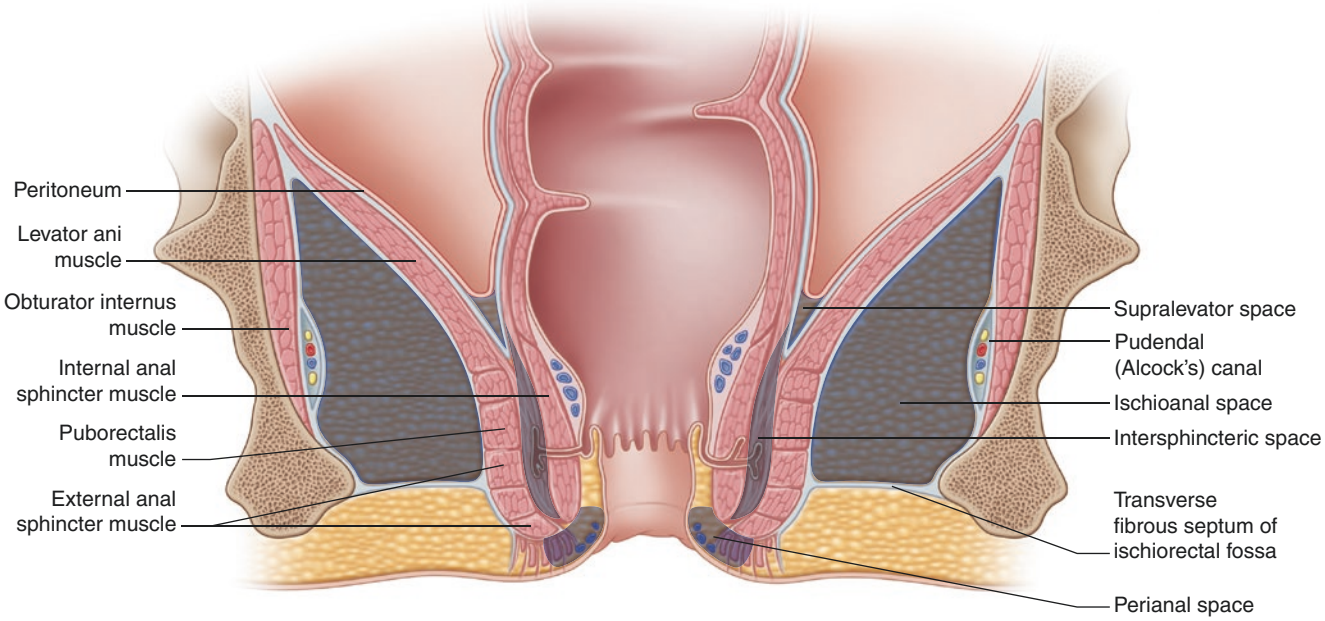


Fig. 1.6 Perianal and perirectal spaces, coronal view

with the intersphincteric space (Fig. 1.6). The perianal space has its cephalad boundary at the dentate line and laterally to the subcutaneous fat of the buttocks or is contained by fibers extending from the conjoined longitudinal muscle often referred to as *corrugator cutis ani* muscle fibers. Otherwise, the perianal space is contained by anoderm.

Intersphincteric Space

The intersphincteric space is the potential space that lies between the internal and external anal sphincter and is continuous with the perianal space. It is of clinical importance as cryptoglandular infections tend to begin in this area and expand elsewhere to create anal fistula [6].

Submucous Space

This space lies between the medial boarder of the internal anal sphincter and the anal mucosa proximal to the dentate line. It is continuous with the submucosa of the rectum. This area contains internal hemorrhoid vascular cushions.

Ischioanal/Ischiorectal Space

The ischioanal (also referred to as ischiorectal) space is the largest anorectal space. It has been described as a pyramid shape with its apex at the levator muscle insertion into the obturator fascia. The medial boarder is thus the levator ani muscle and external anal sphincter. The obturator internus muscle and obturator fascia make up the lateral boarder of the ischioanal space. The posterior boundary is formed by the lower border of the gluteus maximus muscle and the sacrotuberous ligament. The space has an anterior boundary formed by the superficial and deep transverse perineal muscles. The caudal boundary is skin of the perineum. The ischioanal fossa contains adipose tissue, pudendal nerve branches, and superficial branches of the internal pudendal vessels. The right and left ischioanal space communicate posteriorly through the deep postanal space between the levator ani muscle and anococcygeal ligament (Fig. 1.7) [56]. When the ischioanal and perianal spaces are regarded as a single space, it is referred to as the ischioanal fossa [43].

Supralevator Space

The upper boundary of the supralevator space is the peritoneum, the lateral boundary is the pelvic wall, the medial boundary is the rectum, and the inferior boarder is the levator ani muscle (Fig. 1.8).

Superficial and Deep Postanal Spaces

These spaces are located posterior to the anus and inferior to the levator muscle. The superficial postanal space is more caudal and is located between the anococcygeal ligament and the skin. The superficial postanal space allows communication of perianal space sepsis.

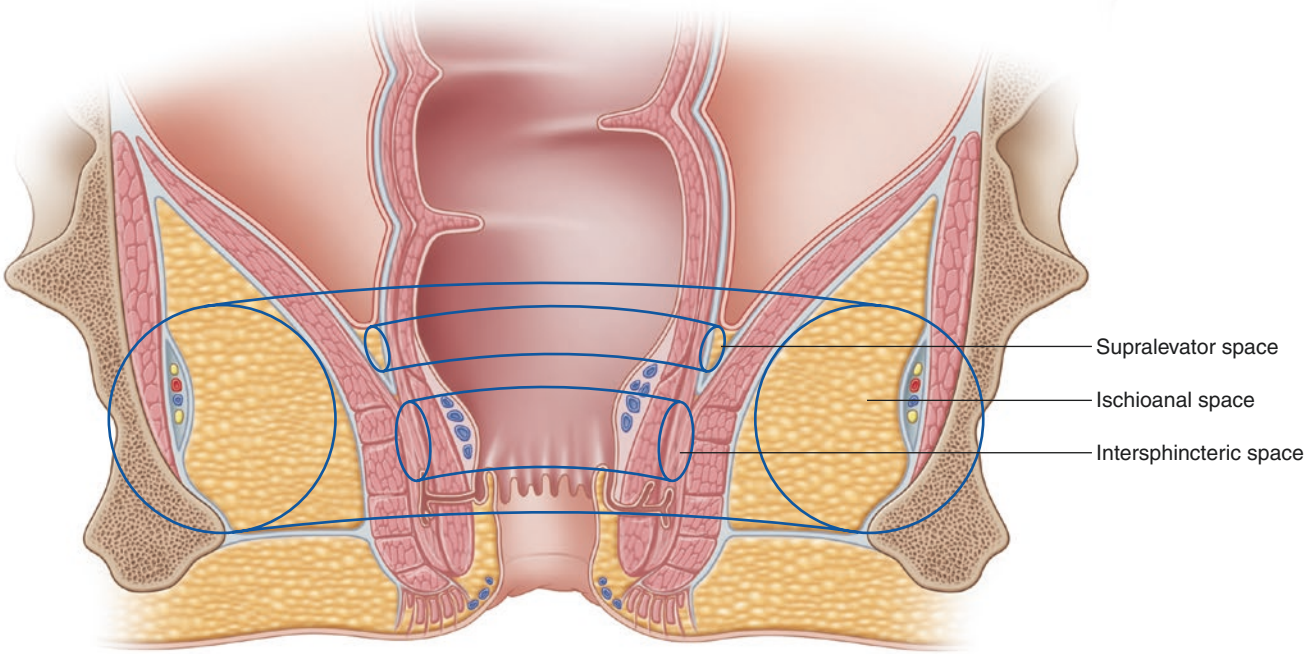
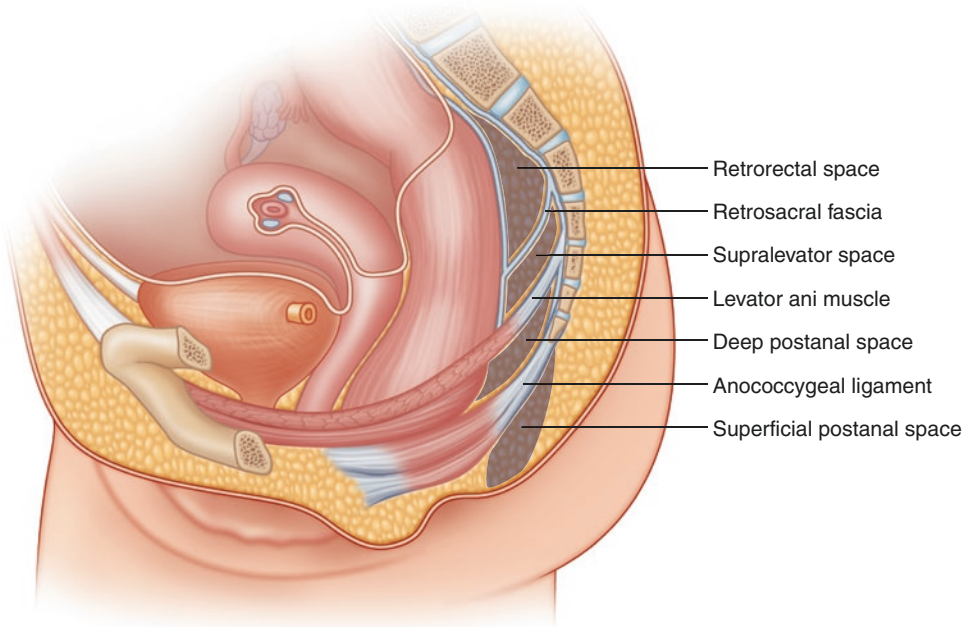


Fig. 1.7 Communication of the anorectal spaces

Fig. 1.8 Perianal and perirectal spaces, lateral view



The deep postanal space (retrosphincteric space of Courtney) [57] is located between the levator ani muscle and the anococcygeal raphe. This space allows ischioanal sepsis to track from one side to the other resulting in the so-called "horseshoe" abscess.

Retrorectal Space

The retrorectal space is found between the presacral fascia and fascia propria. It contains no major blood vessels or nerves. It is limited laterally by the lateral ligaments of the

piriformis fascia and inferiorly by the retrosacral fascia. The fascia propria and presacral fascia come together at the apex of this space [40].

Rectal Blood Supply

The rectum is supplied by the superior, middle, and inferior rectal (hemorrhoidal) arteries (Fig. 1.9). Both the middle and inferior hemorrhoidal vessels are paired arteries, and the superior rectal artery is not.

Superior Rectal Artery

The superior rectal artery (SRA) is the continuation of the inferior mesenteric artery and is so named after the inferior mesenteric artery crosses the left iliac vessels. The SRA gives off a rectosigmoid branch, an upper rectal branch, and then bifurcates into right and left terminal branches in 80% [58] of cases as it descends caudally in the mesorectum. On average, eight terminal branches of the SRA have been identified in the distal rectal wall [21].

Middle Rectal Artery

The middle rectal artery (MRA) has been variably noted in many studies. It may be found on one or both sides of the rectum and has been noted to be present 12–28% of the time [49, 59]. At least one study reported the presence of the middle rectal artery in at least 91% of cadaveric specimens [48]. The MRA originates from the anterior division of the internal iliac or pudendal arteries. Please see the "Lateral Ligament" discussion above for more review on the anatomic course of the middle rectal artery.

Inferior Rectal Artery

The inferior rectal arteries (IRA) are paired vessels that originate as branches of the internal pudendal artery which receives its blood supply from the internal iliac artery. The artery originates in the pudendal canal and is entirely extrapelvic (caudal to the levator ani) in its distribution. The IRA traverses the obturator fascia and the ischiorectal fossa and pierces the wall of the anal canal in the region of the external anal sphincter [40].

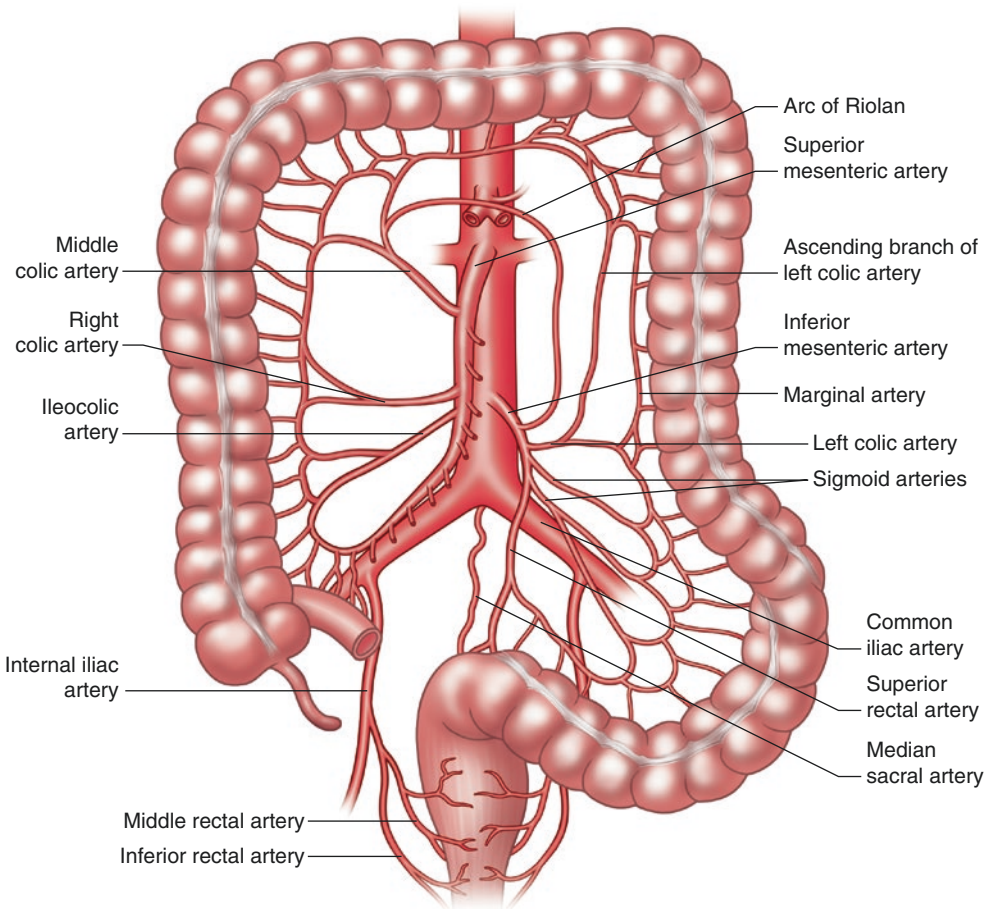


Fig. 1.9 Arterial anatomy of the colon and rectum

Venous and Lymphatic Drainage of the Rectum and Anus

Venous drainage from the rectum and anus occurs via both the portal and systemic systems. Middle and inferior rectal veins drain to the systemic systems via the internal iliac vein, while the superior rectal vein drains the rectum and upper anal canal into the portal system via the inferior mesenteric vein (Fig. 1.10). The two systems of drainage in the rectum, thus, explain the potential development of rectal varices in patients with portal hypertension.

Lymphatics from the upper two-thirds of the rectum drain to the inferior mesenteric lymph nodes and then to the para-aortic lymph nodes. Lymphatic drainage from the lower third of the rectum occurs along the superior rectal artery and laterally along the middle rectal artery to the internal iliac lymph nodes. In the anal canal, lymphatics above the dentate drain to the inferior mesenteric and internal iliac lymph nodes. Below the dentate line, lymphatics drain along the inferior rectal lymphatics to the superficial inguinal nodes.

Innervation of the Rectum and Anus

Sympathetic fibers arise from L1, L2, and L3 and pass through the sympathetic chains and join the preaortic plexus (Fig. 1.11). From there, they run adjacent and dorsal to the inferior mesenteric artery as the mesenteric plexus and innervate the upper rectum. The lower rectum is innervated by the presacral nerves from the hypogastric plexus. Two main hypogastric nerves, on either side of the rectum, carry sympathetic information from the hypogastric plexus to the pelvic plexus. The pelvic plexus lies on the lateral side of the pelvis at the level of the lower third of the rectum adjacent to the lateral stalks (please see discussion of lateral stalks above).

Parasympathetic fibers to the rectum and anal canal originate from S2, S3, and S4 to penetrate through the sacral fora-

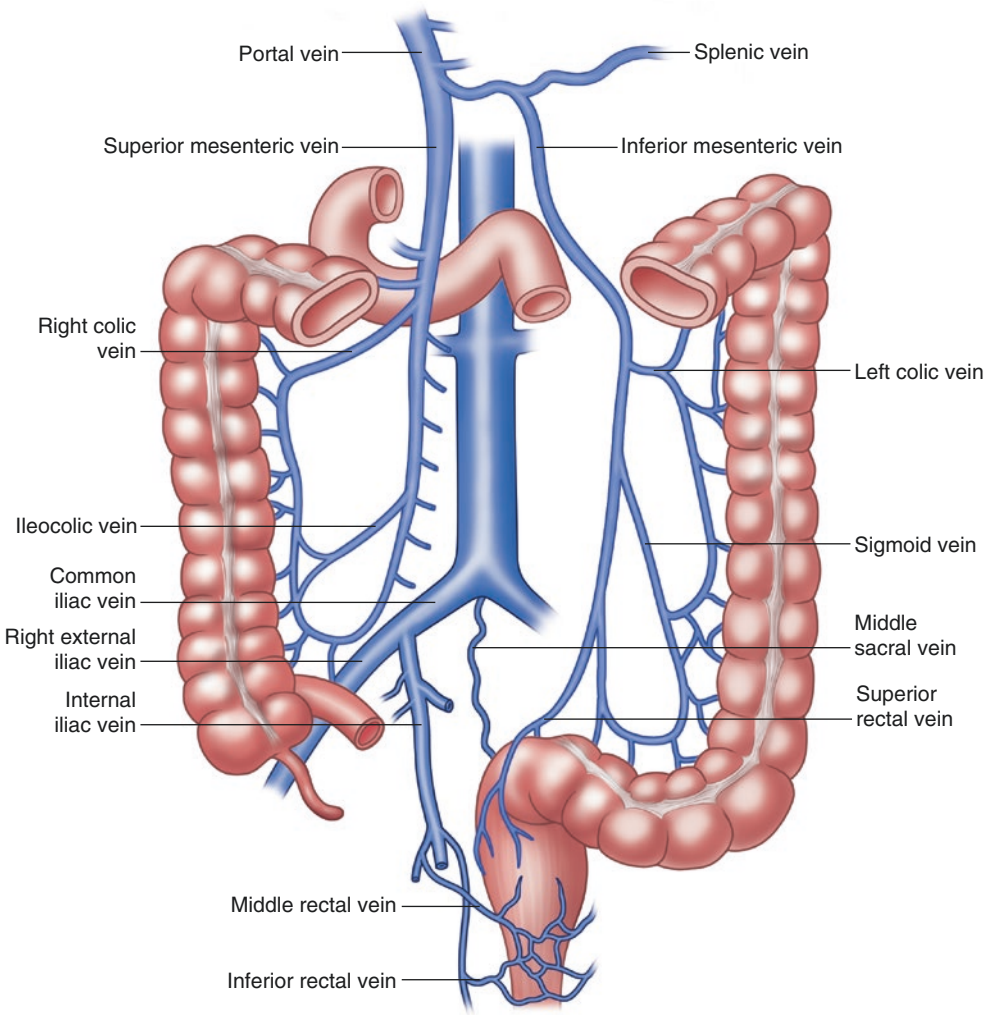


Fig. 1.10 Venous anatomy of the colon and rectum

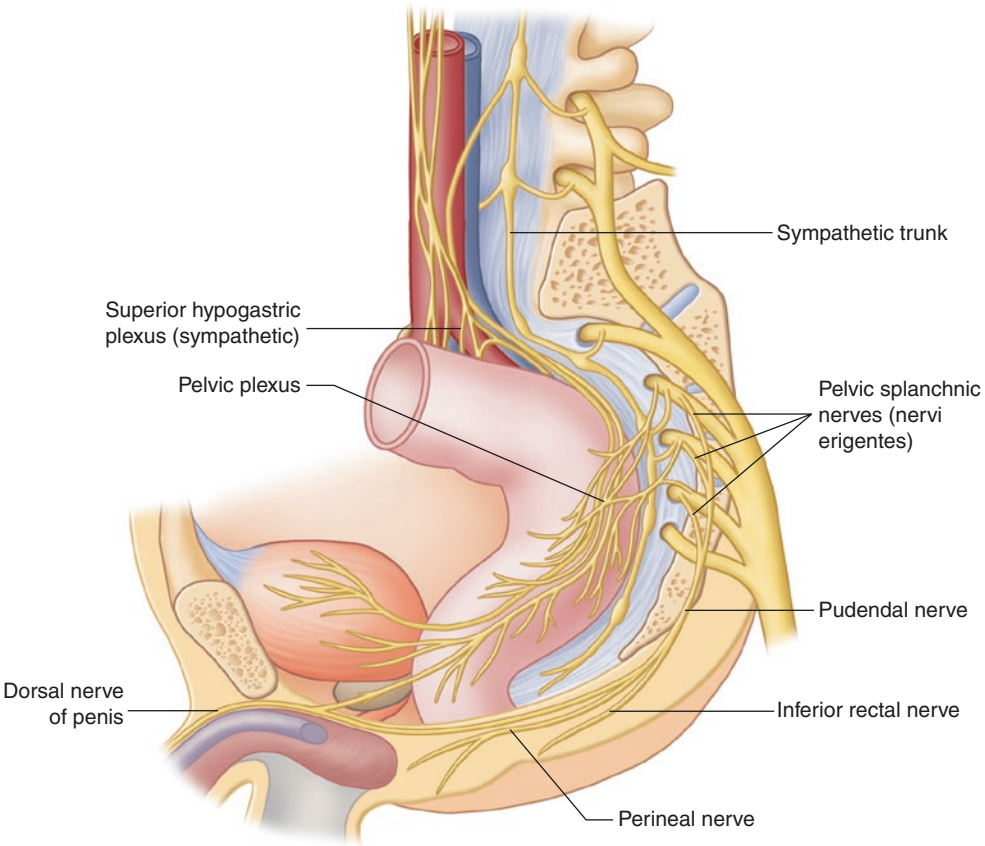


Fig. 1.11 Nerves of the rectum

men and are called the nervi erigentes. These nerves course laterally and anteriorly to join the sympathetic hypogastric nerves and form the pelvic plexus on the pelvic sidewall. From here, postganglionic mixed parasympathetic and sympathetic nerve fibers supply the rectum, genital organs, and anal canal. The periprostatic plexus is considered a subdivision of the pelvic plexus and supplies the prostate, seminal vesicles, corpora cavernosa, vas deferens, urethra, ejaculatory ducts, and bulbourethral glands.

The internal anal sphincter is innervated by sympathetic (L5) and parasympathetic (S2, S3, and S4) nerves following the same route as the nerves to the rectum as noted above. The external anal sphincter is innervated on each side by the inferior rectal branch of the internal pudendal nerve (S2 and S3) and by the perineal branch of S4. Anal sensation is mediated by the inferior rectal branch of the pudendal nerve.

Anatomy of the Colon

The colon is a long tubular organ consisting of muscle and connective tissue with an inner mucosal layer. The diameter of the colon differs depending upon which segment is evaluated and generally decreases from proximal to distal (cecum about 7 cm and sigmoid colon about 2.5 cm in diameter). The overall length is variable with an average length approximating 150 cm. The right and left sides of the colon are fused to the posterior retroperitoneum (secondarily retroperitonealized), while the transverse colon and sigmoid colon are relatively free within the peritoneum. The transverse colon is held in position via its attachments to the right/left colon at the flexures (hepatic and splenic, respectively) and is further fused to the omentum. Generally, the colon is located peripherally within the abdomen with the small bowel located centrally.

There are three classic anatomic points of differentiation between the colon and the small intestine: the appendices epiploicae, the taeniae coli, and the haustra. The appendices epiploicae are non-mesenteric fat protruding from the serosal surface of the colon. They are likely residual from the antimesenteric fat of the embryologic intestine which dissipates (unlike the omentum on the stomach). The taenia coli are three thickened bands of outer, longitudinal muscle of the colon. This outer layer of muscle is indeed circumferentially complete [60] but is considerably thicker in three areas represented by the taenia. The three taeniae have been given separate names by some: *taenia libera* to represent the anterior band, *taenia mesocolica* for the posteromedial band, and *taenia omentalis* for posterolateral band. The bands are continuous from their origin at the base of the appendix until the

rectosigmoid junction where they converge (marking an anatomically identifiable differentiation between the sigmoid colon and rectum). Though they run along the full length of the colon, they are not as long as the bowel wall. This difference in length results in outpouchings of the bowel wall between the taenia referred to as haustra. The haustra are further septated by the plicae semilunares.

Cecum

The proximal most portion of the colon is termed the cecum, a saclike segment of the colon below (proximal to) the ileocecal valve. The cecum is variable in size but generally is about 8 cm in length and 7 cm in diameter. At its base is the appendix. Terminating in the posteromedial area of the cecum is the terminal ileum (ileocecal valve). The cecum is generally covered by visceral peritoneum, with more variability near the transition to the ascending colon (upper or distal cecum). The ileocecal valve is a circular muscular sphincter which appears as a slit-like ("fish-mouth") opening noted on an endoscopic evaluation of the cecum. The valve is not competent in all patients, but when present, its competence leads to the urgency of a colon obstruction as it develops into a closed-loop obstruction. Regulation of ileal emptying into the colon appears to be the prime task in ileocecal valve function [61].

The Appendix

The appendix is an elongated, true diverticulum arising from the base of the cecum. The appendiceal orifice is generally about 3–4 cm from the ileocecal valve. The appendix itself is of variable length (2–20 cm) and is about 5 mm in diameter in the non-inflamed state. Blood is supplied to the appendix via the appendiceal vessels contained within the mesoappendix. This results in the most common location of the appendix being medially on the cecum toward the ileum, but the appendix does have great variability in its location including pelvic, retrocecal, preileal, retroileal, and subcecal. Though traditionally thought to be an unnecessary vestige, modern research points to the appendix which is rarely absent and rarely altered actually playing an important role in immune function and/or the colonic microbiome [62].

Ascending Colon

From its beginning at the ileocecal valve to its terminus at the hepatic flexure where it turns sharply medially to become the transverse colon, the ascending colon measures on average, about 15–18 cm. Its anterior surface is covered in visceral peritoneum, while its posterior surface is fused with the retroperitoneum. The lateral peritoneal reflection can be seen as a thickened line termed the white line of Toldt, which can serve as a surgeon's guide for mobilization of the ascending colon off of its attachments to the retroperitoneum, most notably the right kidney (Gerota's fascia) and the loop of the duodenum located posterior and superior to the ileocolic vessels. The right ureter and the right gonadal vessels pass posteriorly to the ascending mesocolon within the retroperitoneum.

Transverse Colon

The transverse colon traverses the upper abdomen from the hepatic flexure on the right to the splenic flexure on the left. It is generally the longest section of colon (averaging 45–50 cm) and swoops inferiorly as it crosses the abdomen. The entire transverse colon is covered by visceral peritoneum, but the greater omentum is fused to the anterosuperior surface of the transverse colon. Superior to the transverse mesocolon, inferior to the stomach, and posterior to the omentum is the pocket of the peritoneal cavity termed the lesser sac, with the pancreas forming the posterior most aspect. The splenic flexure is the sharp turn from the transversely oriented transverse colon to the longitudinally oriented descending colon. It can be adherent to the spleen and to the diaphragm via the phrenicocolic ligament.

Descending Colon

The descending colon travels inferiorly from the splenic flexure for the course of about 25 cm. It is fused to the retroperitoneum (similarly to the ascending colon) and overlies the left kidney as well as the back/retroperitoneal musculature. Its anterior and lateral surfaces are covered with visceral peritoneum, and the lateral peritoneal reflection (white line of Toldt) is again present.

Sigmoid Colon

The sigmoid colon is the most variable of the colon segments. It is generally 35–45 cm in length. It is covered by visceral peritoneum, thereby making it mobile. Its shape is considered "omega-shaped," but its configuration and attachments are variable. Its mesentery is of variable length but is fused to the pelvic walls in an inverted-V shape creating a recess termed the intersigmoid fossa. Through this recess travel the left ureter, gonadal vessels, and often the left colic vessels.

Rectosigmoid Junction

The end of the sigmoid colon and the beginning of the rectum is termed the rectosigmoid junction. It is noted by the

confluence of the taeniae coli and the end of epiploicae appendices. While some surgeons have historically considered the rectosigmoid junction to be a general area (comprising about 5 cm of distal sigmoid and about 5 cm of proximal rectum), others have described a distinct and clearly defined segment. It is the narrowest portion of the large intestine, measuring 2–2.5 cm in diameter. Endoscopically, it is noted as a narrow and often sharply angulated area above the relatively capacious rectum and above the three rectal valves.

In the early nineteenth century, it was proposed that the sigmoid acts as a reservoir for stool, thus aiding in continence [63]. Subsequently, an area of thickened circular muscle within the wall of the rectosigmoid was described and felt to function as a sphincter of sorts. Historically, it has been variably named the *sphincter ani tertius*, *rectosigmoid sphincter*, and *pylorus sigmoidorectalis* [64–68]. A more recent evaluation of the rectosigmoid junction utilizing anatomic and histologic studies as well as radiographic evaluation concluded that there was an anatomic sphincter at the rectosigmoid junction [69]. Microscopic evaluation of the area does reveal thickening of the circular muscle layer as it progresses toward the rectum. Though not identifiable externally, radiologic evaluation can identify the area as a narrow, contractile segment [69].

Blood Supply

The colon receives blood supply from two main sources, branches of the superior mesenteric artery (SMA) (cecum, ascending, and transverse colon) and branches of the inferior mesenteric artery (IMA) (descending and sigmoid colon) (Fig. 1.9). There is a watershed area between these two main sources located just proximal to the splenic flexure where branches of the left branch of the middle colic artery anastomose with those of the left colic artery. This area represents the border of the embryologic midgut and hindgut. Though the blood supply to the colon is somewhat variable, there are some general common arteries. The cecum and right colon are supplied by the terminus of the SMA, the ileocolic artery. The right colic artery is less consistent and, when present, can arise directly from the SMA, from the ileocolic, or from other sources. The transverse colon is supplied via the middle colic artery, which branches early to form right and left branches. The middle colic artery originates directly from the SMA. The left colon and sigmoid colon are supplied by branches of the IMA, namely, the left colic and a variable number of sigmoid branches. After the final branches to the sigmoid colon, the IMA continues inferiorly as the superior hemorrhoidal (rectal) artery.

Superior Mesenteric Artery

The superior mesenteric artery (SMA) is the second, unpaired anterior branch off of the aorta (the first being the celiac trunk). It arises posterior to the upper edge of the pancreas (near the L1 vertebrae), courses posterior to the pancreas, and then crosses over the third portion of the duodenum to continue within the base of the mesentery. From its left side, the SMA gives rise to up to 20 small intestinal branches, while the colic branches originate from its right side. The most constant of the colic branches is the ileocolic vessel which courses through the ascending mesocolon where it divides into a superior (ascending) branch and an inferior (descending) branch [70]. A true right colic artery is absent up to 20% of the time and, when present, typically arises from the SMA. Alternatively, the right colic artery can arise from the ileocolic vessels or from the middle colic vessels [58, 70, 71]. The middle colic artery arises from the SMA near the inferior border of the pancreas. It branches early to give off right and left branches. The right branch supplies the hepatic flexure and right half of the transverse colon. The left branch supplies the left half of the transverse colon to the splenic flexure. In up to 33% of patients, the left branch of the middle colic artery can be the sole supplier of the splenic flexure [70, 72]. Recent reports describe an accessory middle colic artery (AMCA). One single-center study demonstrates that more than one-third of patients had an AMCA (36.4%) supplying the splenic flexure with about 85% originating off of the SMA and coursing along the inferior border of the pancreas toward the splenic flexure [73].

Inferior Mesenteric Artery

The inferior mesenteric artery (IMA) is the third unpaired, anterior branch off of the aorta, originating 3–4 cm above the aortic bifurcation at the level of the L2 to L3 vertebrae. As the IMA travels inferiorly and to the left, it gives off the left colic artery and several sigmoidal branches. After these branches, the IMA becomes the superior hemorrhoidal (rectal) artery as it crosses over the left common iliac artery. The left colic artery divides into an ascending branch (splenic flexure) and a descending branch (the descending colon). The sigmoidal branches form a fairly rich arcade within the sigmoid mesocolon (similar to that seen within the small bowel mesentery). The superior hemorrhoidal artery carries into the mesorectum and into the rectum. The superior hemorrhoidal artery bifurcates in about 80% of patients.

The Marginal Artery and Other Mesenteric Collaterals

The major arteries noted above account for the main source of blood within the mesentery. However, the anatomy of the mesenteric circulation and the collaterals within the mesentery remain less clear. Haller first described a central artery anastomosing all mesenteric branches in 1786 [74]. When Drummond demonstrated its surgical significance in the early twentieth century, it became known as the marginal artery of Drummond [75, 76]. The marginal artery has been

shown to be discontinuous or even absent in some patients, most notably at the splenic flexure (Griffiths' critical point), where it may be absent in up to 50% of patients [77]. This area of potential ischemia is the embryologic connection between the midgut and hindgut. Inadequacy of the marginal artery likely accounts for this area being most severely affected in cases of colonic ischemia. Another potential (though controversial) site of ischemia is at a discontinuous area of marginal artery located at the rectosigmoid junction termed Sudeck's critical point. Surgical experience would question whether this potential area of ischemia exists; a recent fluorescence study indicates that it does [78], though its clinical importance remains in doubt.

Venous Drainage

Venous drainage of the colon largely follows the arterial supply with superior and inferior mesenteric veins draining both the right and left halves of the colon (Fig. 1.10). They ultimately meet at the portal vein to reach the intrahepatic system. The superior mesenteric vein (SMV) travels parallel and to the right of the artery. The inferior mesenteric vein (IMV) does not travel with the artery but rather takes a longer path superiorly to join the splenic vein. It separates from the artery within the left colon mesentery and runs along the base of the mesentery where it can be found just lateral to the ligament of Treitz and the duodenum before joining the splenic vein on the opposite (superior) side of the transverse mesocolon. Dissecting posterior to the IMV can allow for separation of the mesenteric structures from the retroperitoneal structures during a medial-to-lateral dissection.

Lymphatic Drainage

The colon wall has a dense network of lymphatic plexuses. These lymphatics drain into extramural lymphatic channels which follow the vascular supply of the colon. Lymph nodes are plentiful and are typically divided into four main groups. The *epiploic* group lies adjacent to the bowel wall just below the peritoneum and in the epiploicae. The *paracolic* nodes are along the marginal artery and the vascular arcades. They are most filtering of the nodes. The *intermediate* nodes are situated on the primary colic vessels. The *main* or *principal* nodes are on the superior and inferior mesenteric vessels. Once the lymph leaves the main nodes, it drains into the cisterna chili via the para-aortic chain.

Nervous Innervation

The colon is innervated by the sympathetic and parasympathetic nervous systems and closely follows the arterial blood supply. The sympathetic innervation of the right half of the colon originates from the lower six thoracic splanchnic nerves which synapse within the celiac, preaortic, and superior mesenteric ganglia. The postganglionic fibers then follow the SMA to the right colon. The sympathetic innervation for the left half originates from L1, L2, and L3. Parasympathetic fibers to the right colon come from the posterior (right) branch of the vagus nerve and celiac plexus. They travel along the SMA to synapse with the nerves within the intrinsic autonomic plexuses of the bowel wall. On the left side, the parasympathetic innervation comes from S2, S3, and S4 via splanchnic nerves.

Embryology

Though the embryologic development of the GI system is complex, a working knowledge of the development of the small bowel, colon, and anorectum is critical for a colorectal surgeon as it can aid in understanding pathophysiology and is essential for recognizing surgical planes.

Anus and Rectum

The colon distal to the splenic flexure, including the rectum and the anal canal (proximal to the dentate line), is derived from the hindgut and therefore has vascular supply from the inferior mesenteric vessels (Fig. 1.9). The dentate line (Fig. 1.1) is the fusion plane between the endodermal and ectodermal tubes. The cloacal portion of the anal canal has both endodermal and ectodermal components which develop into the anal transitional zone [79]. The terminal portion of the hindgut or cloaca fuses with the proctodeum (an ingrowth from the anal pit).

The cloaca originates at the portion of the rectum below the pubococcygeal line, while the hindgut originates above it. Before the fifth week of development, the intestinal and urogenital tracts are joined at the level of the cloaca. By the eighth week, the urorectal septum migrates caudally to divide the cloacal closing plate into an anterior urogenital plate and a posterior anal plate. Anorectal rings result from a posterior displacement in the septum and the resultant smaller anal opening. By the tenth week, the anal tubercles fuse into a horseshoe-shaped structure dorsally and into the perineal body anteriorly. The external anal sphincter forms from the posterior aspects of the cloacal sphincter earlier than the development of the internal sphincter. The internal sphincter develops from enlarging fibers of the circular muscle layer of the rectum [80]. The sphincters migrate during their development with the internal sphincter moving caudally, while the external sphincter enlarges cephalad. Meanwhile, the longitudinal muscle descends into the intersphincteric plane [9]. In females, the female genital organs form from the Müllerian ducts and join the urogenital sinus by the 16th week of development. In contrast, in males, the urogenital membrane obliterates with fusion of the genital folds, while the sinus develops into the urethra.

Colon and Small Intestine

The endodermal roof of the yolk sac develops into the primitive gut tube. This initially straight tube is suspended upon a common mesentery. By week 3 of development, it has three discernible segments: namely, the foregut, midgut, and hindgut. The midgut starts below the pancreatic papilla to form the small intestine and the first half of the colon (all supplied by the superior mesenteric artery). The distal colon and rectum, as well as the anal canal, develop from the hindgut and are therefore supplied by the inferior mesenteric artery.

Midgut Rotation

There is a normal process by which the intestinal tract rotates (Fig. 1.12) [81]. The first stage is the physiologic herniation of the midgut, the second stage is its return to the abdomen, and the third stage is the fixation of the midgut. Abnormalities in this

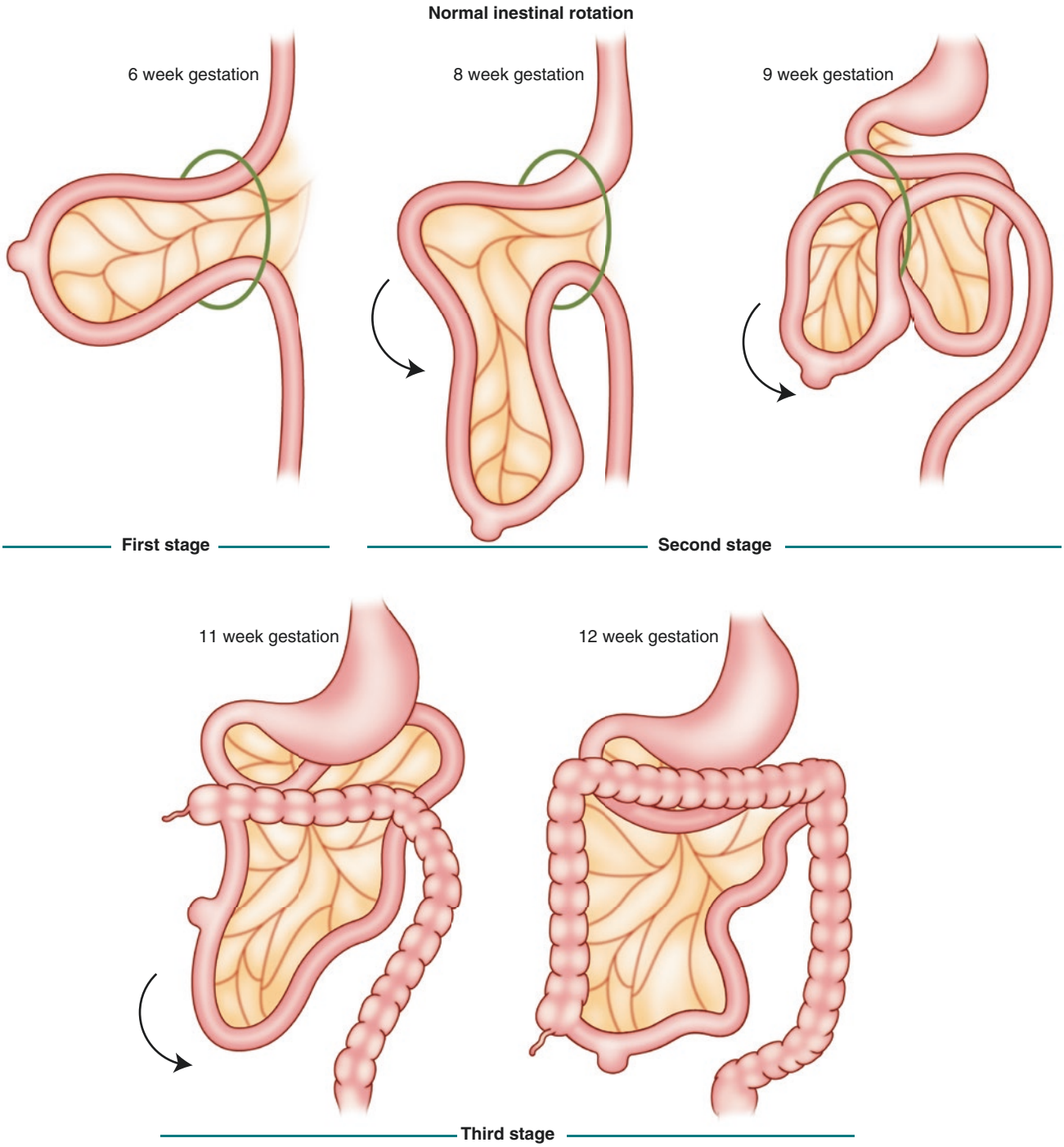


Fig. 1.12 Summary of normal intestinal rotation during development

normal process lead to various malformations (see below). The physiologic herniation (first stage) occurs between weeks 6 and 8 of development. The primitive gut tube elongates over the superior mesenteric artery and bulges out through the umbilical cord (Fig. 1.13). During the eighth week, these contents move in a counterclockwise fashion, turning 90° from the sagittal to the horizontal plane (Fig. 1.14). Anomalies at this stage are rare but include situs inversus, duodenal inversion, and extroversion of the cloaca. During the second stage (tenth week of gestation), the midgut loops return to the peritoneal cavity and simultaneously rotate an additional 180° in the counterclockwise direction (Fig. 1.15). The pre-arterial portion of the duodenum returns to the abdomen first, followed by the counterclockwise rotation around the superior mesenteric vessels, resulting in the duodenum lying behind them. The colon returns after the rotation, resulting in their anterior location. Anomalies in this stage are more common and result in non-rotation, malrotation, reversed rotation, internal hernia, and omphalocele. The third stage (fixation of the midgut) begins once the intestines have returned to the peritoneal cavity and ends at birth. The cecum migrates to the right lower quadrant from its initial position in the upper abdomen (Fig. 1.16). After the completion of this 270° counterclockwise rotation, fusion begins, typically at weeks 12–13. This results in fusion of the duodenum as well as the ascending and descending colons (Fig. 1.17).

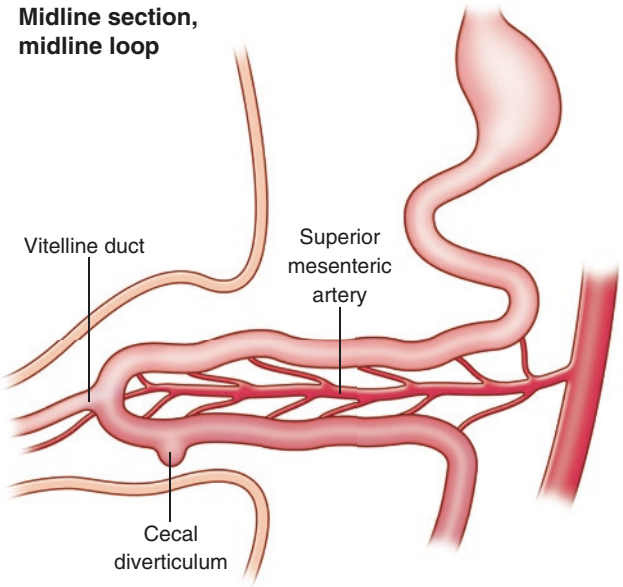


Fig. 1.13 Elongation of the midgut loop

Major Anomalies of Rotation

Non-rotation

The midgut returns to the peritoneum without any of the normal rotation. This results in the small intestine being on the right side of the abdomen and the colon on the left side (Fig. 1.18). This condition can remain asymptomatic (a finding noted at laparoscopy or laparotomy) or result in volvulus affecting the entirety of the small intestine. The twist generally occurs at the duodenojejunal junction as well as the midtransverse colon.

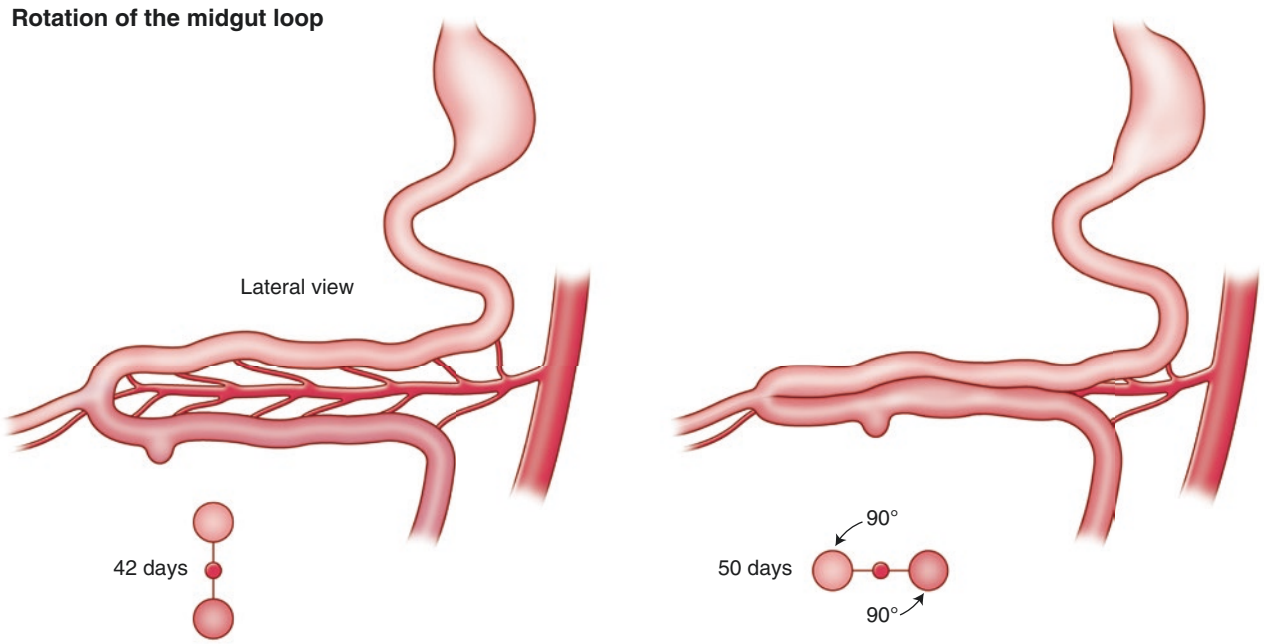


Fig. 1.14 Rotation of the midgut loop

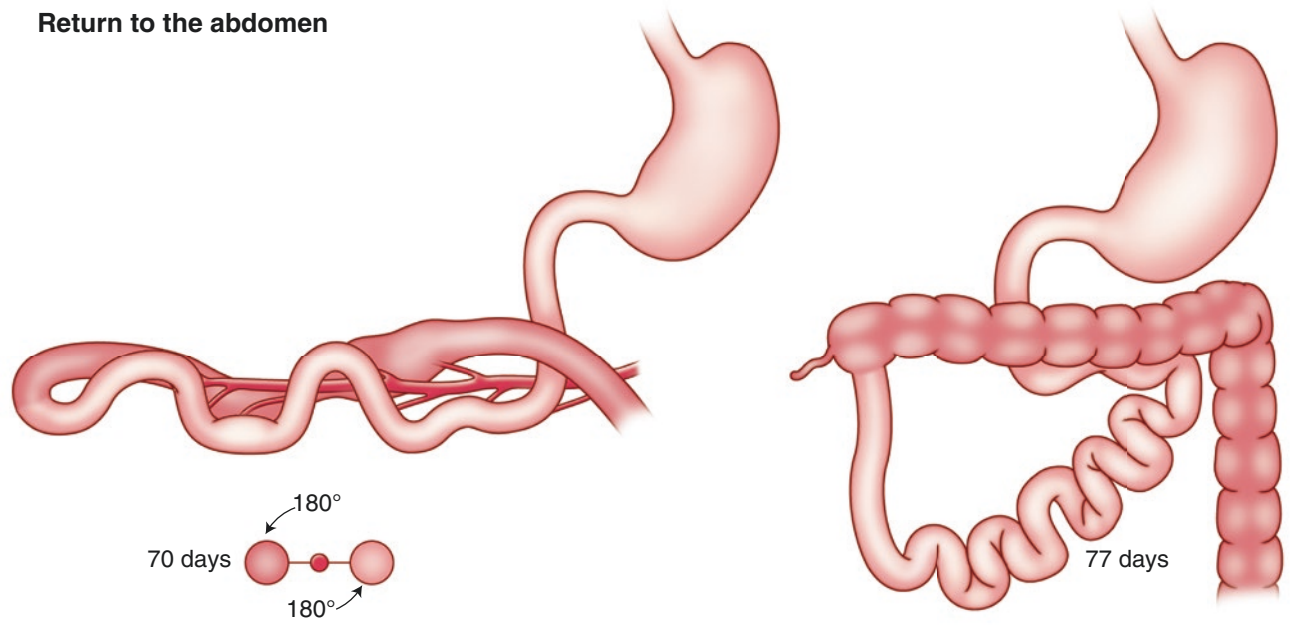


Fig. 1.15 Return of the intestinal loop to the abdomen

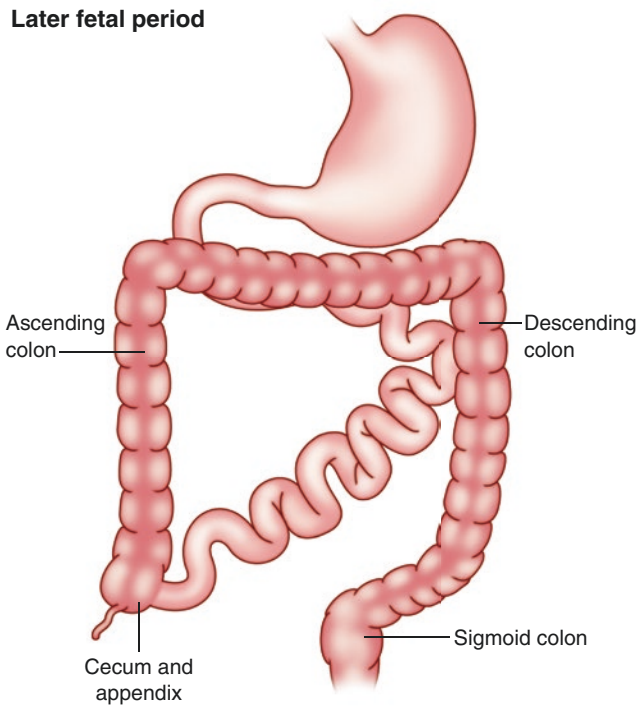


Fig. 1.16 Later fetal development

Malrotation

There is normal initial rotation, but the cecum fails to complete the normal 270° rotation around the mesentery. This results in the cecum being located in the mid-upper abdomen with lateral bands (Ladd's bands) fixating it to the right abdominal wall (Fig. 1.19). These bands can result in extrinsic compression of the duodenum.

Reversed Rotation

Clockwise (rather than counterclockwise) rotation of the midgut results in the transverse colon being posterior to the superior mesenteric artery while the duodenum lies anterior to it.

Omphalocele

An omphalocele is, basically, the retention of the midgut within the umbilical sac and its failure to return to the peritoneal cavity. The bowel remains enclosed in a membrane as it herniates through a defect larger than 4 cm [82].

Internal Hernias

Internal hernias, as well as congenital obstructive bands, can cause congenital bowel obstructions. These are considered failures of the process of fixation (the third stage

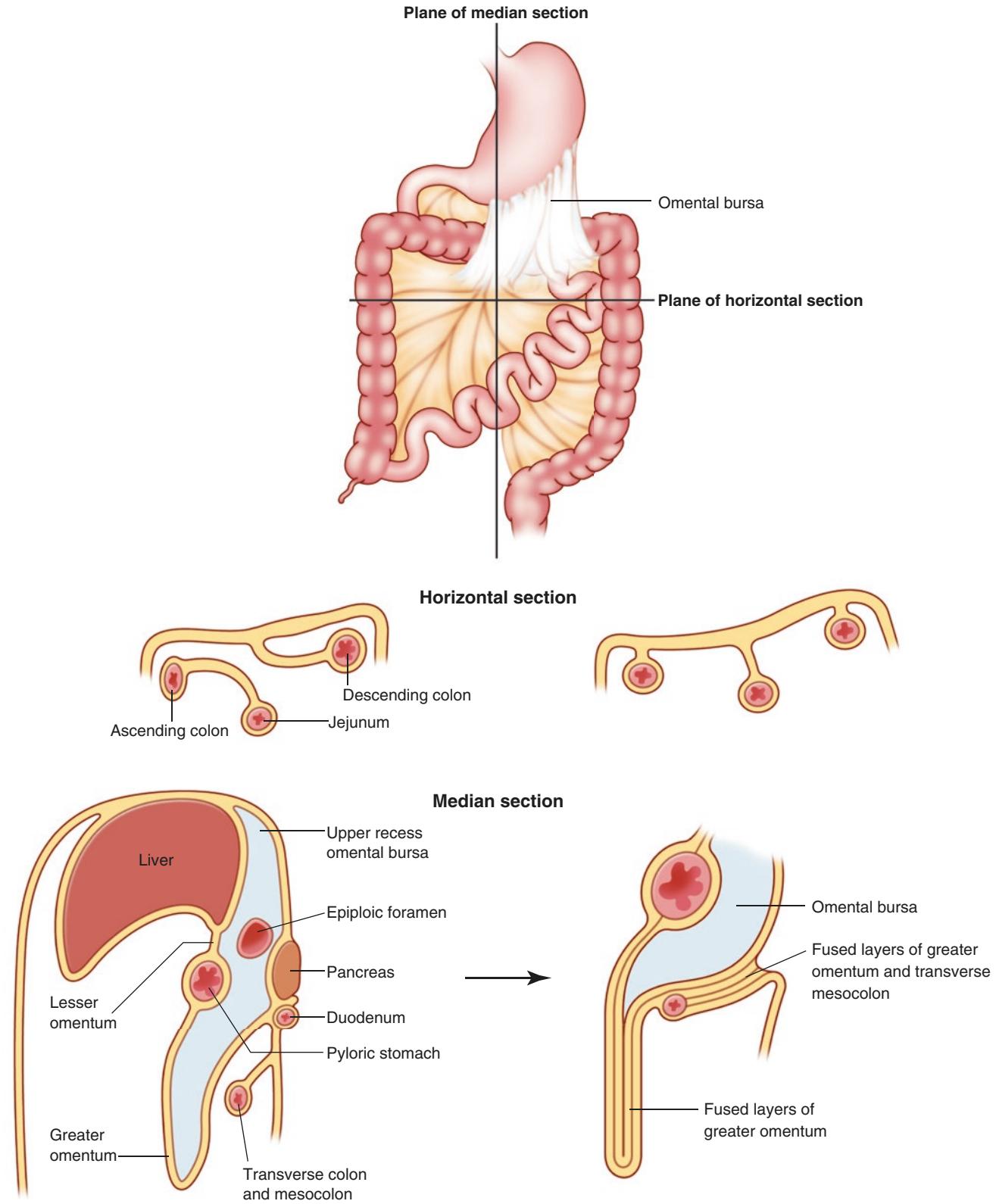


Fig. 1.17 Development of the mesentery and omental fusion

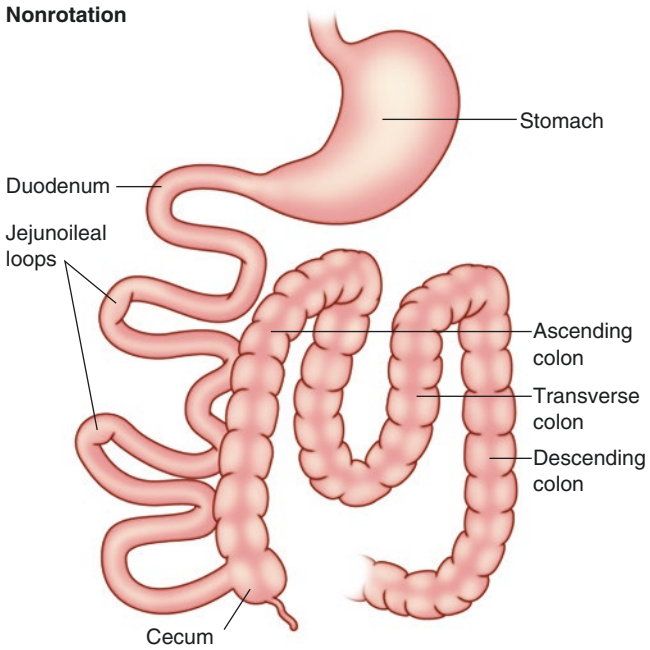


Fig. 1.18 Intestinal non-rotation

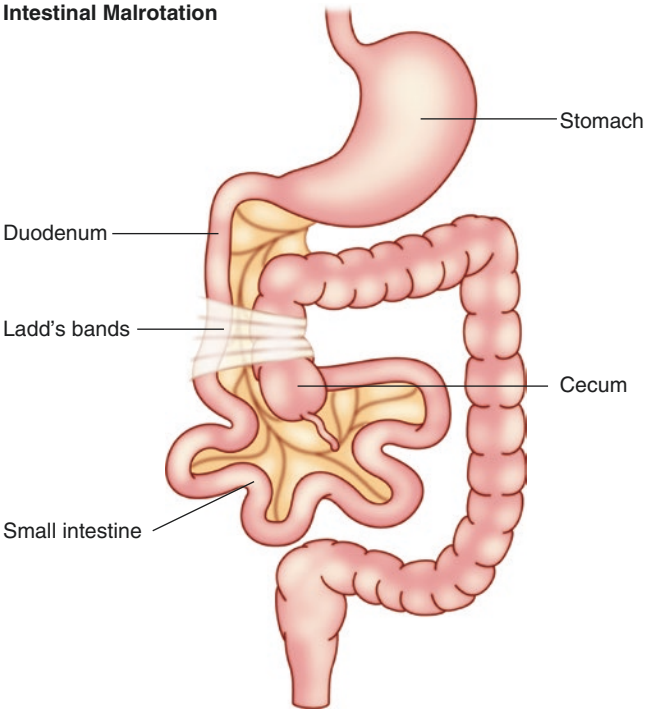


Fig. 1.19 Intestinal malrotation

of rotation). This can be the result of an incomplete fusion of the mesothelium or when structures are abnormally rotated. Retroperitoneal hernias can occur in various positions, most notably paraduodenal, paracecal, and intersigmoid.

Other Congenital Malformations of the Colon and Small Intestine

Proximal Colon Duplication

There are three general types of colonic duplication: mesenteric cysts, diverticula, and long colon duplication [83]. Mesenteric cysts are lined with intestinal epithelium and variable amounts of smooth muscle. They are found within the colonic mesentery or posterior to the rectum (within the mesorectum). They may be closely adherent to the bowel wall or separate from it. They generally present as a mass or with intestinal obstruction as they enlarge. Diverticula can be found on the mesenteric or antimesenteric sides of the colon and are outpouchings of the bowel wall. They often contain heterotopic gastric or pancreatic tissue. Long colonic duplications of the colon are the rarest form of duplication. They parallel the functional colon and often share a common wall throughout most of their length. They usually run the entire length of the colon and rectum, and there is an association with other genitourinary abnormalities.

Meckel's Diverticulum

A Meckel's diverticulum is the remnant of the vitelline or omphalomesenteric duct (Fig. 1.13). It arises from the antimesenteric aspect of the terminal ileum, most commonly within 50 cm of the ileocecal valve. They can be associated with a fibrous band connecting the diverticulum to the umbilicus (leading to obstruction), or it may contain ectopic gastric mucosa or pancreatic tissue (leading to bleeding or perforation) (Fig. 1.20). An indirect hernia containing a Meckel's diverticulum is termed a Littre's hernia. Meckel's diverticulum is generally asymptomatic and, per autopsy series, is found in up to 3% of the population [84]. Surgical complications, which are more common in children than adults, include hemorrhage, obstruction, diverticulitis, perforation, and umbilical discharge. Generally, there is no hard indication for excision of an incidentally discovered Meckel's diverticulum, though its removal is generally safe [85, 86].

Atresia of the Colon

Colonic atresia, representing only 5% of all gastrointestinal atresias, is a rare cause of congenital obstruction. They are likely the result of vascular compromise during development [87]. They vary in severity from a membranous diaphragm blocking the lumen to a fibrous cord-like remnant, on to a complete absence of a segment [88].

Hirschsprung's Disease

This nonlethal anomaly, which is more common in males, results from the absence of ganglion cells within the myenteric plexus of the colon. It is caused by interruption of the normal migration of the neuroenteric cells from the neural

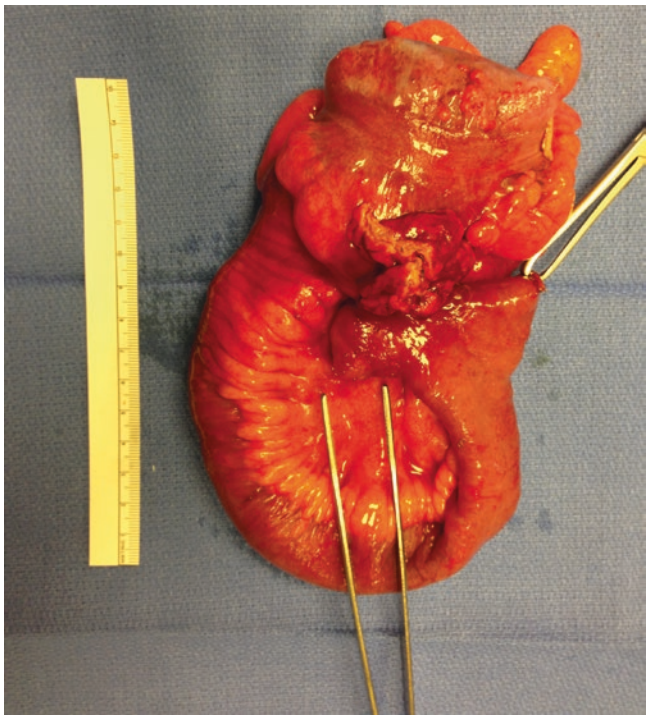


Fig. 1.20 Perforated Meckel's diverticulum with fistula to the ileum

crest before they reach the rectum. This results in dilation and hypertonicity of the proximal colon. The extent of the aganglionosis is variable, though the internal sphincter is always involved. Its severity is dependent upon the length of the involved segment. It will be discussed fully in a subsequent chapter.

Anorectal Malformations

Abnormalities in the normal development of the anorectum can be attributed to "developmental arrest" at various stages of normal development. These abnormalities are often noted in concert with spinal, sacral, and lower limb defects, as noted by Duhamel, and theorized to be related to a "syndrome of caudal regression" [89]. Indeed, skeletal and urinary anomalies are associated in up to 70% [90], while digestive tract anomalies (e.g., tracheoesophageal fistula or esophageal stenosis) and cardiac and abdominal wall abnormalities are also noted in patients with anorectal anomalies.

Anal Stenosis

While anal stenosis in a newborn is relatively common, noted in 25–39% of infants, symptomatic stenosis is only noted in 25% of these children [91]. The majority of these children undergo spontaneous dilation in the first 3–6 months of life.

Membranous Atresia

This very rare condition is characterized by the presence of a thin membrane of skin between the blind end of the anal canal and the surface. It is also termed the covered anus. It is more common in males.

Anal Agenesis

The rectum develops to below the puborectalis where either it ends in an ectopic opening (fistula) in the perineum, vulva, or urethra or it ends blindly (less commonly). The sphincter is present at its normal site.

Anorectal Agenesis

Anorectal agenesis is the most common type of "imperforate anus." More common in males, the rectum ends well caudal to the surface, and the anus is represented by a dimple with the anal sphincter usually being normal in location. In most cases, there is a fistula to the urethra or vagina. High fistulae (to the vagina or urethra) with anorectal agenesis develop as early as the sixth or seventh week of gestation, while the low fistulae (perineal) or anal ectopia develop later, in the eighth or ninth week of development.

Rectal Atresia or "High Atresia"

In rectal atresia, the rectum and the anal canal are separated from one another by an atretic portion. It is embryologically the distal most type of colon atresia but is still considered an anorectal disorder clinically.

Persistent Cloaca

This rare condition, which only occurs in female infants, is the result of total failure of descent of the urorectal septum. It occurs at a very early stage of development.

Acknowledgments This chapter builds on previous chapters written by José Marcio Neves Jorge and Angelita Habr-Gama in the first and second editions of this textbook and by Steven Mills and Joseph Carmichael in the third edition of this textbook.

References

1. Milligan ET, Morgan CN. Surgical anatomy of the anal canal: with special reference to anorectal fistulae. Lancet. 1934;2(5804):1150–6.
2. Taithongchai A, et al. Comparing the diagnostic accuracy of 3 ultrasound modalities for diagnosing obstetric anal sphincter injuries. Am J Obstet Gynecol. 2019;221(2):134.e1–9.
3. Khatri G, de Leon AD, Lockhart ME. MR imaging of the pelvic floor. Magn Reson Imaging Clin N Am. 2017;25(3):457–80.
4. Nivatvongs S, Stern HS, Fryd DS. The length of the anal canal. Dis Colon Rectum. 1981;24(8):600–1.
5. Morren GL, Beets-Tan RG, van Engelshoven JM. Anatomy of the anal canal and perianal structures as defined by phased-array magnetic resonance imaging. Br J Surg. 2001;88(11):1506–12.
6. Parks AG. Pathogenesis and treatment of fistuila-in-ano. Br Med J. 1961;1(5224):463–9.

7. Jay N, et al. Colposcopic appearance of anal squamous intraepithelial lesions: relationship to histopathology. Dis Colon Rectum. 1997;40(8):919–28.
8. Lilius HG. Fistula-in-ano, an investigation of human foetal anal ducts and intramuscular glands and a clinical study of 150 patients. Acta Chir Scand Suppl. 1968;383:7–88.
9. Barleben A, Mills S. Anorectal anatomy and physiology. Surg Clin North Am. 2010;90(1):1–15. Table of Contents.
10. Milligan ET, Morgan CN, Jones LE, Officer R. Surgical anatomy of the anal canal, and the operative treatment of haemorrhoids. Lancet. 1937:1119–24.
11. Sboarina A, et al. Shape and volume of internal anal sphincter showed by three-dimensional anorectal ultrasonography. Eur J Radiol. 2012;81(7):1479–82.
12. Haas PA, Fox TA Jr. The importance of the perianal connective tissue in the surgical anatomy and function of the anus. Dis Colon Rectum. 1977;20(4):303–13.
13. Treitz W. Ueber einen neuen Muskel am Duodenum des Menschen, uber elsatische Sehnen, und einige andere anatomische Verhaltnisse. Vierteljahrschrift Praktische Heilkunde (Prager). 1853;37:133–44.
14. Chang SC, Shih JJ, Lee H. Review of treitz's muscles and their implications in a hemorrhoidectomy and hemorrhoidopexy. Fu-Jen Journal of Medicine. 2006;4(1):1–6.
15. Thomson WH. The nature of haemorrhoids. Br J Surg. 1975;62(7):542–52.
16. Goligher JC, Leacock AG, Brossy JJ. The surgical anatomy of the anal canal. Br J Surg. 1955;43(177):51–61.
17. Bollard RC, et al. Normal female anal sphincter: difficulties in interpretation explained. Dis Colon Rectum. 2002;45(2):171–5.
18. Hussain SM, Stoker J, Lameris JS. Anal sphincter complex: endoanal MR imaging of normal anatomy. Radiology. 1995;197(3):671–7.
19. Wunderlich M, Swash M. The overlapping innervation of the two sides of the external anal sphincter by the pudendal nerves. J Neurol Sci. 1983;59(1):97–109.
20. Haas PA, Fox TA Jr, Haas GP. The pathogenesis of hemorrhoids. Dis Colon Rectum. 1984;27(7):442–50.
21. Schuurman JP, Go PM, Bleys RL. Anatomical branches of the superior rectal artery in the distal rectum. Color Dis. 2009;11(9):967–71.
22. Stelzner F. Hemorrhoids and other diseases of the conpus cavernosum recti and anal canal. Dtsch Med Wochenschr. 1963;88:689–96.
23. Mittal RK, et al. Purse-string morphology of external anal sphincter revealed by novel imaging techniques. Am J Physiol Gastrointest Liver Physiol. 2014;306(6):G505–14.
24. DeLancey JO, et al. Comparison of levator ani muscle defects and function in women with and without pelvic organ prolapse. Obstet Gynecol. 2007;109(2 Pt 1):295–302.
25. Shafik A. New concept of the anatomy of the anal sphincter mechanism and the physiology of defecation. II. Anatomy of the levator ani muscle with special reference to puborectalis. Investig Urol. 1975;13(3):175–82.
26. Malakorn S, et al. Simplified anal sphincter anatomy. Int J Color Dis. 2016;31(8):1567.
27. Betschart C, et al. Comparison of muscle fiber directions between different levator ani muscle subdivisions: in vivo MRI measurements in women. Int Urogynecol J. 2014;25(9):1263–8.
28. Levi AC, Borghi F, Garavoglia M. Development of the anal canal muscles. Dis Colon Rectum. 1991;34(3):262–6.
29. Grigorescu BA, et al. Innervation of the levator ani muscles: description of the nerve branches to the pubococcygeus, iliococcygeus, and puborectalis muscles. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(1):107–16.
30. Wallner C, et al. Evidence for the innervation of the puborectalis muscle by the levator ani nerve. Neurogastroenterol Motil. 2006;18(12):1121–2.
31. Shafik A. A new concept of the anatomy of the anal sphincter mechanism and the physiology of defecation. VIII. Levator hiatus and tunnel: anatomy and function. Dis Colon Rectum. 1979;22(8):539–49.
32. Andrew BP, et al. Enlargement of the levator hiatus in female pelvic organ prolapse: cause or effect? Aust N Z J Obstet Gynaecol. 2013;53(1):74–8.
33. DeLancey JO, et al. Comparison of the puborectal muscle on MRI in women with POP and levator ani defects with those with normal support and no defect. Int Urogynecol J. 2012;23(1):73–7.
34. Heald RJ, Moran BJ. Embryology and anatomy of the rectum. Semin Surg Oncol. 1998;15(2):66–71.
35. Najarian MM, et al. Determination of the peritoneal reflection using intraoperative proctoscopy. Dis Colon Rectum. 2004;47(12):2080–5.
36. Chapuis P, et al. Mobilization of the rectum: anatomic concepts and the bookshelf revisited. Dis Colon Rectum. 2002;45(1):1–8. discussion 8-9
37. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery–the clue to pelvic recurrence? Br J Surg. 1982;69(10):613–6.
38. Nomina Anatomica, 6th Ed.; 1989, Singapore: Churchill Livingstone.
39. Quirke P, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. Lancet. 2009;373(9666):821–8.
40. Church JM, Raudkivi PJ, Hill GL. The surgical anatomy of the rectum–a review with particular relevance to the hazards of rectal mobilisation. Int J Color Dis. 1987;2(3):158–66.
41. Sato K, Sato T. The vascular and neuronal composition of the lateral ligament of the rectum and the rectosacral fascia. Surg Radiol Anat. 1991;13(1):17–22.
42. Crapp AR, Cuthbertson AM. William Waldeyer and the rectosacral fascia. Surg Gynecol Obstet. 1974;138(2):252–6.
43. Gordon PH, Nivatvongs S. Principles and practice of surgery for the colon, rectum, and anus. 3rd ed. New York, NY: Informa Healthcare USA, Inc.; 2007.
44. Lindsey I, et al. Anatomy of Denonvilliers' fascia and pelvic nerves, impotence, and implications for the colorectal surgeon. Br J Surg. 2000;87(10):1288–99.
45. Richardson AC. The rectovaginal septum revisited: its relationship to rectocele and its importance in rectocele repair. Clin Obstet Gynecol. 1993;36(4):976–83.
46. Corman ML. Classic articles in colonic and rectal surgery. A method of performing abdominoperineal excision for carcinoma of the rectum and of the terminal portion of the pelvic colon: by W. Ernest Miles, 1869–1947. Dis Colon Rectum. 1980;23(3):202–5.
47. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet. 1986;1(8496):1479–82.
48. Nano M, et al. Contribution to the surgical anatomy of the ligaments of the rectum. Dis Colon Rectum. 2000;43(11):1592–7; discussion 1597–8.
49. Lin M, et al. The anatomy of lateral ligament of the rectum and its role in total mesorectal excision. World J Surg. 2010;34(3):594–8.
50. Gorsch RV. Proctologic anatomy. 2nd ed. Baltimore: Williams & Wilkins Co.; 1955.
51. Ikard RW. Spiral rectal valves: anatomy, eponyms, and clinical significance. Clin Anat. 2015;28(4):436–41.
52. Houston J. John Houston 1802–1845. Observations on the mucous membrane of the rectum. 1830. Dis Colon Rectum. 1987;30(11):906–8.
53. Abramson DJ. The valves of Houston in adults. Am J Surg. 1978;136(3):334–6.
54. Kohlrausch O. Zur Anatomie und Physiologie der Beckenorgane. Leipzig: Verlag von S.Hirzel; 1854.

55. Beck DE, Wexner SD. Fundamentals of anorectal surgery. New York: McGraw-Hill; 1992.
56. Llauger J, et al. The normal and pathologic ischiorectal fossa at CT and MR imaging. Radiographics. 1998;18(1):61–82; quiz 146.
57. Courtney H. The posterior subsphincteric space; its relation to posterior horseshoe fistula. Surg Gynecol Obstet. 1949;89(2):222–6.
58. Michels NA, Siddharth P, Kornblith P, Parke WW. The variant blood supply to the small and large intestines: its importance in regional resections. A new anatomic study based on four hundred dissections with a complete review of the literature. J Int Coll Surg. 1963;39:127–70.
59. Ayoub SF. Arterial supply to the human rectum. Acta Anat (Basel). 1978;100(3):317–27.
60. Fraser ID, et al. Longitudinal muscle of muscularis externa in human and nonhuman primate colon. Arch Surg. 1981;116(1):61–3.
61. Guyton AC. Textbook of medical physiology. Philadelphia: WB Saunders; 1986.
62. Girard-Madoux MJH, et al. The immunological functions of the Appendix: an example of redundancy? Semin Immunol. 2018;36:31–44.
63. O'Beirne J, editor. New views of the process of defecation and their application to the pathology and treatment of diseases of the stomach, bowels and other organs. Dublin: Hodges and Smith; 1833.
64. Hyrtl J. Handbuch der topographischen anatomie und ihrer praktisch medicinisch-chirurgischen anwendungen. II. Band, 4. Aufl. Wien: Braumüller; 1860.
65. Mayo WJ. A study of the rectosigmoid. Surg Gynecol Obstet. 1917;25:616–21.
66. Cantlie J. The sigmoid flexure in health and disease. J Trop Med Hyg. 1915;18:1–7.
67. Otis WJ. Some observations on the structure of the rectum. J Anat Physiol. 1898;32:59–63.
68. Balli R. The sphincters of the colon. Radiology. 1939;33:372–6.
69. Shafik A, et al. Rectosigmoid junction: anatomical, histological, and radiological studies with special reference to a sphincteric function. Int J Color Dis. 1999;14(4–5):237–44.
70. Sonneland J, Anson BJ, Beaton LE. Surgical anatomy of the arterial supply to the colon from the superior mesenteric artery based upon a study of 600 specimens. Surg Gynecol Obstet. 1958;106(4):385–98.
71. Steward JA, Rankin FW. Blood supply of the large intestine. Its surgical considerations. Arch Surg. 1933;26:843–91.
72. Griffiths JD. Surgical anatomy of the blood supply of the distal colon. Ann R Coll Surg Engl. 1956;19(4):241–56.
73. Miyake H, et al. Evaluation of the vascular anatomy of the left-sided colon focused on the accessory middle colic artery: a single-Centre study of 734 patients. Color Dis. 2018;20(11):1041–6.
74. Haller A. The large intestine. In: Cullen W, editor. First lines of physiology. A reprint of the 1786 edition (Soursces of Science 32). New York: Johnson; 1966. p. 139–40.
75. Drummond H. Some points relating to the surgical anatomy of the arterial supply of the large intestine. Proc R Soc Med Proctol. 1913;7:185–93.
76. Drummond H. The arterial supply of the rectum and pelvic colon. Br J Surg. 1914;1:677–85.
77. Meyers CB. Griffiths' point: critical anastomosis at the splenic flexure. Am J Roentgenol. 1976;126:77.
78. Watanabe J, et al. Evaluation of the intestinal blood flow near the rectosigmoid junction using the indocyanine green fluorescence method in a colorectal cancer surgery. Int J Color Dis. 2015;30(3):329–35.
79. Skandalakis JE, Gray SW, Ricketts R. The colon and rectum. In: Skadalakis JE, Gray SW, editors. Embryology for surgeons. The embryological basis for the treatment of congenital anomalies. Baltimore: Williams & Wilkins; 1994. p. 242–81.
80. Nobles VP. The development of the human anal canal. J Anat. 1984;138:575.
81. Soffers JH, et al. The growth pattern of the human intestine and its mesentery. BMC Dev Biol. 2015;15:31.
82. Kelly KB, Ponsky TA. Pediatric abdominal wall defects. Surg Clin North Am. 2013;93(5):1255–67.
83. McPherson AG, Trapnell JE, Airth GR. Duplication of the colon. Br J Surg. 1969;56(2):138–42.
84. Benson CD. Surgical implications of Meckel's diverticulum. In: Ravitch MM, Welch KJ, Benson CD, editors. Pediatric surgery. Chicago: Year Book Medical Publishers; 1979. p. 955.
85. Zani A, et al. Incidentally detected Meckel diverticulum: to resect or not to resect? Ann Surg. 2008;247(2):276–81.
86. Park JJ, et al. Meckel diverticulum: the Mayo Clinic experience with 1476 patients (1950–2002). Ann Surg. 2005;241(3):529–33.
87. Fomolo JL. Congenital lesions: intussusception and volvulus. In: Zuidema GD, editor. Shackelford's surgery of the alimentary tract. Philadelphia: WB Saunders; 1991. p. 45–51.
88. Louw JH. Investigations into the etiology of congenital atresia of the Colon. Dis Colon Rectum. 1964;7:471–8.
89. Duhamel B. From the mermaid to anal imperforation: the syndrome of caudal regression. Arch Dis Child. 1961;36(186):152–5.
90. Moore TC, Lawrence EA. Congenital malformations of the rectum and anus. II. Associated anomalies encountered in a series of 120 cases. Surg Gynecol Obstet. 1952;95(3):281–8.
91. Brown SS, Schoen AH. Congenital anorectal stricture. J Pediatr. 1950;36(6):746–51.

Colonic Physiology

2

Glenn T. Ault and Jennifer S. Beaty

Key Concepts

- Colonic innervation is supplied by both extrinsic and intrinsic pathways. The extrinsic pathways are derived from the autonomic nervous system. The parasympathetic input is excitatory, while the sympathetic input is inhibitory to colonic motor function. The intrinsic consists of the myenteric plexus.
- The interstitial cells of Cajal (ICC) are the primary pacemaker cells of the enteric nervous system.
- The short-chain fatty acid (SCFA) butyrate is the primary energy source of the colon. It is produced by the colon as a result of fermentation of complex carbohydrates by colonic flora.
- The colon absorbs sodium and water and secretes bicarbonate and potassium. Aldosterone mediates the process of active sodium absorption in the colon.
- Colonic contractile events are divided into (1) segmental contractions and (2) propagated contractions, including low-amplitude propagating contractions (LAPC) and high-amplitude propagating contractions (HAPC). The main function of HAPC is to propagate colonic contents toward the anus.

> No organ in the body is so misunderstood, so slandered and so maltreated as the colon. Its sorrows are numerous and real. (Sir Arthur F. Hurst. 1921 [1])

Embryology

Familiarity with the complex embryologic process of colon and rectal development is important to understanding its function and pathologic processes. During the third and fourth weeks of gestation, the primitive gut arises from the cranio-caudal and lateral folding of the dorsal endoderm-lined yolk sac. The mucosa arises from the endodermal layer, while the muscular wall, connective tissue, and outer serosal surface arise from the mesodermal layer. By the fourth week of gestation, three distinct regions (foregut, midgut, and hindgut) have differentiated based on their blood supply. The foregut, supplied primarily by the celiac artery, consists of the distal end of the esophagus, stomach, and initial portion of the duodenum. The midgut, supplied by the superior mesenteric artery, begins distal to the confluence of the common bile duct in the third portion of the duodenum and includes the proximal two-thirds of the transverse colon. This portion of the intestine maintains a connection to the yolk sac via the vitelline duct. Absence of its obliteration results in a Meckel's diverticulum. The hindgut, which comprises the rest of the distal GI tract, includes the distal transverse colon, descending colon, sigmoid colon, and rectum. This is supplied by the inferior mesenteric artery [2].

During the fifth week of gestation, the midgut undergoes a rapid elongation which exceeds the capacity of the abdominal cavity. This results in a physiologic herniation through the abdominal wall at the umbilicus. Through the sixth week of gestation, continued elongation results in a 90° counterclockwise rotation around the superior mesenteric artery. The small intestine continues its significant growth, forming loops, while the caudal end enlarges into the cecal bud. During the tenth week of gestation, herniated bowel returns to the abdominal cavity, completing an additional 180° counterclockwise loop. Anomalies of this stage of development may include nonrotation, malrotation, reversed rotation, internal hernia, and omphalocele. After the bowel is returned to the abdominal cavity, the disposition of the embryonic proximal jejunum is on the left and the primitive colon is on the right. The cecum is the last component to reenter the abdomen. It is initially located in the right upper quadrant but then migrates inferiorly to the right iliac fossa, as the dorsal mesentery suspending the ascending colon shortens and then recedes [3] (Fig. 2.1). As the cecal bud descends,

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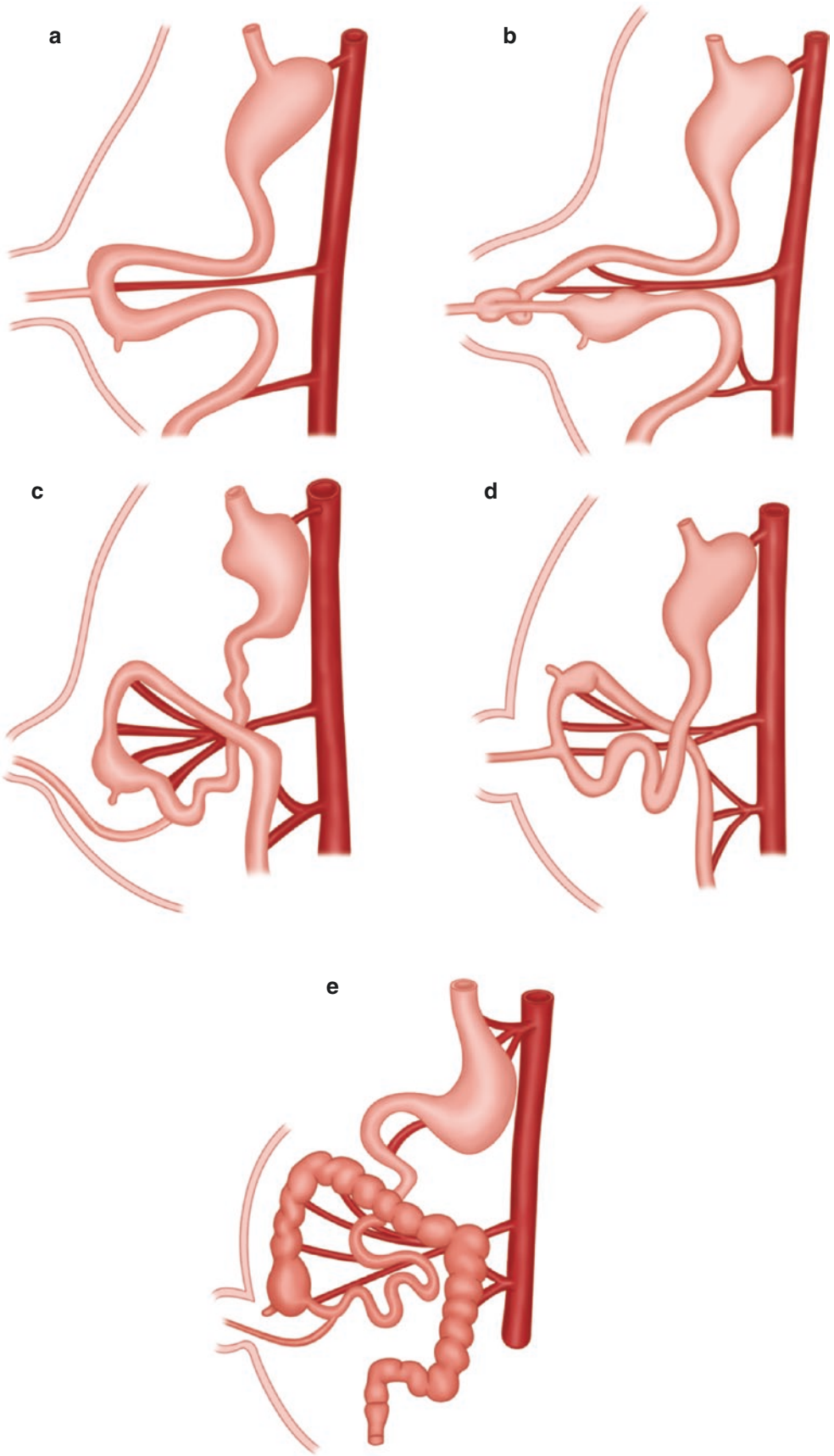

Fig. 2.1 Rotation of the midgut around the superior mesenteric artery. Rotation of the midgut around the superior mesenteric artery. (**a**) Formation of a hairpin loop around the superior mesenteric artery around fifth week. (**b**) Herniation of the midgut into the umbilicus around sixth week and rotation 90 degrees counterclockwise around the superior mesenteric artery. (**c**) Return of the intestines into the abdomen around tenth week. (**d**) Further rotation of the intestines within the abdominal cavity around 11th week, so that the cecum is positioned in the right upper quadrant. (**e**) Fixation of the cecum in the right lower quadrant, thus completing intestinal rotation (270 degrees total). (Reused from From Danowitz [3]. *Edorium Journal of Anatomy and Embryology follows an open-access publishing policy. All articles are published and distributed under the terms of the Creative Commons Attribution International License. Edorium Journal of Anatomy and Embryology Open Access Copyright and License Agreement. All articles published in Edorium Journal of Anatomy and Embryology are open-access articles, published and distributed under the terms of the Creative Commons Attribution 4.0 International License, which permits reproduction, distribution, derives and commercial use, provided the original work is properly cited and authors and publisher are properly identified*)

the appendix appears as a narrow diverticulum. The loss of the dorsal mesentery of the ascending and descending colon produces their retroperitoneal fixation, absent in the cecum, transverse colon, and sigmoid colon [2].

The embryology of the distal rectum is more complex. It initially begins as the cloaca which is a specialized area comprising endodermal and ectodermal tissue. The cloaca exists as a continuation between the urogenital and GI tracts; however, during the sixth week of gestation, it begins to divide and differentiate into the anterior urogenital, posterior anorectal, and sphincter components. At the same time, the urogenital and GI tracts become separated by caudal migration of the urogenital septum. During the tenth week of gestation, while the majority of the midgut is returning to the abdomen, the external anal sphincter is formed in the posterior cloaca as the descent of the urogenital septum becomes complete. The internal anal sphincter is formed during the 12th week of gestation by enlargement and specialization of the circular muscle layer of the rectum [2].

Colonic Anatomy

Introduction

Human fecal production is approximately 128 g/day, increased by high dietary fiber intake. The chemical composition and pH of the fecal output are influenced by diet, with the major organic component (25–54% of dry solid) of feces derived from bacterial biomass [4]. The colonic epithelium is highly efficient at absorbing sodium, chloride, water, and short-chain fatty acids. In addition, the colonic epithelium secretes bicarbonate, potassium chloride, and mucus. Under normal conditions, the colon receives approximately 1500 to 2000 mL of fluid material from the ileum over a 24-hour period, absorbing all but 100 mL of fluid and 1 mEq of sodium and chloride, resulting in excretion of feces with a sodium concentration of approximately 30 mmol/l and potassium concentration of 75 mmol/l [5]. Colonic absorptive capacity can increase up to 5 or 6 liters and 800–1000 mEq of sodium and chloride daily when challenged by larger fluid loads entering the cecum, a feature that allows the large bowel to compensate for impaired absorption in the small intestine. Several factors determine colonic absorption ability, including volume of fluid, composition of fluid, and rate of flow of luminal fluid. Since the work of Cannon in 1902, the proximal colon has been recognized to be the primary site responsible for storage, mixing, and absorption of water and electrolytes [6]. While the rectosigmoid colon functions primarily as a conduit, it can also participate in this compensatory absorptive response.

Colonic Wall Anatomy

There are four layers to the colonic wall: mucosa, submucosa, muscularis propria, and serosa. The mucosa consists of epithelium, lamina propria, and muscularis mucosae (Fig. 2.2). The epithelium lines the luminal surface of the colon. The submucosal layer is just deep to the epithelium and contains vasculature, lymphatics, and Meissner's

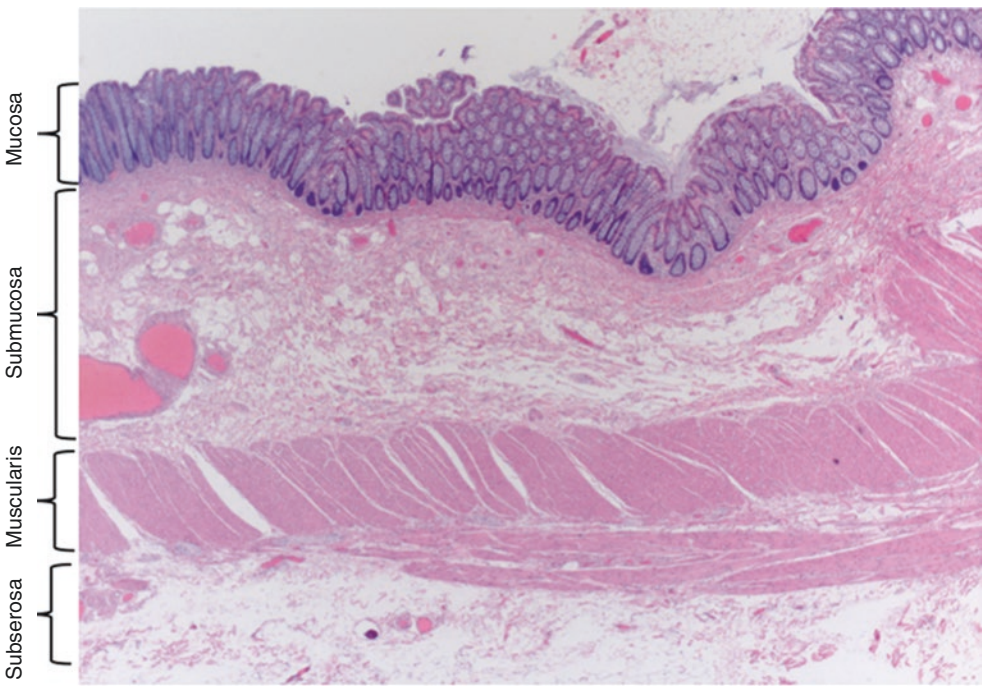

Fig. 2.2 Normal colonic mucosa. H&E, 250×. The layers of the normal colonic wall are indicated by the brackets. (*Courtesy of Julieta E. Barroeta, MD*)

nerve plexus. The submucosa consists largely of loose connective tissue with collagen and elastin fibrils. The muscular layers of the large intestine are composed of both longitudinally and circularly arranged fibers. Longitudinal muscle fibers are concentrated into three flat bands called the taenia coli. These run from the cecum to the rectum, where the fibers fan out to form a more continuous longitudinal coat. The circular layer of muscle fibers is continuous from the cecum to the anal canal, where it increases in thickness to form the internal anal sphincter. Auerbach's myenteric plexus is found between the circular and longitudinal smooth muscle layers. The interstitial cells of Cajal (ICC) are specialized mesenchymal, c-kit-positive cells. The ICC are thought to primarily serve as the pacemaker cell of the enteric nervous system, linking the colonic submucosa electrochemically with the myenteric plexus. There are multiple subtypes of ICC dispersed throughout the musculature of the colon, and controversy exists surrounding their distribution [7]. The ICC are the cells of origin of GI stromal tumors (GISTs) which arise from the colonic wall rather than the mucosa. The serosa is the outermost layer of the colon and is surrounded by visceral peritoneum [8]. The colonic epithelium is highly specialized with multiple ion channels, carrier proteins, and pumps. An in-depth review of these mechanisms is well beyond the scope of this chapter.

Epithelial Types

There are three main types of colonic epithelial cells: enterocytes, goblet cells, and neuroendocrine cells. Enterocytes are simple columnar epithelial cells. They are the major cell type in colonic epithelium, and they play important roles in nutrient absorption and in secretion. Goblet cells secrete mucus to lubricate the passage of food through the intestines. Enterocytes and goblet cells comprise nearly 95% of the epithelial cells in the colon. Neuroendocrine cells are known to act as chemoreceptors, initiating digestive actions, detecting harmful substances, and initiating protective responses [9].

All types of epithelial cells differentiate from common stem cells, which are located at the bottom of the crypts, and most differentiated cells migrate to the surface epithelium (Fig. 2.3). The epithelium lining is continuously renewed by dividing cells every 4–5 days. Crypt epithelium is highly proliferative and relatively undifferentiated and secretes chloride. The surface epithelium, in contrast, has low proliferative activity, is well-differentiated, and is highly absorptive. Ion absorption and secretion occurs at both the surface and crypt levels [10].

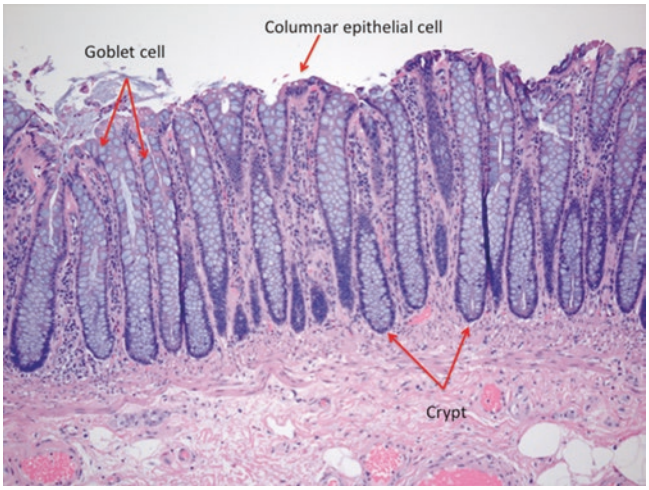

Fig. 2.3 Normal colonic mucosa. H&E, 1000×. Epithelial cell types are clearly visible including goblet cells and columnar epithelial cells. The crypts are the source of the continually regenerating mucosal cells. (*Courtesy of Julieta E. Barroeta, MD*, used with permission)

Secretory Role of Colonic Epithelium

Sodium

Absorption of sodium and secretion of bicarbonate in the colon are active processes, occurring against an electrochemical gradient. This process resides primarily in the crypt cells and is responsible for maintaining a liquid chyme. Ninety percent of sodium is actively absorbed in exchange for secretion of potassium. The transcellular secretion of chloride accounts for most of the secretory activity. Chloride enters the cell through a sodium carrier located in the basolateral membrane. The majority of sodium chloride absorption occurs in the proximal colon and is driven primarily through the electroneutral absorption by tightly coupled luminal Na^+/H^+ and Cl^-/HCO_3^- exchange. The sodium gradient is established by Na $^+$-K $^+$-ATPase, and each pump cycle results in the extrusion of three sodium ions in exchange for the basolateral uptake of two potassium ions, resulting in the net transfer of one positively charged sodium ion across the basolateral membrane (Fig. 2.4). The resulting secretion of sodium and potassium establishes an osmotic gradient drawing water into the lumen [10]. The epithelial Na^+/H^+ exchange is a pleiotropic membrane transport mechanism that participates in intestinal NaCl transport. It also helps to regulate basic cellular functions and the extracellular milieu to facilitate other nutrient absorption and to regulate the gut microbial microenvironment [11].

In the distal colon, the epithelial sodium channel (ENAC) mediates sodium absorption. Sodium is taken up by the ENAC on the luminal side and is excreted on the basolateral

surface by the Na $^{+}$-K $^{+}$-ATPase. Chloride is absorbed through the luminal cystic fibrosis conductance regulator (CFTR) and is then excreted on the basolateral side via multiple mechanisms, including KCl cotransporter (KCCl), Cl^{-} channels, and Cl^{-}/HCO_3^{-} anion exchangers. The net result is tight regulation of electrolyte secretion in excreted stool (Fig. 2.4) [2].

Clinical applications of abnormalities associated with sodium continue to emerge. For example, *Clostridium difficile*, the leading cause of nosocomial diarrhea and pseudomembranous colitis, also exerts inhibitory effects on epithelial Na^{+}/H^{+} exchange mechanism. However, in inflammatory bowel disease (IBD), both electrogenic sodium transport mediated by sodium channels and electroneutral Na^{+}/H^{+}

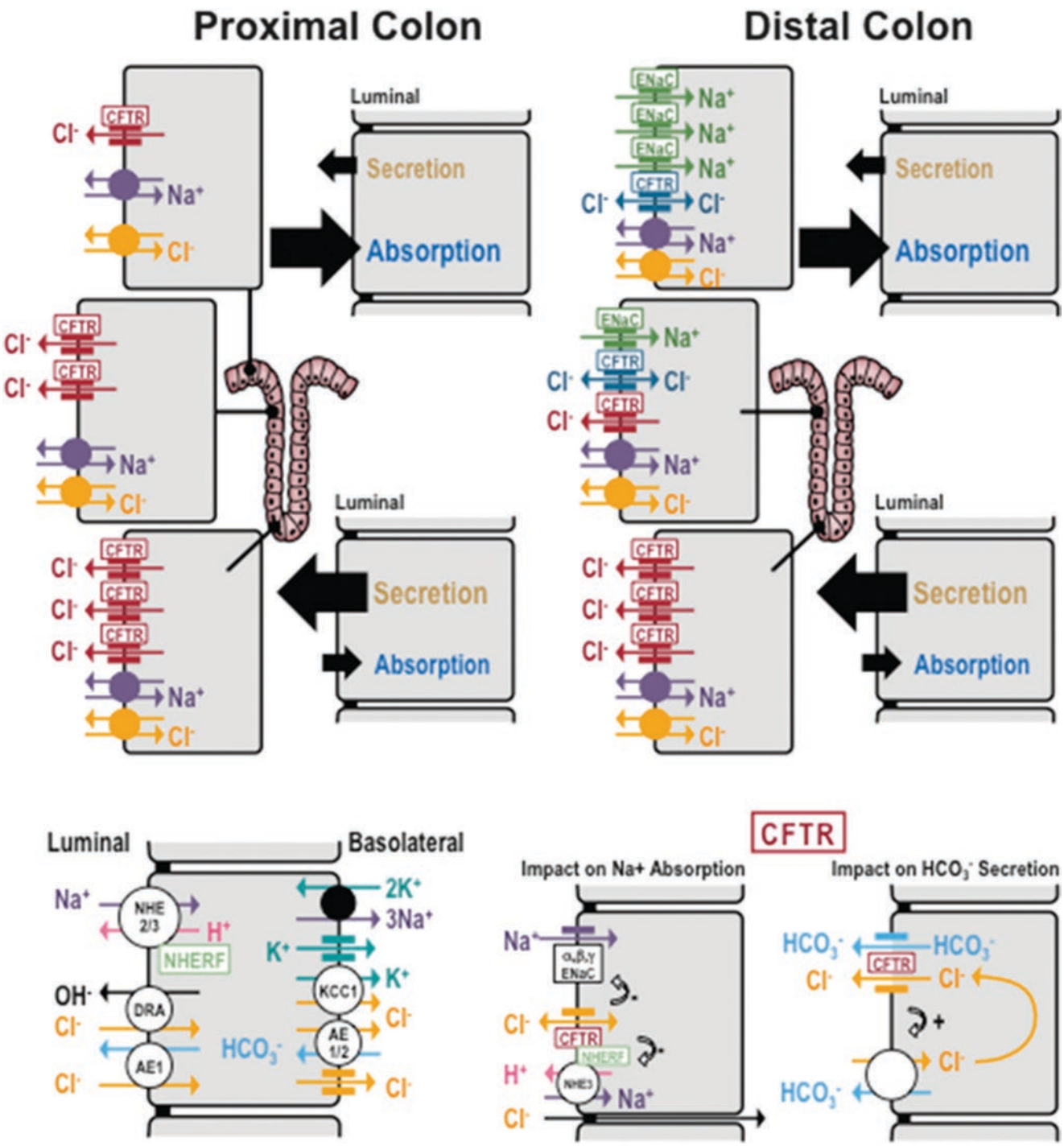

Fig. 2.4 Schematic of ion-transport channels in proximal and distal colonocytes. (*Courtesy of Robin Noel*, used with permission)

exchange-coupled NaCl absorption are reduced [12]. The Na^+/H^+ exchangers are frequent targets of inhibition in gastrointestinal pathologies, by either intrinsic factors (e.g., bile acids, inflammatory mediators) or infectious agents and associated microbial toxins [11]. A separate Cl^-/OH^- exchange is represented by a protein called DRA (downregulated in colonic adenomas). Human DRA mutations are responsible for congenital chloride diarrhea [13].

In infectious diarrhea, active and excessive chloride secretion is predominant. Cholera is a classic example leading to significant watery diarrhea. If uncontrolled, it can lead to the loss of large quantities of fluid and electrolytes, which can result in dehydration and electrolyte imbalances, and ultimately death. In this instance, cholera toxin binds to the brush border of crypt cells and increases intracellular adenylyl cyclase activity. Adenylyl cyclase synthesizes cAMP from ATP. The result is a dramatic increase in intracellular cAMP that stimulates active Cl^- and $HCO3^-$ secretion into the lumen. Water follows the osmotic gradient and enters the lumen leading to a secretory diarrhea.

Potassium

The colonic epithelial apical and basolateral membranes are permeable to potassium. There is a high concentration of intracellular potassium maintained by the Na^+-K^+ pump; therefore, some potassium will leak passively across the apical membrane of epithelial cells. The concentration of potassium in the colonic lumen remains roughly equal to the serum potassium (4 or 5 mEq/L). In the colon, net potassium secretion occurs. Because of potassium secretion and the exchange of chloride for bicarbonate in the colon, prolonged diarrhea results in hypokalemic metabolic acidosis. This also contributes to the alkaline pH of stool water.

Aldosterone

Mineralocorticoids can decrease the sodium concentration in fecal water from 30 to 2 mEq/L and increase the potassium concentration from 75 to 150 mEq/L. There is an increase in sodium permeability of the brush border membrane caused by the activation of new sodium channels. In addition, aldosterone increases the number of sodium pump molecules in the basolateral membrane. The influence of aldosterone on sodium transport is exerted at two points. In the distal colon, epithelial Na^+-K^+-ATPase is activated by aldosterone. In the proximal colon, the Na^+-H^+ exchange is activated by aldosterone. Therefore, aldosterone works by two different mechanisms, in different portions of the colon, to conserve sodium at the expense of potassium.

Mechanism for Water Absorption

The human colon has a nominal mucosal surface area of about 2000 cm^2 [14]; however, the total absorptive area is even greater because colonic crypt cells are capable of absorption as well as secretion [15]. The continued production of solutes by colonic bacteria, together with the relative impermeability of the colonic membrane to water, usually causes stool water to be hypertonic, 350–400 milliosmoles (mOsm)/L, to plasma. The volume of fluid moving from blood to lumen (secretion) is less than that moving from the lumen to the blood (absorption), thus resulting in net absorption. Absorption generally results from the passive movement of water across the epithelial membrane in response to osmotic and hydrostatic pressures. The autonomic nervous system has effects on NaCl transport affecting absorption. Adrenergic (α-receptor) or anticholinergic stimuli tend to increase absorption [10].

Short-Chain Fatty Acid Absorption

In the proximal colon, bacteria ferment organic carbohydrates to short-chain fatty acids (SCFA), predominantly acetate, propionate, and butyrate. Butyrate is the main energy substrate for the colonic epithelium. SCFA provides approximately 10% of the daily caloric requirements [16]. SCFA are among the most important microbial metabolites that interact with host cells, with up to 100 mMols of SCFA produced in the colonic lumen by bacteria. Since luminal SCFA are absorbed by colonic epithelial cells into the submucosa and the systemic circulation, a variety of SCFA signaling pathways are likely involved in acute and long-term physiological responses to luminal bacterial activity [17].

SCFA are potent stimuli of sodium and water absorption in the colon, with butyrate being the most effective. SCFA are rapidly absorbed from the colon which augments sodium, chloride, and water absorption. SCFA have several potentially therapeutic effects in vitro. They regulate proliferation, differentiation, gene expression, immune function, and colonic wound healing. In acute diarrhea, fecal SCFA concentrations are reduced, and this may contribute to impaired sodium absorption. SCFA potentially reduce inflammation in ulcerative colitis and diversion colitis. Butyrate has also been hypothesized to reduce the risk of colon cancer [18].

Vitamin K Absorption

The lipid-soluble vitamin K plays an essential role in facilitating blood coagulation by activating clotting factors; it also plays a role in signal transduction, cell proliferation, and bone and cartilage metabolism. Vitamin K is widely distributed in our diets and is also produced by the normal colon microbiota. Humans cannot synthesize vitamin K endogenously and, thus, must obtain it from exogenous sources via intestinal absorption. Absorption of dietary vitamin K in the small intestine is carrier-mediated and is an energy-dependent process, while absorption in the microbiota-generated vitamin K in the colon is via passive diffusion [19].

Colonic Innervation

The gastrointestinal tract is densely innervated to provide information on its luminal contents, processes regulating digestion and absorption, and potential threats [20].

The enteric nervous system is the largest single division of the autonomic nervous system (ANS), containing between 200 and 600 million enteric neurons throughout the GI tract [21]. The colon and rectum are innervated by nerves of both extrinsic and intrinsic origin. The extrinsic pathways originate from the central and autonomic (sympathetic and parasympathetic) nervous systems. Autonomic pathways run along parasympathetic and sympathetic chains. Each of these pathways include afferent (sensory) and efferent (motor) innervation. The intrinsic innervation consists of the enteric nervous system. Two major sets of ganglia are found in the colon. The myenteric or Auerbach's plexus is located between the longitudinal and circular smooth muscle layers and plays a crucial role in colonic smooth muscle function. The submucosal or Meissner's plexus regulates ion transport. The extreme importance of these two plexuses is clear in children with Hirschsprung's disease in which the ganglia of the myenteric and submucosal plexuses are congenitally absent. The aganglionic segments do not relax and peristalsis is disturbed resulting in severe constipation [22].

Extrinsic innervation to the large intestine comes from both parasympathetic and sympathetic branches of the ANS. Colonic motility is modulated by sympathetic neurons in prevertebral ganglia, which has potent effects on colonic function (Fig. 2.5). The proximal regions of the large intestine are sympathetically innervated by fibers that originate from the superior mesenteric ganglion. More distal regions receive input from the inferior mesenteric ganglion. There is evidence for ongoing tonic inhibition of colonic secretion, since disrupting the pathway causes a substantial increase in secretion. This is largely mediated by a strong inhibitory drive to secretomotor neurons in submucosal ganglia, via α-2-adrenergic receptors [23]. Sympathetic activation also directly contracts sphincters via indirect effects (i.e., by reducing acetylcholine release from cholinergic neurons) and inhibits activation of enteric neurons. Both actions delay GI and colonic transit. The distal rectum and anal canal are innervated by sympathetic fibers from the hypogastric plexus.

There are two pathways of parasympathetic innervation. The cecum and the ascending and transverse portions of the colon are innervated by the vagus nerve, whereas the descending and sigmoid areas of the colon and the rectum are innervated by pelvic nerves from the sacral region of the spinal cord. The pelvic nerves enter the colon near the rectosigmoid junction and project orally and aborally within the plane of the myenteric plexus. The vagus and pelvic nerves consist primarily of preganglionic efferent fibers and many afferent fibers. The efferent fibers synapse with the nerve cell bodies of the myenteric and other intrinsic plexuses. The external anal sphincter, a striated muscle, is innervated by the somatic pudendal nerves. Sacral parasympathetic pathways to the colon primarily synapse onto myenteric neurons.

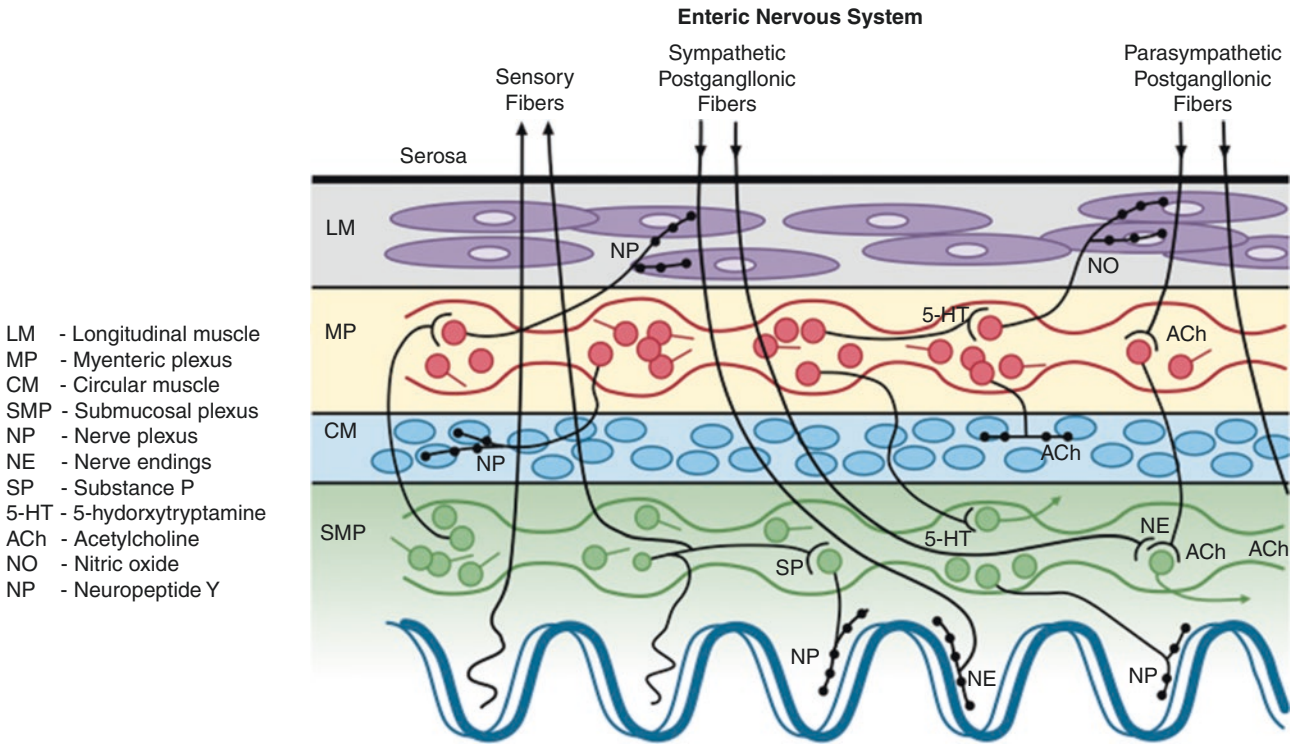

Fig. 2.5 Schematic representation of the components of the enteric nervous system. (*Courtesy of Robin Noel*, used with permission)

Excitatory pathways are important for colonic propulsive activity, especially during defecation; damage to these pathways can cause severe constipation [24].

As in other regions of the gut, several diverse chemicals serve as mediators at presynaptic and postsynaptic junctions within the autonomic innervation to the large intestine. Acetylcholine (ACh) and tachykinins such as substance P serve as major excitatory mediators, and nitric oxide (NO), vasoactive intestinal peptide (VIP), and possibly adenosine triphosphate (ATP) serve as major inhibitory mediators. Transmission between the pudendal nerves and the external anal sphincter is mediated by ACh [10].

Pain

The sensation of pain appears to be mediated by different afferents depending on the location of the GI tract undergoing the noxious stimulus. Pain from the rectum primarily involves pelvic pathways. Inflammation (or inflammatory mediators) can change both the response properties of specific classes of sensory neurons and the involvement of specific ascending pathways, which is relevant in post-inflammatory hypersensitivity and postinfectious irritable bowel syndrome (IBS) [25].

Visceral sensory neurons activate reflex pathways that control gut function and give rise to important sensation, such as fullness, bloating, nausea, discomfort, urgency, and pain. Sensory neurons are organized into three central nervous system pathways: vagal, thoracolumbar, and lumbosacral [22]. Experimental distension of the descending or sigmoid colon is perceived as a sensation of cramping, gas, or pressure in the lower abdomen, lower back, or perineum [26].

Both central and peripheral mechanisms have been suggested to be involved in the development of pain symptoms. Several studies have provided evidence that IBS is associated with a dysregulation of the brain-gut axis, with peripheral sensory alterations dominating in some patients and disturbed central processing dominating in others [27]. It is now widely accepted that an altered visceral sensitivity through abnormal endogenous pain processing plays an important role in the pathogenesis of IBS [28]. IBS is associated with decreased epithelial expression of the serotonin-selective reuptake transporter (SERT) in many studies; however, it is unknown if the disturbance is responsible for the symptoms of IBS [29].

Colonic Motility

The motor function of the colon includes propulsion, accommodation, and rapid emptying of a variable portion of the colon during defecation. In addition, the colon must be able to store fecal material until socially acceptable to eliminate. Colonic motility is mediated by the enteric nervous system in association with autonomic parasympathetic and sympathetic input and with input from the extrinsic nervous system. Colonic motility is characterized by patterns of contraction of longitudinal and circular muscle layers with elimination of feces. Motility is integrated with colonic secretion and absorption. Propulsion is achieved by numerous motor events including individual contractions, contractile bursts, high-amplitude propagated contractions (HAPCs), and possibly changes in tone [22]. Accommodation, storage, and distribution of material within the colon are mediated by colonic tone. Tone and phasic activity in the colon show considerable diurnal variation, increasing slowly after a meal, reducing during sleep, and increasing dramatically upon waking [30]. HAPCs occur more frequently during the morning, during the postprandial period, and preceding defecation [30–32]. The colonic motor response to eating consists of an increase in phasic and tonic contractile activity that begins within several minutes of ingestion of a meal and continues for a period of up to 3 hours. This response is influenced by both the caloric content and composition of the meal with fat and carbohydrate stimulating colonic motor activity, while amino acids and protein inhibit motor activity [30].

A more prolonged state of contraction, referred to as tone, is not regulated by slow waves and may be recognized clearly in the colon (response to feeding), as well as in some sphincteric regions. Tone is regulated by actin-myosin interaction mediated by cellular mechanisms that are modulated by neurogenic and mechanical stimuli. Phasic contractions, such as those regulating lumen occlusion, may be superimposed on tonic activity. Thus, tone can increase the efficiency of phasic contractions by diminishing the diameter of the lumen. Tone also modifies wall tension in response to gut filling and is therefore one determinant of perception of distension.

This motor input interacts with myogenic mechanisms to create regional patterns of contraction and relaxation which mix and propel content. It is likely that regular contractile bursts – colonic motor complexes – do occur, each burst occurring once or twice per hour and lasting approximately 6 minutes [22]. Periodic or cyclic motor activity is evident more clearly in the rectum, the so-called rectal motor complexes. They do not appear to be synchronized with the small intestinal motor migrating complexes, and their precise function and regulation remain unclear [22].

The anorectum functions in defecation and continence. Defecation is achieved through the integration of a series of motor events and involves both striated and smooth muscle. A sensation of rectal fullness is generated by rectal afferents when colonic contents reach the rectum. Rectal filling also induces the rectoanal inhibitory or rectosphincteric reflex

that leads to internal anal sphincter relaxation and external sphincter contractions. At this stage, the individual can decide to postpone or proceed with defecation. To facilitate defecation, the puborectalis muscle and external anal sphincter relax, thereby straightening the rectoanal angle and opening the anal canal. The propulsive force enabling defecation is generated by contractions of the rectosigmoid, diaphragm, and the muscles of the abdominal wall to propel the rectal contents through the open sphincter. The internal anal sphincter is a continuation of the smooth muscle of the rectum, is under sympathetic control, and provides approximately 80% of normal resting anal tone. The external anal sphincter and pelvic floor muscles are striated muscles innervated by sacral roots and the pudendal nerve.

Modulators of Colonic Motility

Muscarinic agonists (i.e., hyoscamine) and cholinesterase inhibitors (i.e., neostigmine) increase colonic motility. The α-2 adrenergic antagonist yohimbine also increases colonic motility and promotes fluid and electrolyte absorption, while the α-2 agonist clonidine reduces motility. Clonidine reduces colonic tone and phasic pressure activity, as well as the colonic perception of distention which can increase colonic compliance. Clonidine can be used to treat diarrhea predominant IBS.

Serotonin 5-HT receptors (5-HT_3) antagonists such as alosetron increase colonic compliance, reduce postprandial rectal motor activity, improve stool consistency, delay colon transit, and reduce rectal sensitivity in IBS. Alosetron was approved for IBS-diarrhea predominant in women [33]. A systematic review of published clinical trials through the Food and Drug Administration (FDA) Adverse Events Reporting System documented the risk of ischemic colitis was higher with alosetron than placebo (0.15% vs. 0.0%) [34], and it was subsequently withdrawn from the market.

A newer high selectivity affinity 5-HT_4 receptor agonist, prucalopride, has been approved by the FDA. Extensive cardiovascular assessment suggests it does not affect the Q-T interval. For chronic constipation patients, prucalopride can be used to accelerate intestinal and colonic transit [35, 36].

The GI tract contains three opioid receptors (δ, μ, κ), with the gastrointestinal effects mediated primarily by μ receptors. Opioids reduce neuronal excitability and release of neurotransmitters. Morphine increases colonic phasic segmental activity, reduces fasting colonic tone, and attenuates the gastrocolonic response. Opioids also increase fluid absorption partly by delaying transit and increasing mucosal contact time. Opioid-induced constipation or opioid bowel dysfunction is common, affecting 41–81% of patients treated with opioids [18].

Lubiprostone is a synthetic bicyclic fatty acid derived from prostaglandin E1 that activates apical CIC-2 chloride channels. Lubiprostone also activates prostaglandin EP receptors and the apical cystic fibrosis transmembrane regulator (CFTR), causing intestinal fluid secretion [37]. These secretory effects likely explain why lubiprostone accelerates small intestinal and colonic transit in healthy subjects. Lubiprostone does not affect colonic motor activity in healthy individuals [38] but is approved by the FDA for treating chronic constipation and female constipation predominant IBS [18, 39].

Bile acids infused directly into the human sigmoid and rectum at concentrations of 5 mmol/L stimulated colonic phasic contractions; however, such concentrations are seldom achieved in the colon unless there has been an ileal resection. Rectal infusion of chenodeoxycholic acid at physiological concentrations stimulates proximal colonic propagated contractions and increases rectal sensitivity. Hence, chenodeoxycholic acid accelerates colonic transit in healthy subjects. These effects have pathophysiological and therapeutic consequences. When enterohepatic circulation of bile acids is disrupted by ileal disease (e.g., Crohn's disease, surgical resection, or radiation ileitis) or idiopathic mechanisms (idiopathic bile-acid malabsorption), bile acids spill into the colon, causing diarrhea. Idiopathic bile-acid malabsorption may explain diarrhea in some patients with IBS. From a therapeutic perspective, delayed-release chenodeoxycholic acid, results in accelerated colonic transit and improved bowel function in females with constipation-predominant IBS [18].

Laxatives work either via osmotic effects (e.g., polyethylene glycol-based solutions, magnesium citrate-based products, sodium phosphate-based products, and nonabsorbable carbohydrates [lactulose, sorbitol]) or by stimulating colonic propulsive activity [18]. Osmotic agents, which are hypertonic, pull fluid into the intestinal lumen, causing diarrhea.

Stimulant laxatives (e.g., bisacodyl, sodium picosulfate, and glycerol) stimulate HAPC wave sequences, thereby leading to mass movements; bisacodyl and sodium picosulfate also have anti-absorptive plus secretory effects [18, 40, 41]. Bisacodyl exerts its motor effect through mucosal afferent nerve fibers, because the response can be blocked by topical mucosal application of lidocaine [18].

While sacral nerve stimulation is approved by the FDA to treat fecal incontinence, its role for treating constipation is unclear [42]. Sacral nerve stimulation modulates the extrinsic nerves innervating the pelvic floor and colon. In addition, stimulation of the S3 root also induces propulsive activity throughout the entire colon and has been shown to increase stool frequency in patients with slow transit constipation [43]. In Kamm's study, colonic transit was assessed in 27 of 45 patients with medically refractory chronic constipation who proceeded to permanent sacral nerve stimula-

tion [42]. Of these 27 patients, 20 had delayed colonic transit before but only 9 had delayed transit after sacral nerve stimulation.

Microbiome

A normally functioning GI tract has healthy, well-established colonizing microbiota in its mucosa and lumen, which are major contributors to the maintenance of whole-body homeostasis. It is well established that the species composition and relative abundance of the gut microbiota are impacted by the diet, lifestyle, and overall health of an individual. Humans have developed a commensalistic relationship with the gut microbiome. Over time, this relationship has evolved to become a mutual and interdependent one, in which the physiologic activity of the microbiota has a significant impact on the host and the activity of the host impacts the genera comprising the microbiota. In support of life, gut microbial metabolism supplies the host with short-chain fatty acids and essential vitamins (vitamins B and K) and contributes to the synthesis and absorption of essential amino acids.

The adult human intestine contains approximately 110 trillion bacteria. Gas chromatography-mass spectrometry analysis detected more than 700 volatile organic compounds from human feces [44]. Our microbiota is established in the period after birth and although it can be modulated by factors, such as diet, illness, and antibiotic treatment, is relatively resistant to change in later life. The microbial composition changes along the length of the gut, in response to changes in the luminal environment including presence of nutrients, acidity, and oxygen content. Microbial diversity has been used as an index of a "healthy" microbiota, but this is probably a simplistic notion as some beneficial plant foods will decrease diversity yet produce a beneficial host response. There is considerable variability that likely depends predominantly on diet and lifestyle [45].

The role the human microbiome plays in health and disease is actively under investigation. The composition of feces is altered in diseases such as IBS [46], IBD, colorectal cancer [47], and autism [48], implicating that the pathogenesis of these diseases is associated with dysbiosis. Several studies demonstrate alterations in the fecal and colonic mucosal microbiome in constipation and diarrhea. Absent interventional trials, it is unclear whether these associations reflect cause and effect. However, even after adjusting for demographic features, diet, and colonic transit, the microbiome discriminated between health and constipation with an accuracy of 92% [18].

Patients with IBD have altered microbiota, and they may have changes in their gut microbiota that precede a diagnosis. IBD is thought to be an aberrant immune response to luminal content including the microbiota. A shift in the delicate balance (dysbiosis) of "good" bacteria and "bad" pro-inflammatory bacteria may be important for the development and maintenance of IBD. For example, *Roseburia* spp. are decreased in those already diagnosed with IBD, and as such, the manipulation of the microbiota using antibiotics, probiotics, and prebiotics might be useful in treating IBD [49, 50]. Crohn's disease (CD) is associated with lower overall microbial diversity when compared to healthy controls. The abundance of both the *Proteobacteria* and *Bacteroidetes* was significantly higher in CD when compared to healthy controls and those with ulcerative colitis (UC). Low numbers and the absence of *Faecalibacterium prausnitzii*, a common member of the healthy gut microbial community, have been associated with UC. Antibiotics have been used to treat IBD with the goal of decreasing concentrations of bacteria in the lumen and altering the community composition.

These observations and many others have been the motivating force for the National Institutes of Health (NIH) Human Microbiome Project (NIH HMP) [51]. The NIH HMP is a roadmap for biomedical research and has three main goals: (1) utilize new high-throughput screening technology to characterize the microbiome more completely by studying multiple body sites from 250 "normal" individuals; (2) determine if there are associations between changes in the microbiome and health and disease; and (3) standardize data resources and new technologies for the wider scientific community [52, 53]. Phase II of this project has begun, and it aims to examine changes in three microbiome-associated conditions: (1) preterm birth, (2) IBD, and (3) type 2 diabetes [54–57].

The indigenous human microbiome is dominated by two bacterial phyla: *Firmicutes* and *Bacteroidetes*. In many studies, the *Firmicutes* and *Bacteroidetes* account for greater than 98% of the bacteria present in the human gut. It has long been appreciated that different classes of antibiotics affect the human gut microbial community, both targeted and off-target [58, 59]. The use of antibiotics can open niches that were otherwise occupied and allow for new species (good or bad) to take up residency [60].

For example, changes in human gut microbiome community structure after exposure to the fluoroquinolone antibiotic, ciprofloxacin, have shown that much of the community is altered [61]. Dethlefsen et al. reported that all aspects of the gut microbiome community, that is, diversity, richness, and evenness, were decreased and the abundance of approximately one-third of the species present was changed [61]. The loss of diversity may cause acute human disease by impacting the role of the microbiome on nutrition, metabolism, and pathogen resistance. After antibiotic treatment was stopped, many of the communities rebounded and closely resembled the original community. In some cases, it took nearly 6 months for the microbiome to rebound. It has been

suggested that broad-spectrum antibiotics, especially those with activity against anaerobes, might cause longer-lasting changes in the gut microbial community [62].

Conclusion

The colorectum is a complex organ with multiple roles in homeostasis. By increasing understanding of its anatomy and complex physiology, the colorectal surgeon can gain a better understanding of the etiology of derangements in pathophysiologic conditions. In addition, a thorough understanding of colorectal physiology allows an opportunity to develop new therapies based on its known functions. These examples are demonstrated with much greater detail throughout other chapters of the text.

References

1. Hurst AF. An address on the sins and sorrows of the colon. Delivered before the harrogate medical society on November 26, 1921. Br Med J. 1922;1(3207):941–3.
2. Bleier JIS, Wilkins KB. Colonic physiology. In: Beck DE, Roberts P, Saclarides T, Senagore A, Stamos M, Wexner SD, ed. The ASCRS textbook of colon and rectal surgery, 3rd ed. New York: Springer Science +Business LLC: 2016; pg 27–28.
3. Danowitz M, Solounias N. Embryology, comparative anatomy, and congenital malformations of the gastrointestinal tract. Edorium J Anat Embryo. 2016;3:39–50. (embryology figure).
4. Rose C, Parker A, Jefferson B, Cartmell E. The characterization of feces and urine; a review of the literature to inform advanced treatment technology. Crit Rev Environ Sci Technol. 2015;45:1827–79.
5. Phillips SF, Giller J. The contribution of the colon to electrolyte and water conservation in man. J Lab Clin Med. 1973;81:733–46.
6. Cannon WB. The movements of the intestines studied by means of the Röentgen rays. Am J Phys. 1902;6:251–77.
7. Othman A, Al-Shboul. The importance of interstitial cells of cajal in the gastrointestinal tract. Saudi J Gastroenterol. 2013;19(1):3–15.
8. Sellers RS, Morton D. The colon: from banal to brilliant. Toxicol Pathol. 2014;42(1):67–81.
9. Cox HM. Neuroendocrine peptide mechanisms controlling intestinal epithelial function. Current Opinion Pharmacol. 2016;31:50–6.
10. Johnson LR. Fluid and electrolyte absorption. In LR Johnson Ed, Gastrointestinal physiology, 9th ed. Elsevier 2019;121–125.
11. Gurney MA, Laubitz D, Ghishan FK, et al. Pathophysiology of intestinal Na+/H+ exchange. Cell Mol Gastroenterol Hepatol. 2017;3(1):27–40.
12. Sandle GI. Pathogenesis of diarrhea in ulcerative colitis: new views on an old problem. J Clin Gastroenterol. 2005;39:S49–52.
13. Kunzelmann K, Mall M. Electrolyte transport in the mammalian colon: mechanisms and implications for disease. Physiol Rev. 2002;82(1):245–89.
14. Edmonds CJ. Absorption of sodium and water by human rectum measured by a dialysis method. Gut. 1971;12:356–62.
15. Singh SK, Binder HJ, Boron WF, et al. Fluid absorption in isolated perfused colonic crypts. J Clin Invest. 1995;96:2373–9.
16. Bergman EN. Energy contributions of volatile fatty acids from the gastrointestinal tract in various species. Physiol Rev. 1990;70:567–90.
17. Kiela PR, Ghishan FK. Na+/H+ exchange in mammalian digestive tract. In: Said HM, Ghishan FK, editors. Physiology of the gastrointestinal tract. 6th ed. London: Academic Press, Elselvier; 2018. p. 1273–316.
18. Bharucha AE, Brookes SJH. Neurophysiologic mechanisms of human large intestinal motility. In: Said HM, Ghishan FK, editors. Physiology of the gastrointestinal tract. 6th ed. London: Academic Press, Elselvier; 2018. p. 517–64.
19. Said HM. Intestinal absorption of vitamin K: cellular and molecular mechanisms. In: Said HM, editor. Physiology of the gastrointestinal tract. 6th ed. London: Academic Press, Eselvier; 2018. p. 1197–9.
20. Brookes SJ, Spencer NJ, Costa M, et al. Extrinsic primary afferent signaling in the gut. Nat Rev Gastroenterol Hepatol. 2013;10:286–96.
21. Furness JB. Disorders of motility and secretion and therapeutic targets in the enteric nervous system. In: Furness, editor. The enteric nervous system. Oxford: Blackwell Publishing; 2006. p. 200–11.
22. Boeckxstaens G, Camilleri M, Sifrim D, et al. Fundamentals of neurogastroenterology: physiology/motility – sensation. Gastroenterology. 2016;150:1292–304.
23. Lomax AE, Sharkey KA, Furness JB. The participation of the sympathetic innervation of the gastrointestinal tract in disease states. Neurogastroenterol Motil. 2010;22:7–18.
24. Knowles CH, Scott SM, Lunnis PJ. Slow transit constipation: a disorder of pelvic autonomic nerves? Dig Dis Sci. 2001;46:389–401.
25. Keszthelyi D, Troost FJ, Masclee AA. Irritable bowel syndrome: methods, mechanisms, and pathophysiology. Methods to assess visceral hypersensitivity in irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol. 2012;303:G141–54.
26. Ness TJ, Metcalf AM, Gebhart GF. A psychophysiological study in humans using phasic colonic distension as a noxious visceral stimulus. Pain. 1990;43:377–86.
27. Azpiroz F, Bouin M, Camilleri M, et al. Mechanisms of hypersensitivity in IBS and functional disorders. Neurogastroenterol Motil. 2007;10:62–88.
28. Mertz H, Naliboff B, Munakata J, Niazi N, Mayer EA. Altered rectal perception is a biological marker of patients with irritable bowel syndrome. Gastroenterology. 1995;109:40–52.
29. Mawe GM, Hoffman JM. Serotonin signaling in the gut-functions and therapeutic targets. Nat Rev Gastroenterol Hepatol. 2013;10:473–86.
30. Rao SS, Sadeghi P, Beaty J. Ambulatory 24-hour colonic manometry in slow-transit constipation. Am J Gastroenterol. 2004;99(12):2405–16.
31. Furukawa Y, Cook IJ, Panagopoulos V, et al. Relationship between sleep patterns and human colonic motor patterns. Gastroenterology. 1994;107:1372–81.
32. Bampton PA, Dinning PG, Kennedy ML, et al. Prolonged multipoint recording of colonic manometry in the unprepared human colon: providing insight into potentially relevant pressure wave parameters. Am J Gastroenterol. 2001;96:1838–48.
33. Cremonini F, Delgado-Aros S, Camilleri M. Efficacy of alosetron in irritable bowel syndrome: a meta-analysis of randomized controlled trials. Neurogastroenterol Motil. 2003;15:79–86.
34. Camilleri M. Is there an experimental basis for the development of ischaemic colitis as a result of the 5-HT3 antagonist treatment? Neurogastroenterol Motil. 2007;19:77–84.
35. Ford A, Suares N. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. Gut. 2011;60:209–18.
36. Bouras EP, Camilleri M, Burton DD, et al. Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder. Gastroenterol. 2001;120:354–60.

37. Ao M, Venkatasubramanian J, Boonkaewwan C, et al. Lubiprostone activated Cl secretion via cAMP signaling and increases membrane CFTR in the human colon carcinoma cell line, T84. Dig Dis Sci. 2011;56:339–51.
38. Sweetser S, Busciglio IA, Camilleri M, et al. Effect of a chloride channel activator, lubiprostone, on colonic sensory and motor functions in healthy subjects. Am J Physiol Gastrointest Liver Physiol. 2009;296:G295–301.
39. Schey R, Rao SSC. Lubiprostone for the treatment of adults with constipation and irritable bowel syndrome. Dig Dis Sci. 2011;56:1619–25. Motility in physiology of the gastrointestinal tract. 6th Ed. Elsevier; 2018, pp 517–64.
40. Manabe N, Cremonini F, Camilleri M, et al. Effects of bisacodyl on ascending colon emptying and overall colonic transit in healthy volunteers. Ailment Pharmacol Ther. 2009;30:930–6.
41. Ewe K, Holker B. The effect of a diphenolic laxative (Bisacodyl) on water and electrolyte transport in the human colon (author's transl). Klin Wochenschr. 1974;52:827–33.
42. Kamm MA, Dudding TC, Melenhorst J, et al. Sacral nerve stimulation for intractable constipation. Gut. 2010;59:33–40.
43. Dinning PG, Fuentealba SE, Kennedy ML, et al. Sacral nerve stimulation induces pan-colonic propagating pressure waves and increases defecation frequency in patients with slow-transit constipation. Color Dis. 2007;9:123–32.
44. Garner CE, Smith S, de Lacy CB, et al. Volatile organic compounds from feces and their potential for diagnosis of gastrointestinal disease. FASEB J. 2007;21:1675–88.
45. Spohn SN, Young VB. Gastrointestinal microbial ecology with perspectives on health and disease. In: Physiology of the gastrointestinal tract. 6th ed: Elsevier; 2018. p. 737–53.
46. Ahmed I, Greenwood R, Costello BL, et al. An investigation of fecal volatile organic metabolites in irritable bowel syndrome. PLoS One. 2013;8:e58204.
47. Nyangale EP, Mottram DS, Gibson GR. Gut microbial activity, implications for health and disease: the potential role of metabolite analysis. J Proteome Res. 2012;11:5573–85.
48. Adams JB, Johansen LJ, Powell LD, et al. Gastrointestinal flora and gastrointestinal status in children with autism-comparisons to typical children and correlation with autism severity. BMC Gastroenterol. 2011;11:22.
49. Imhann F, Vich Vila A, Bonder MJ, et al. Interplay of host genetics and gut microbiota underlying the onset and clinical presentation of inflammatory bowel disease. Gut. 2018;67:108–19.
50. Nitzan O, Elias M, Peretz A, et al. Role of antibiotics for treatment of inflammatory bowel disease. World J Gastroenterol. 2016;22:1078–87.
51. Peterson J, Garges S, Giovanni M, et al. The NIH human microbiome project. Genome Res. 2009;19:2317–23.
52. Proctor LM. The human microbiome project in 2011 and beyond. Cell Host Microbe. 2011;10:287–91.
53. Gevers D, Knight R, Petrosino JF, et al. The human microbiome project: a community resource for the healthy human microbiome. PLoS Biol. 2012;10(8):e1001377.
54. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature. 2012;486(7402):207–14.
55. Human Microbiome Project Consortium. A framework for human microbiome research. Nature. 2012;486:215–21.
56. Integrative HMP (iHMP) Research Network Consortium. The Integrative Human Microbiome Project: dynamic analysis of microbiome-host omics profiles during periods of human health and disease. Cell Host Microbe. 2014;16(3):276–89.
57. Bouchie A. White house unveils National Microbiome Initiative. Nat Biotechnol. 2016;34(6):580.
58. Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell. 2006;124(4):837–48.
59. Sullivan A, Edlund C, Nord NE. Effect of antimicrobial agents on the ecological balance of human microflora. Lancet Infect Dis. 2001;1(2):101–14.
60. De La Cochetiere MF, Durand T, Lalande V, et al. Effect of antibiotic therapy on human fecal microbiota and the relation to the development of. Microb Ecol. 2008;56:395–402.
61. Dethlefsen L, Huse S, Sogin ML, et al. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. PLoS Biol. 2008;6:2383–400.
62. Modi SR, Collins JJ, Relman DA. Antibiotics and the gut microbiota. J Clin Invest. 2014;124:4212–8.

Anorectal Physiology

3

Pasithorn A. Suwanabol and Scott E. Regenbogen

Key Concepts

- Maintenance of fecal continence and defecation are complex processes requiring both voluntary and involuntary reflexes that have yet to be fully characterized.
- Normal continence is dependent on coordination between neuronal reflexes, sensory and motor pathways, the rectum, anal sphincters, and pelvic floor and requires adequate rectal compliance and competence of the anal sphincter.
- During defecation, sensory mechanisms allow the rectum to stretch to accommodate feces, the pelvic floor muscles relax, and intraabdominal pressure increases. Simultaneously, the puborectalis relaxes and straightens the anorectal angle, the anal canal shortens, and the pelvic floor descends. Finally, the anal sphincters relax and evacuation is initiated.
- Anatomy and physiology of the rectum and anus are intrinsically related, allowing physiologic testing to be exceedingly useful for diagnosis and management of anorectal pathologies.
- Disorders of continence can derive from deficits of mental, anatomic, and physiologic functions, including reflexes, sensory and motor nerves, and the muscles of the rectum, sphincters, and pelvic floor.
- Functional defecatory disorders frequently coexist with urogynecologic conditions likely due to the shared musculature of the pelvic floor and urogenital diaphragm, as well as from the overlap in peripheral innervation and spinal nerve roots.

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Introduction

Recognition and appropriate management of anorectal pathology require an understanding of both anatomy and physiology of the rectum, anus, and pelvic floor. The purpose of this chapter is to review the anatomy and innervation of the rectum and anus, characterize normal continence and defecation, and provide an overview of physiologic testing relevant to anorectal physiology and pathophysiology. In addition, we will briefly review the pathophysiology of functional disorders of the anus and rectum.

In general, defecation and maintenance of fecal continence are complex processes requiring both voluntary and involuntary reflexes that have yet to be fully characterized. Much of what is known is based on an understanding of pathologic disorders and functional studies among healthy subjects or animals. Despite our incomplete understanding of anorectal physiology, it is critical to gain as much knowledge of normal and abnormal physiology as possible as it will enable the surgeon to advise and intervene when needed.

Anatomy

For detailed discussion of the anatomy and physiology of the rectum and anus, please refer to Chap. 1.

The rectum serves as a reservoir for feces, measuring approximately 12–15 cm in length, yet its proximal and distal margins continue to be debated – particularly in light of differences in treatment approaches for lower gastrointestinal cancers [1]. The rectum, which is identified in the abdomen by the lack of haustra, taeniae, or epiploica, is located along the curve of the sacrum and coccyx and becomes the anal canal as it passes through the levators [2]. The rectal wall contains a layer of longitudinal smooth muscle and a layer of circular smooth muscle that are in continuity with the gastrointestinal tract [3]. The rectum encompasses three folds, known as the valves of Houston, which do not contain all the muscle wall layers and are not believed to serve any

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specific function. The middle valve corresponds to the anterior peritoneal reflection and is the most consistent with regard to location and its presence [2].

Like the rectum, the definition of the anus or anal canal is controversial and is distinguished by embryologic origin and mucosal histology or by its function. The embryologic anal canal, which does not incorporate anal function, is defined as the area from the anal verge to the dentate line [2]. First described by Milligan and Morgan in 1934 in order to guide anorectal surgery, the functional or surgical anal canal begins where the rectum enters the pelvic hiatus and passes through the puborectalis. It encompasses the area from the anal verge to the anorectal ring and is surrounded by the anal sphincters and the puborectalis [4]. On average, the functional or surgical anal canal measures approximately 2.5–5 cm in length and is shorter in females [5]. The anal canal is characterized by columnar mucosa above the dentate line and squamous epithelia below, which are important as they represent two separate inputs, supplied by different aspects of the arterial-venous, lymphatic, and nervous systems [6]. Above the dentate line, the anal canal is supplied and drained by the hypogastric vessels and innervated by the sympathetic and parasympathetic nervous systems. Below the dentate line, the anal canal is supplied by the inferior hemorrhoidal vessels and innervated by the somatic nervous system [2] The 1–2 cm area between these two regions is known as the transition or cloacogenic zone, which is composed of columnar, transitional, and stratified squamous epithelium [6].

The anal sphincter complex consists of the internal anal sphincter (IAS), the conjoined longitudinal muscle (CLM), and the external anal sphincter (EAS). The IAS is a 2–3 mm thick circular band composed of the distal inner circular smooth muscle layer of the rectum, which is always maximally contracted to prevent involuntary loss of stool and flatus [3]. The IAS is encompassed proximally by the levator ani and distally by the superficial external sphincter muscle and subcutaneous external straited anal sphincter muscle [7, 8]. The CLM, located between the IAS and the EAS, is composed of the fibers of the outer layer of the rectum at the level of the anorectal ring and runs distally to the puborectalis muscle [9]. The CLM's functions are unclear, but it may contribute minimally to maintaining continence and defecation [10, 11]. More importantly, the CLM may act as a scaffolding for the entire anal sphincter complex [12]. The EAS comprises striated muscle as a continuation of the puborectalis muscle and is attached anteriorly to the perineal body and posteriorly to the anococcygeal ligament. The EAS is in constant state of tonic contractile activity, even at rest, and voluntarily contracts during any threat of incontinence [13].

The pelvic floor muscles include the levator ani, which consists of the pubococcygeus, puborectalis, and iliococcygeus (Fig. 3.1). These muscles function to support the viscera of the pelvic cavity and play a key role in defecation [7]. The pubococcygeus arises from the posterior pubis, travels alongside the anorectal junction, and inserts into the anococcygeus ligament and the coccyx. The puborectalis is a U-shaped

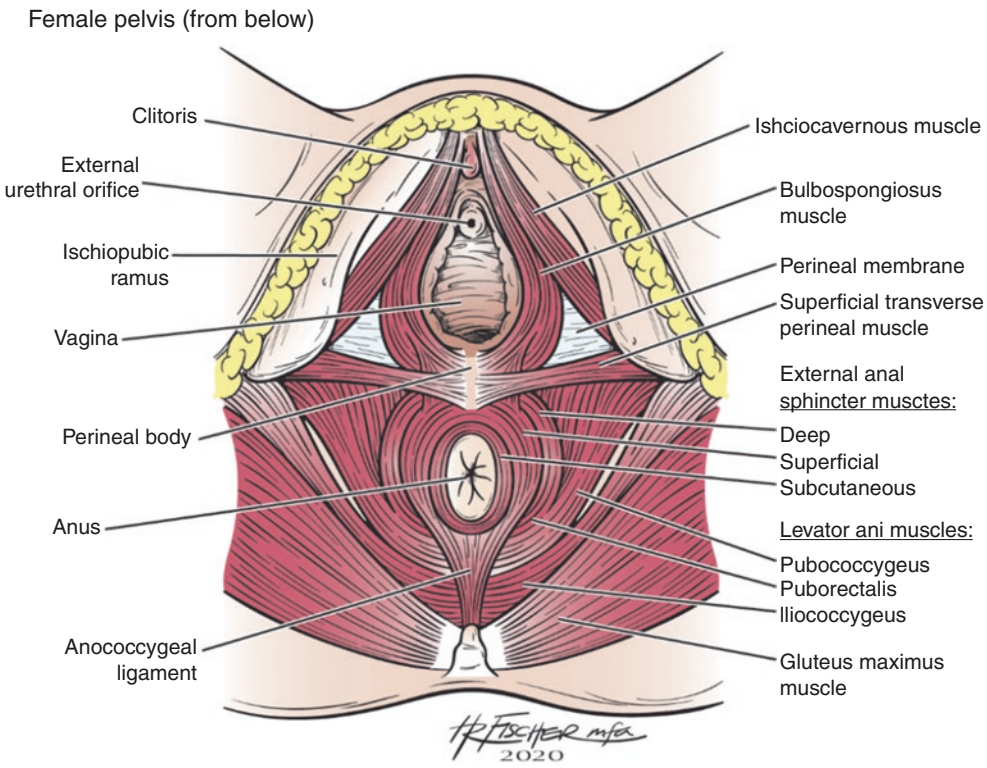

Fig. 3.1 Muscles of the pelvic floor. (Illustration created by H.R. Fischer, MFA)

muscle that slings the anorectal junction to the posterior pubis to pull the rectum anteriorly and forms the anorectal angle. It is palpable on digital rectal exam as the top of the anorectal ring [3]. The iliococcygeus arises from the ischial spine and obturator fascia, travels inferiorly and medially, and inserts into the anococcygeal raphe and coccyx [2].

Physiology

Innervation of the Anus and Pelvic Floor

Sympathetic nerves derived from L1, L2, and L3 join the preaortic plexus, which then extend to form the hypogastric plexus below the aorta. These then join parasympathetic fibers called nervi erigentes (S2, S3, and S4) to form the pelvic plexus (Fig. 3.2) [14]. Motor innervation of the IAS is supplied by the sympathetic (L5) and parasympathetic nerves (S2, S3, and S4) from the autonomic nervous system. In contrast, the EAS is supplied by the inferior rectal branch of the pudendal nerve (S2 and S3) and by the perineal branch of S4 from the somatic nervous system. Unilateral transection of the pudendal nerve does not impact EAS function due to fiber crossover at the spinal cord level [15]. The sacral roots of S3 and S4, the perineal branch, and the inferior rectal nerve of the pudendal nerve innervate the levator ani [16]. The pudendal nerve branches supply the pubococcygeus and puborectalis, whereas direct sacral nerves S3 and S4 innervate the iliococcygeus [17].

Upper anal canal sensory innervation is supplied by both free and organized sensory nerve endings, including Meissner's corpuscles (touch), Krause's bulbs (temperature), Golgi-Mazzoni bodies (pressure), and genital corpuscles (friction) [18, 19]. Within the transition zone of the anal canal, these organized nerve endings may play a role in sampling [20]. The inferior rectal branch of the pudendal nerve provides anal sensation and may provide some maintenance of fecal continence [2, 21, 22]. In addition, it may play a smaller role in discriminating between solid and gas [23].

Normal Continence

Normal continence requires adequate rectal compliance to accommodate fecal contents and competence of the anal sphincter to resist propulsive forces of the distal gastrointestinal tract, assess its contents, and release them under voluntary control [7, 24]. Although normal continence is incompletely understood, it is known to be dependent on complex coordination between neuronal reflexes, sensory and motor pathways, the rectum, anal sphincters, and pelvic floor [25, 26].

Rectal Sensation and Compliance

Rectal sensation encompasses the feeling of both rectal filling and anal reflexes, which is distinct from the rest of the lower gastrointestinal tract where distension evokes pain [27, 28]. The rectum's function is to store feces, which requires the ability to accommodate volumes of feces without substantially altering rectal pressures. Accommodation is reliant on both the content and the contractile state of the rectum [3, 29]. Baseline rectal pressure is low (approximately 5 mmHg) compared to anal canal pressures, which measure approximately 10–14 times that of the rectum. This pressure differential may allow for stool deferment, forcing stool back into the sigmoid and rectum, until defecation is initiated [19]. Although the rectum does not have proprioceptive receptors, rectal compliance may be due to unique, slowly adapting mechanoreceptors that respond to tension and rapid distension, termed rectal intra-ganglionic laminar endings (rIGLEs) [30]. This idea is consistent with the observation that rectal filling sensations coincide with increased rectal pressure during rectal distension [27]. Instead, defecation is sensed at the level of the levators and the anal canal, which may underlie the preserved sense of defecation among patients after proctectomy with ileoanal or coloanal anastomoses [31, 32].

Anorectal Reflexes

The rectoanal inhibitory reflex (RAIR) is an intrinsic intramural reflex critical to normal continence. It occurs in response to distension of the rectum, relaxing the upper IAS to allow fecal material or flatus to interact with specialized receptors in the upper anal canal. This sampling enables flatus to pass without fecal incontinence as the lower IAS resting pressure, the contraction of the EAS, and puborectalis push feces to the upper rectum and delays defecation [3, 33, 34]. The RAIR occurs every 8–10 minutes and lasts less than 10 seconds [35, 36]. The RAIR is absent in those with Hirschsprung's disease due to the absence of myenteric ganglia in the rectum [37]. Furthermore, injury or alteration to the RAIR may play a role in patients with poor functional outcome or incontinence after rectal resection [38–41].

Less studied anorectal reflexes include the cutaneous anal sphincter reflex, the bulbocavernosus reflex, and the cough-anal reflex. The cutaneous anal sphincter reflex is defined as contractions of the EAS with touch or pain of the anal skin, while the bulbocavernosus reflex is characterized by contractions of the EAS when squeezing the glans penis or clitoris. The bulbocavernosus reflex can also occur when a urethral catheter is removed. Finally, the cough-anal reflex is described as contractions of the EAS when coughing or sniffing. The cough-anal reflex is important in maintaining continence during sudden increases of intraabdominal pressures, such as coughing, sneezing, or laughing [42].

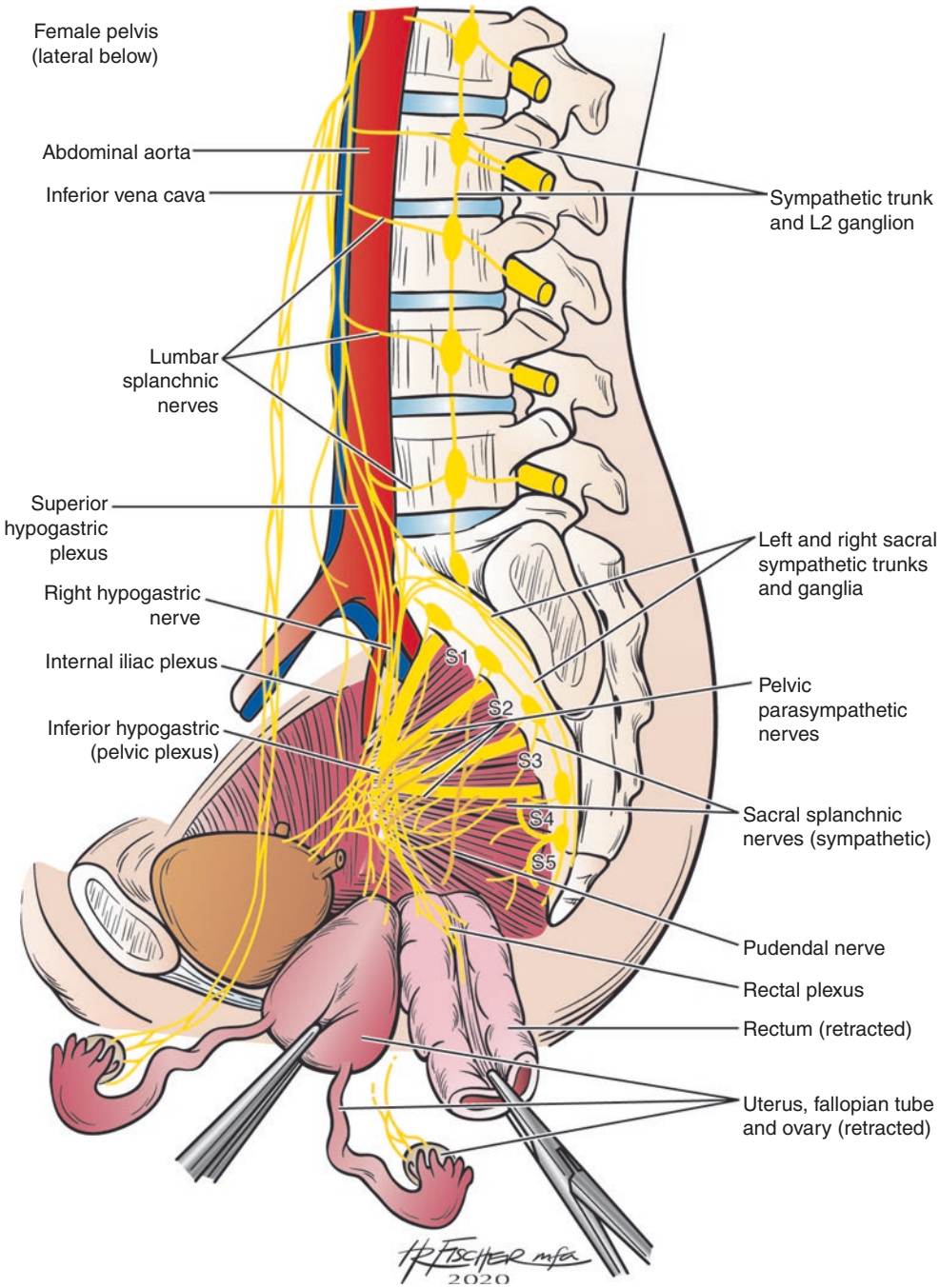

Fig. 3.2 Innervation of the anus and pelvic floor. (Illustration created by H.R. Fischer, MFA)

Internal and External Anal Sphincters

The IAS constitutes approximately 50–70% of resting tone or pressure and is maximally contracted at rest, with the hemorrhoid complexes accounting for an additional 15% of resting tone or pressure [2, 43–46]. Hemorrhoid complexes contribute to continence by expanding to create a seal proximal to the anal opening [46]. Due to the intrinsic function of smooth muscle, most of the resting tone is due to myogenic tone, which is characterized by slow, constant waves of contraction [42, 47]. The IAS receives additional excitatory sympathetic input and inhibitory parasympathetic input, which are mediated by nitric oxide [3, 48–50]. Injury to the IAS leads to passive fecal incontinence or leakage, whereas injury to the EAS is associated with urge fecal incontinence [3, 51]. Whereas the EAS plays a smaller role in resting tone, its primary contribution to continence involves voluntary or reflexive contraction in response to rectal distention and threat of incontinence, for example, during increases in intraabdominal pressure [3, 52]. Similarly, defecation may be deferred by contraction of the EAS to oppose increased rectal pressure. After EAS contraction, the sensation of urgency and tenesmus will diminish over a period of time

that allows rectal adaptation to occur [53–55]. The EAS differs from the IAS, however, in its fatigability, demonstrated by the deferment of large volumes of stool for mere seconds or minutes, despite normal rectal compliance [27, 56].

Puborectalis and the Pelvic Floor

As briefly described above, the puborectalis is a striated muscle that acts as a sling located at the anorectal junction, from which a 90- to 100-degree angle is formed at rest. Its critical role in continence is believed to be due to this anorectal angle. Theories for its underlying mechanism include that the puborectalis pushes the anterior rectal wall against the upper anal canal, preventing feces from passing distally, particularly during times of increased intraabdominal pressure (known as the flap-valve theory), or that the puborectalis acts as a deeper sphincter mechanism that works in coordination with the EAS [27, 31].

Normal Defecation

Defecation requires coordination between the colon and movement of its contents, increases in intraabdominal and rectal pressures, and finally, pelvic floor relaxation. First, sensory mechanisms allow the rectum to stretch to accommodate feces once fecal material or flatus is sensed. In response to distension of the rectum, the IAS reflexively relaxes. The RAIR response requires an intact subcutaneous nervous plexus in order to function and is under autonomic control. The RAIR allows distinction between feces and flatus as well as solid and liquid waste, and the initiation of defecation [2, 24, 57]. If defecation is not desired, the anal sphincters will contract and the rectum will continue to distend until the individual becomes aware [27]. However, the urge to defecate lasts only a few seconds and is controlled by continued EAS contraction (conscious suppression) [27, 56]. Sampling may continue throughout this process even with a full rectum [27, 56].

During defecation, the pelvic floor muscles relax and the intraabdominal pressure increases (Valsalva). Several actions occur simultaneously: (1) the puborectalis relaxes and lengthens, which straightens of the anorectal angle; (2) the CLM contracts, which leads to shortening of the anal canal; and (3) the pelvic floor descends. Finally, the anal sphincters relax and evacuation is initiated by the rectosigmoid contractions, which propel feces through the anal canal [3, 11, 26, 27, 58]. A squatting or hip flexion position facilitates this process by optimally straightening the anorectal angle and increasing intraabdominal pressure [59]. Sensory input from the anus ensures that the contractions continue until the rectum is completely emptied [27, 60]. Anal closure at the end of defecation is termed the "closing reflex" and is described as an exaggerated contraction of the EAS and restoration of IAS resting tone [27].

Physiologic Testing

Please refer to Chap. 55 for an in-depth discussion of pelvic floor testing. In general, the surgeon is uniquely equipped to understand the rectum and anus through a combination of dissection in the operating room, endoscopic evaluation, and physiologic investigation. It should be stressed that the anatomy of the rectum and anus is intrinsically related to its physiology, which is why physiologic testing can prove to be highly beneficial in the diagnosis and appropriate management of anorectal pathologies [2, 61, 62].

Anal Manometry

Using a pressure-sensitive catheter in the rectum and anal canal, manometry is a test that measures sphincter function including resting tone and maximum squeeze pressure, presence of RAIR, response to cough or Valsalva reflex, and anal canal length [26, 63, 64]. Resting tone (normal 40–80 mmHg) is due to the resting pressure of the IAS and the length of the anal canal, which is known as the high-pressure zone (normal 2.0–4.0 cm). Maximum squeeze pressure reflects EAS function (normal 40–80 mmHg) [2, 43]. Presence of the RAIR is determined by inflating a balloon in the distal rectum. The absence of RAIR is found in impaired myenteric nerve plexus such as Hirschsprung's disease or following proctectomy as described above [65–68]. Due to limited knowledge of normal defecation and lack of standardization of the technique and normal values even between healthy patient populations (e.g., younger vs. older, males vs. females), interpretation of anal manometry results may be challenging [2, 69, 70].

Pudendal Nerve Terminal Motor Latency

Neurophysiological testing of the pudendal nerve, which again innervates the EAS, is performed by stimulation at the site where the nerve enters the ischiorectal fossa at the level of the coccyx [3]. Pudendal nerve terminal motor latency (PNTML) measures the time between the stimulation of the pudendal nerve and contraction of the EAS. Normal values are approximately 2 ± 0.2 milliseconds [42, 69, 71]. Prolonged or abnormal values demonstrating neuropathy can be seen in those with idiopathic fecal incontinence, rectal prolapse, or sphincter injuries [3, 72]. However, PNTML testing is operator dependent and limited by low sensitivity and specificity [42].

Balloon Insufflation

Rectal sensation and compliance are tested by balloon insufflation, which measures the first detectable sensation, the urge to defecate, and the maximum tolerable volume [28, 73]. Urge to defecate is characterized by an increase in compliance, as indicated by volume increasing with pressure changes. This represents "adaptive relaxation" of the rectum [7]. Delayed sensation or hyposensitivity manifests at higher volumes for these three parameters and may be detected in those with neuropathies or altered rectal reservoirs. Hypersensitivity is characterized by reduced sensory threshold to rectal distension, lower volumes for the three parameters, and complaints of urgency and frequency. Hypersensitivity is often demonstrated in those with inflammatory bowel disease, proctitis, and functional bowel disorders [3, 55, 74–76].

Defecography

Defecography is a dynamic study to assess the defecatory process, specifically, the function of the pelvic floor during defecation (Fig. 3.3) [77, 78]. The most common method to perform defecography involves the instillation of liquid barium and air into the rectum followed by barium paste into the rectum and/or vagina depending on clinical indication. With the patient sitting on a commode and attempting to recreate normal defecation, radiographs are obtained at rest, during squeeze, and during Valsalva [79]. The anorectal angle and perineal descent are commonly measured, as well as whether paradoxical contraction of the puborectalis occurs [77, 78, 80].

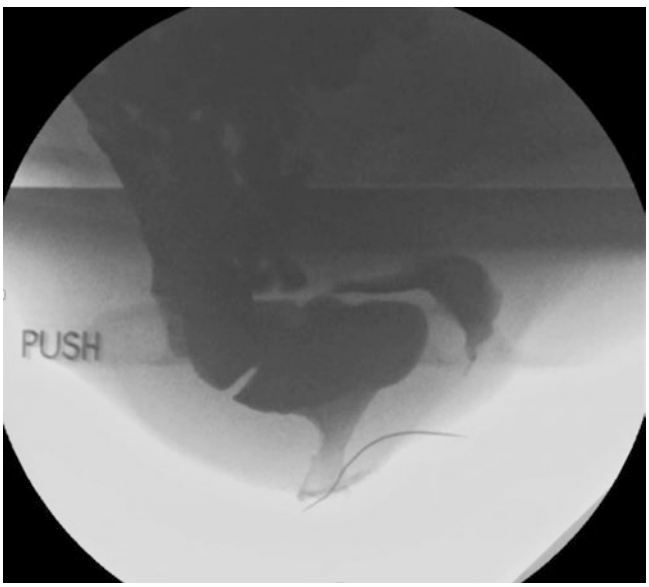

Fig. 3.3 Defecography demonstrating anterior rectocele. (Courtesy of G. Kwakye, MD, used with permission)

Functional Anorectal Disorders

In this chapter, we will discuss the physiologic features and considerations in the evaluation of functional disorders. The diagnostic workup algorithms and management strategies will be discussed in later chapters and are cross-referenced wherever relevant.

Fecal Incontinence

Anal continence requires integrated and coordinated mental, anatomic, and physiologic functions, including reflexes, sensory and motor nerves, and the muscles of the rectum, sphincters, and pelvic floor. Thus, disorders of continence can derive from deficits in any of these contributors, or as a result of high stool volume or liquid consistency, even in patients with normal anatomy and function [81]. Yet, the various mechanisms of continence are likely somewhat redundant, as single, isolated deficits in any one of these functions may often be tolerated without symptomatic incontinence. For example, the functional consequences of obstetric trauma suffered during childbearing years may not be experienced until decades later, as compensatory mechanisms are weakened or disrupted [82]. These observations suggest that the physiologic etiology of fecal incontinence is most often multifactorial [83].

Fecal incontinence due to sphincter muscle defects may result from iatrogenic injury associated with sphincterotomy, fistula surgery, and hemorrhoidectomy or from obstetric injury or other trauma (Fig. 3.4). Idiopathic fecal incontinence, in the absence of defined functional bowel disorder or anatomic deficit, is most commonly associated with denervation of the pelvic floor and/or sphincter muscles. This nerve dysfunction may itself be idiopathic, for example associated with advanced age, or may be secondary to trauma from obstetric injury, chronic prolonged straining, distention from constipation, or outlet dysfunction [84, 85]. There is evidence of decreased sphincter pressures in older adults, and in women especially after menopause [86–88]. Pudendal nerve terminal motor latencies are likewise observed to be prolonged in older women.

Compared to individuals with normal continence, patients with idiopathic fecal incontinence are more likely to have evidence of pelvic floor motor neuropathy, including lower anal canal resting and voluntary contraction pressures, longer pudendal nerve terminal motor latency, and higher thresholds to mucosal electrosensitivity in the anal canal [89]. On average, these patients have reduced anal resting pressures and reduced squeeze pressures, as well as lower volume and pressure thresholds for the urge to defecate [90]. In addition, compared to continent controls, patients with fecal incontinence tend to exhibit significant impairment of anal sensation [91]. This combination of motor and sensory

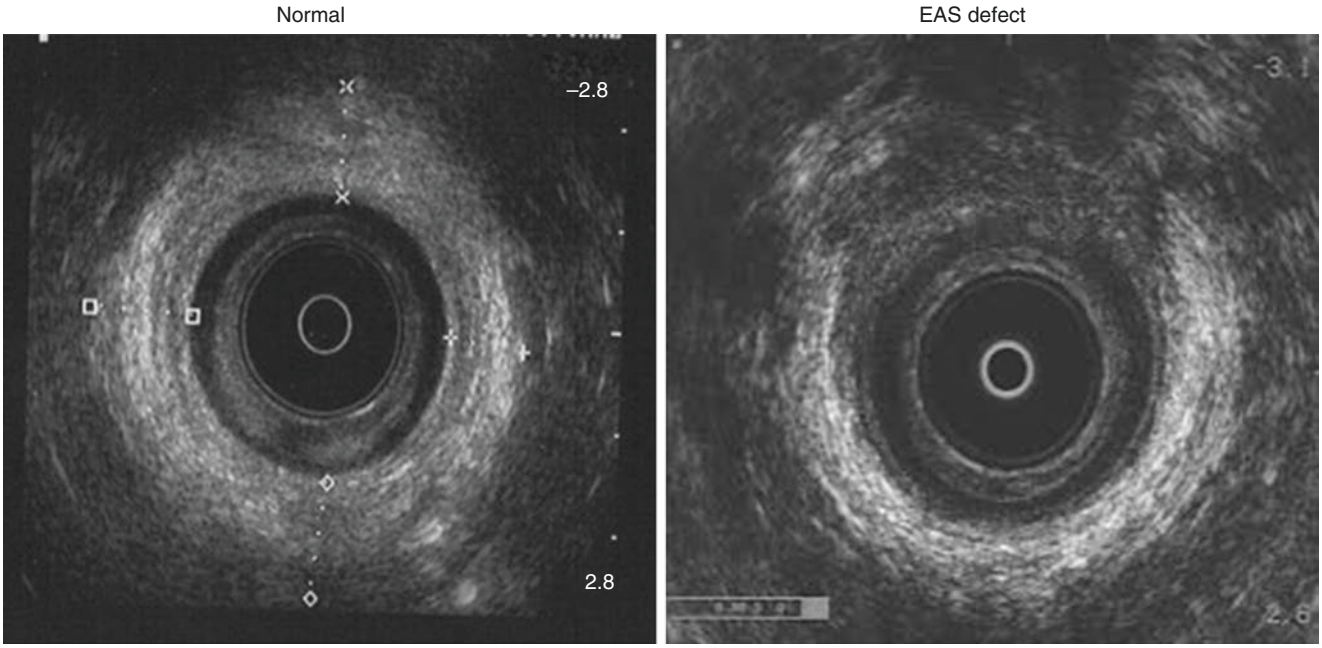

Fig. 3.4 Endorectal ultrasound. (Courtesy of S. Menees, MD, used with permission)

deficits may underlie the ameliorative effects of sacral nerve and posterior tibial nerve stimulation, which can influence neural innervation for both the sensory and motor functions of the anus and rectum. These findings also motivate the rationale for manometry and pudendal nerve terminal motor latency testing in the evaluation of incontinence, as discussed in Chap. 59. The etiology of this deficit has been proposed to be repeated traction on the pudendal nerve and consequent denervation of the external anal sphincter and fibrous replacement [92].

Additional insights into the pathophysiology of fecal incontinence come from the evaluation of patients with spinal cord injuries and other neurologic diseases. Loss of rectal sensation may contribute to deficits in RAIR, while exaggerated, unopposed stimulation during distention may induce involuntary sphincter relaxation, and impaired spinal reflex activity may reduce rectal compliance [82, 93, 94]. Incontinence in this setting may therefore derive from any combination of the following, depending on the level and completeness of injury: decreased anal sphincter resting tone, loss of voluntary control, or loss of anorectal reflexes.

Disorders of Defecation

In patients with constipation associated with anal outlet dysfunction, physiological abnormalities may include inadequate defecatory propulsion, dyssynergic defecation, or some combination thereof. Obstructed defecation can also be associated with pathologic anatomic conditions, including rectocele, intussusception, prolapse, or stricture. The diagnostic evaluation of defecatory disorders is discussed in detail in Chaps. 56 and 57.

Patients with idiopathic outlet dysfunction may exhibit a variety of manometric anomalies, including elevated anal resting pressures, but this finding varies widely and may be normal in many of these patients [95]. Some may have impaired rectal sensation, or decreased RAIR, which may reduce the autonomic emptying response, but these findings are also varied among numerous studies [96, 97]. The finding that women with new-onset constipation following a hysterectomy experienced decreased rectal sensory perception implies a role for the parasympathetic plexus of nerves, which reach the rectum via the lateral vaginal walls as they are susceptible to injury during lateral pelvic dissection [98]. Some have suggested that decreased rectal tone and intrarectal pressure with straining are consistent with findings in those with idiopathic constipation, implying that diminished propulsion contributes to the outlet dysfunction [99, 100].

In other patients, obstructed defecation may result from dyssynergic contraction of the external anal sphincter and/or puborectalis muscle during efforts to evacuate the rectum. Patients with obstructed defecation exhibit clinically significant limitation of emptying despite puborectalis activity, as demonstrated through electromyography (EMG), and adequate rectal pressure with straining [101]. These patients will exhibit paradoxical increase in puborectalis muscle contraction during EMG with straining and Valsalva maneuver, also known as anismus [100, 102]. Nevertheless,

the anatomic physiologic correlates of defecatory disorders may not reliably predict the clinical syndrome. In one study, there was no difference in the degree of perineal descent or the manometric assessment of the external anal sphincter between patients with incontinence and patients with obstructed defecation [103].

Anorectal Pain

In the absence of identifiable anatomic source of pain from trauma, fissure, thrombosed hemorrhoid, abscess, tumor, or other finding, idiopathic or functional anorectal pain disorders may be diagnosed. These pain syndromes have been subclassified as either chronic proctalgia (chronic or recurring pain lasting more than 20 minutes, without identifiable source) or proctalgia fugax (episodes lasting less than 20 minutes, with resolution between episodes). Patients with chronic proctalgia may be considered to have levator ani syndrome if digital rectal exam with posterior traction on the puborectalis muscle reproduces the pain [104]. On occasion, either of these conditions may arise following anorectal surgery, but they are more commonly associated with psychological disturbances, including anxiety and post-traumatic stress [105]. The physiologic findings from manometry or other testing are variable.

Urogynecological Considerations

Functional defecatory disorders, including fecal incontinence, obstructed defecation, rectal prolapse, rectocele, enterocele, sigmoidocele, and anorectal pain, frequently coexist with urogynecologic conditions such as urinary incontinence or retention, uterine prolapse or procidentia, and chronic pelvic pain. These relationships likely result from the shared musculature of the pelvic floor and urogenital diaphragm, as well as from the overlap in peripheral innervation and spinal nerve roots. The overlap between colorectal and gynecologic surgical considerations will be discussed in more detail in Chap. 65.

References

1. D'Souza N, de Neree tot Babberich MPM, D'Hoore A, et al. Definition of the rectum: an international, expert-based Delphi consensus. Ann Surg. 2019; https://doi.org/10.1097/SLA.0000000000003251.
2. Garza A, Beart RW. Anatomy and embryology of the anus, rectum, and colon. In: Corman's colon and rectal surgery. 6th ed. Philadelphia; 2014.
3. Gurjar SV, Jones OM. Physiology: evacuation, pelvic floor and continence mechanisms. Surgery. Lippincott Williams & Wilkins, Philadelphia; 2011; https://doi.org/10.1016/j.mpsur.2011.05.010.
4. Milligan ETC, Morgan CN. Surgical anatomy of the anal canal. With special reference to anorectal fistulae. Lancet. 1934; https://doi.org/10.1016/S0140-6736(00)82376-4.
5. Nivatvongs S, Stern HS, Fryd DS. The length of the anal canal. Dis Colon Rectum. 1981; https://doi.org/10.1007/BF02605754.
6. Carmichael JC, Mills S. Anatomy and embryology of the colon, rectum, and anus. The ASCRS textbook of colon and rectal surgery; 2016. https://doi.org/10.1007/978-3-319-25970-3_1.
7. Barleben A, Mills S. Anorectal anatomy and physiology. Surg Clin North Am. 2010; https://doi.org/10.1016/j.suc.2009.09.001.
8. Parks AG. Pathogenesis and treatment of fistula-in-ano. Br Med J. 1961; https://doi.org/10.1136/bmj.1.5224.463.
9. Tsukada Y, Ito M, Watanabe K, et al. Topographic anatomy of the anal sphincter complex and levator ani muscle as it relates to intersphincteric resection for very low rectal disease. Dis Colon Rectum. 2016; https://doi.org/10.1097/DCR.0000000000000565.
10. Haas PA, Fox TA. The importance of the perianal connective tissue in the surgical anatomy and function of the anus. Dis Colon Rectum. 1977; https://doi.org/10.1007/BF02586429.
11. Shafik AA. New concept of the anatomy of the anal sphincter mechanism and the physiology of defecation. III. The longitudinal anal muscle: anatomy and role in anal sphincter mechanism. Investig Urol. 1976;13(4):271–7.
12. Courtney H. Anatomy of the pelvic diaphragm and anorectal musculature as related to sphincter preservation in anorectal surgery. Am J Surg. 1950; https://doi.org/10.1016/0002-9610(50)90208-X.
13. Floyd WF, Walls EW. Electromyography of the sphincter ani externus in man. J Physiol. 1953; https://doi.org/10.1113/jphysiol.1953.sp005024.
14. Kelli MBD, David AR. Colon, rectum, and anus | Schwartz's principles of surgery, 10e | AccessMedicine | McGraw-Hill Medical. Principals of surgery; McGraw-Hill Education: New York; 2015.
15. Wunderlich M, Swash M. The overlapping innervation of the two sides of the external anal sphincter by the pudendal nerves. J Neurol Sci. 1983; https://doi.org/10.1016/0022-510X(83)90084-9.
16. Wallner C, Maas CP, Dabhoiwala NF, Lamers WH, DeRuiter MC. Evidence for the innervation of the puborectalis muscle by the levator ani nerve. Neurogastroenterol Motil. 2006; https://doi.org/10.1111/j.1365-2982.2006.00846.x.
17. Grigorescu BA, Lazarou G, Olson TR, et al. Innervation of the levator ani muscles: description of the nerve branches to the pubococcygeus, iliococcygeus, and puborectalis muscles. Int Urogynecol J. 2008; https://doi.org/10.1007/s00192-007-0395-8.
18. Taylor I, Duthie HL, Smallwood R, Linkens D. Large bowel myoelectrical activity in man. Gut. 1975; https://doi.org/10.1136/gut.16.10.808.
19. Gordon PH. Anorectal anatomy and physiology. Gastroenterol Clin N Am. 2001; https://doi.org/10.1016/S0889-8553(05)70164-3.
20. DUTHIE HL, GAIRNS FW. Sensory nerve-endings and sensation in the anal region of man. Br J Surg. 1960; https://doi.org/10.1002/bjs.18004720602.
21. Miller R, Bartolo DCC, Cervero F, Mortensen NJ. Anorectal sampling: a comparison of normal and incontinent patients. J Surg. 1988; https://doi.org/10.1002/bjs.1800750116.
22. Schraffordt SE, Tjandra JJ, Eizenberg N, Dwyer PL. Anatomy of the pudendal nerve and its terminal branches: a cadaver study. ANZ J Surg. 2004; https://doi.org/10.1046/j.1445-1433.2003.02885.x.
23. Cherry DA, Rothenberger DA. Pelvic floor physiology. Surg Clin North Am. 1988; https://doi.org/10.1016/S0039-6109(16)44682-7.
24. Lubowski DZ, Meagher AP, Smart RC, Butler SP. Scintigraphic assessment of colonic function during defaecation. Int J Color Dis. 1995; https://doi.org/10.1007/BF00341204.
25. Mellgren A. Fecal incontinence. Surg Clin North Am. 2010; https://doi.org/10.1016/j.suc.2009.10.006.

26. Bharucha AE. Pelvic floor: anatomy and function. Neurogastroenterol Motil. 2006; https://doi.org/10.1111/j.1365-2982.2006.00803.x.
27. Bajwa A, Fellow R, Emmanuel A. The physiology of continence and evacuation. Best Pract Res Clin Gastroenterol. 2009; https://doi.org/10.1016/j.bpg.2009.06.002.
28. Goligher JC, Hughes ESR. Sensibility of the rectum and colon. Its role in the mechanism of anal continence. Lancet. 1951; https://doi.org/10.1016/S0140-6736(51)92242-8.
29. Fox M, Thumshirn M, Fried M, Schwizer W. Barostat measurement of rectal compliance and capacity. Dis Colon Rectum. 2006; https://doi.org/10.1007/s10350-005-0295-2.
30. Lynn PA, Brookes SJH. Function and morphology correlates of rectal nerve mechanoreceptors innervating the guinea pig internal anal sphincter. Neurogastroenterol Motil. 2011; https://doi.org/10.1111/j.1365-2982.2010.01593.x.
31. Parks AG. Anorectal incontinence. J R Soc Med. 1975; https://doi.org/10.1177/003591577506801105.
32. Scharli AF, Kiesewetter WB. Defecation and continence – some new concepts. Dis Colon Rectum. 1970; https://doi.org/10.1007/BF02617635.
33. Gowers WR. The automatic action of the sphincter ani. Proc R Soc London. 1877;26:77–84. https://doi.org/10.1098/rspl.1877.0013.
34. Sangwan YP, Coller JA, Barrett RC, Murray JJ, Roberts PL, Schoetz DJ. Distal rectoanal excitatory reflex: a reliable index of pudendal neuropathy? Dis Colon Rectum. 1995; https://doi.org/10.1007/BF02049725.
35. Russo A, Sun WM, Sattawatthamrong Y, et al. Acute hyperglycaemia affects anorectal motor and sensory function in normal subjects. Gut. 1997; https://doi.org/10.1136/gut.41.4.494.
36. Lane RHS, Parks AG. Function of the anal sphincters following colo-anal anastomosis. Br J Surg. 1977; https://doi.org/10.1002/bjs.1800640820.
37. Emir H, Akman M, Sarimurat N, Kiliç N, Erdoğan E, Söylet Y. Anorectal manometry during the neonatal period: its specificity in the diagnosis of hirschsprung's disease. Eur J Pediatr Surg. 1999; https://doi.org/10.1055/s-2008-1072221.
38. Matzel KE, Stadelmaier U, Muehldorfer S, Hohenberger W. Continence after colorectal reconstruction following resection: impact of level of anastomosis. Int J Color Dis. 1997; https://doi.org/10.1007/s003840050086.
39. Lee SJ, Park YS. Serial evaluation of anorectal function following low anterior resection of the rectum. Int J Color Dis. 1998; https://doi.org/10.1007/s003840050169.
40. Lewis WG, Holdsworth PJ, Stephenson BM, Finan PJ, Johnston D. Role of the rectum in the physiological and clinical results of coloanal and colorectal anastomosis after anterior resection for rectal carcinoma. Br J Surg. 1992; https://doi.org/10.1002/bjs.1800791032.
41. Saigusa N, Belin B, Choi H-J, et al. Recovery of the rectoanal inhibitory reflex after restorative proctocolectomy: does it correlate with nocturnal continence? Dis Colon Rectum. 2003; https://doi.org/10.1097/01.DCR.0000049345.21202.99.
42. Van Koughnett JAM, Da Silva G. Anorectal physiology and testing. Gastroenterol Clin North Am. 2013; https://doi.org/10.1016/j.gtc.2013.08.001.
43. Bennett RC, Duthie HL. The functional importance of the internal anal sphincter. Br J Surg. 1964; https://doi.org/10.1002/bjs.1800510514.
44. Lestar B, Penninckx F, Kerremans R. The composition of anal basal pressure – an in vivo and in vitro study in man. Int J Color Dis. 1989; https://doi.org/10.1007/BF01646870.
45. DUTHIE HL, WATTS JM. Contribution of the external anal sphincter to the pressure zone in the anal canal. Gut. 1965; https://doi.org/10.1136/gut.6.1.64.
46. Stelzner F. The morphological principles of anorectal continence. Prog Pediatr Surg. 1976; https://doi.org/10.1016/s0022-3468(76)80128-5.
47. Karulf RE, Coller JA, Bartolo DCC, et al. Anorectal physiology testing. Dis Colon Rectum. 1991; https://doi.org/10.1007/bf02049930.
48. Jones OM, Brading AF, McC Mortensen NJ. The physiology, pharmacology and therapeutic manipulation of the internala anal sphincter. Can J Gastroenterol. 2002; https://doi.org/10.1155/2002/417530.
49. De Lorijn F, De Jonge WJ, Wedel T, Vanderwinden JM, Benninga MA, Boeckxstaens GE. Interstitial cells of cajal are involved in the afferent limb of the rectoanal inhibitory reflex. Gut. 2005; https://doi.org/10.1136/gut.2004.051045.
50. Rattan S, Sarkar A, Chakder S. Nitric oxide pathway in rectoanal inhibitory reflex of opossum internal anal sphincter. Gastroenterology. 1992; https://doi.org/10.1016/0016-5085(92)91093-J.
51. Kumar D, Waldron D, Williams NS, Browning C, Hutton MRE, Wingate DL. Prolonged anorectal manometry and external anal sphincter electromyography in ambulant human subjects. Dig Dis Sci. 1990; https://doi.org/10.1007/BF01540414.
52. Frenckner B, Euler CV. Influence of pudendal block on the function of the anal sphincters. Gut. 1975; https://doi.org/10.1136/gut.16.6.482.
53. Gee AS, Durdey P. Urge incontinence of faeces is a marker of severe external anal sphincter dysfunction. Br J Surg. 1995; https://doi.org/10.1002/bjs.1800820910.
54. Engel AF, Kamm MA, Bartram CI, Nicholls RJ. Relationship of symptoms in faecal incontinence to specific sphincter abnormalities. Int J Color Dis. 1995; https://doi.org/10.1007/BF00298538.
55. Chan CLH, Scott SM, Williams NS, Lunniss PJ. Rectal hypersensitivity worsens stool frequency, urgency, and lifestyle in patients with urge fecal incontinence. Dis Colon Rectum. 2005; https://doi.org/10.1007/s10350-004-0774-x.
56. Poylin V, Cataldo TE. Anal physiology: the physiology of continence and defecation. The ASCRS textbook of colon and rectal surgery; 2016. https://doi.org/10.1007/978-3-319-25970-3_3.
57. Gang Y. What is the desirable stimulus to induce the rectoanal inhibitory reflex? Dis Colon Rectum. 1995; https://doi.org/10.1007/BF02053859.
58. Brookes SJ, Dinning PG, Gladman MA. Neuroanatomy and physiology of colorectal function and defaecation: from basic science to human clinical studies. Neurogastroenterol Motil. 2009; https://doi.org/10.1111/j.1365-2982.2009.01400.x.
59. Palit S, Lunniss PJ, Scott SM. The physiology of human defecation. Dig Dis Sci. 2012; https://doi.org/10.1007/s10620-012-2071-1.
60. McCrea GL, Miaskowski C, Stotts NA, Macera L, Varma MG. Pathophysiology of constipation in the older adult. World J Gastroenterol. 2008; https://doi.org/10.3748/wjg.14.2631.
61. Nicholls RJ. Fecal incontinence. In: Corman's colon and rectal surgery. 6th ed; Lippincott Williams & Wilkins, Philadelphia; 2014.
62. Sands DR, Wexner SD. Setting up a colorectal physiology laboratory. In: Corman's colon and rectal surgery. 6th ed; Lippincott Williams & Wilkins, Philadelphia; 2014.
63. Schouten WR, van Vroonhoven TJ. A simple method of anorectal manometry. Dis Colon Rectum. 1983; https://doi.org/10.1007/BF02554982.
64. Vela AR, Rosenberg AJ. Anorectal manometry: a new simplified technique. Am J Gastroenterol. 1982; https://doi.org/10.1111/j.1572-0241.1982.tb04853.x.
65. Carmona JA, Ortiz H, Perez-Cabañas I. Alterations in anorectal function after anterior resection for cancer of the rectum. Int J Color Dis. 1991; https://doi.org/10.1007/BF00300205.
66. Zbar AP, Jonnalagadda R, Duthie GS. Parameters of the rectoanal inhibitory reflex in different anorectal disorders [1] (mul-

tiple letters). Dis Colon Rectum. 2003; https://doi.org/10.1007/s10350-004-6601-6.
67. Yin S, Zhao K. Research progress of rectoanal inhibitory reflex. Zhonghua Wei Chang Wai Ke Za Zhi. 2015;18(12):1284–7.
68. Guinet A, Verollet D, Rufin SD, Ismael SS, Raibaut P, Amarenco G. Qualitative and quantitative analysis of rectoanal inhibitory reflex (RAIR) modulation in functional bowel disorders. Int J Color Dis. 2011; https://doi.org/10.1007/s00384-010-1105-4.
69. Wexner SD, Marchetti F, Salanga VD, Corredor C, Jagelman DG. Neurophysiologic assessment of the anal sphincters. Dis Colon Rectum. 1991; https://doi.org/10.1007/BF02049902.
70. Coller JA. Clinical application of anorectal manometry. Gastroenterol Clin N Am. 1987;16(1):17–33.
71. Jorge JMN, Wexner SD, Ger GC, Salanga VD, Nogueras JJ, Jagelman DG. Cinedefecography and electromyography in the diagnosis of nonrelaxing puborectalis syndrome. Dis Colon Rectum. 1993; https://doi.org/10.1007/BF02238594.
72. Ricciardi R, Mellgren AF, Madoff RD, Baxter NN, Karulf RE, Parker SC. The utility of pudendal nerve terminal motor latencies in idiopathic incontinence. Dis Colon Rectum. 2006; https://doi.org/10.1007/s10350-006-0529-y.
73. Hire T. Studies on anal function in continent and incontinent patients. Scand J Gastroenterol. 1974;9(suppl 24):7–55.
74. Loening-Baucke V, Metcalf AM, Shirazi S. Anorectal manometry in active and quiescent ulcerative colitis. Am J Gastroenterol. 1989;84(8):892–7.
75. Yeoh EEK, Holloway RH, Fraser RJ, et al. Anorectal dysfunction increases with time following radiation therapy for carcinoma of the prostate. Am J Gastroenterol. 2004; https://doi.org/10.1111/j.1572-0241.2004.04037.x.
76. Madoff RD, Orrom WJ, Rothenberger DA, Goldberg SM. Rectal compliance: a critical reappraisal. Int J Color Dis. 1990; https://doi.org/10.1007/BF00496148.
77. Kuijpers HC, Bleijenberg G, de Morree H. The spastic pelvic floor syndrome – large bowel outlet obstruction caused by pelvic floor dysfunction: a radiological study. Int J Color Dis. 1986; https://doi.org/10.1007/BF01648836.
78. Ott DJ, Donati DL, Kerr RM, Chen MYM. Defecography: results in 55 patients and impact on clinical management. Abdom Imaging. 1994; https://doi.org/10.1007/BF00198197.
79. Brennan D, Williams G, Kruskal J. Practical performance of defecography for the evaluation of constipation and incontinence. Semin ultrasound, CT MRI. 2008. doi:https://doi.org/10.1053/j.sult.2008.10.003.
80. Paquette IM, Bleier JIS. Anorectal physiology testing. Fundamentals of anorectal surgery; 2019. https://doi.org/10.1007/978-3-319-65966-4_3.
81. Desforges JF, Madoff RD, Williams JG, Caushaj PF. Fecal incontinence. N Engl J Med. 1992; https://doi.org/10.1056/NEJM199204093261507.
82. Rao SSC. Pathophysiology of adult fecal incontinence. Gastroenterology; 2004. https://doi.org/10.1053/j.gastro.2003.10.013.
83. Rao SSC, Patel RS. How useful are manometric tests of anorectal function in the management of defecation disorders? Am J Gastroenterol. 1997;92(3):469–75.
84. Yu SWB, Rao SSC. Anorectal physiology and pathophysiology in the elderly. Clin Geriatr Med. 2014; https://doi.org/10.1016/j.cger.2013.10.003.
85. Snooks SJ, Swash M, Setchell M, Henry MM. Injury to innervation of pelvic floor sphincter musculature in childbirth. Lancet. 1984; https://doi.org/10.1016/S0140-6736(84)90766-9.
86. Laurberg S, Swash M. Effects of aging on the anorectal sphincters and their innervation. Dis Colon Rectum. 1989; https://doi.org/10.1007/BF02562120.
87. Loening-Baucke V, Anuras S. Effects of age and sex on anorectal manometry. Am J Gastroenterol. 1985; https://doi.org/10.1111/j.1572-0241.1985.tb01974.x.
88. McHugh SM, Diamant NE. Effect of age, gender, and parity on anal canal pressures – contribution of impaired anal sphincter function to fecal incontinence. Dig Dis Sci. 1987; https://doi.org/10.1007/BF01296139.
89. Rogers J, Henry MM, Misiewicz JJ. Combined sensory and motor deficit in primary neuropathic faecal incontinence. Gut. 1988; https://doi.org/10.1136/gut.29.1.5.
90. Bharucha AO, Fletcher JG, Harper CM, et al. Relationship between symptoms and disordered continence mechanisms in women with idiopathic faecal incontinence. Gut. 2005; https://doi.org/10.1136/gut.2004.047696.
91. Miller R, Bartolo DCC, Cervero F, Mortensen NJMC. Differences in anal sensation in continent and incontinent patients with perineal descent. Int J Color Dis. 1989; https://doi.org/10.1007/BF01648550.
92. Parks AG, Swash M, Urich H. Sphincter denervation in anorectal incontinence and rectal prolapse. Gut. 1977; https://doi.org/10.1136/gut.18.8.656.
93. Kadam-Halani PK, Arya LA, Andy UU. Clinical anatomy of fecal incontinence in women. Clin Anat. 2017; https://doi.org/10.1002/ca.22951.
94. Preziosi G, Raptis DA, Raeburn A, Panicker J, Emmanuel A. Autonomic rectal dysfunction in patients with multiple sclerosis and bowel symptoms is secondary to spinal cord disease. Diseases of the colon and rectum; 2014. https://doi.org/10.1097/DCR.0000000000000048.
95. Molnar D, Taitz LS, Urwin OM, Wales JKH. Anorectal manometry results in defecation disorders. Arch Dis Child. 1983; https://doi.org/10.1136/adc.58.4.257.
96. Shouler P, Keighley MRB. Changes in colorectal function in severe idiopathic chronic constipation. Gastroenterology. 1986; https://doi.org/10.1016/0016-5085(86)90941-8.
97. Loening-Baucke VA, Kabir YM. Abnormal anal sphincter response in chronically constipated children. J Pediatr. 1982; https://doi.org/10.1016/S0022-3476(82)80637-9.
98. Varma JS, Smith AN. Neurophysiological dysfunction in young women with intractable constipation. Gut. 1988; https://doi.org/10.1136/gut.29.7.963.
99. Grotz RL, Pemberton JH, Levin KE, Bell AM, Hanson RB. Rectal wall contractility in healthy subjects and in patients with chronic severe constipation. Ann Surg. 1993; https://doi.org/10.1097/00000658-199312000-00010.
100. Rao SSC, Welcher KD, Leistikow JS. Obstructive defecation: a failure of rectoanal coordination. Am J Gastroenterol. 1998; https://doi.org/10.1111/j.1572-0241.1998.00326.x.
101. Roberts JP, Womack NR, Hallan RI, Thorpe AC, Williams NS. Evidence from dynamic integrated proctography to redefine anismus. Br J Surg. 1992; https://doi.org/10.1002/bjs.1800791140.
102. Preston DM, Lennard-Jones JE. Anismus in chronic constipation. Dig Dis Sci. 1985; https://doi.org/10.1007/BF01318172.
103. Bartolo DCC, Read NW, Jarratt JA, Read MG, Donnelly TC, Johnson AG. Differences in anal sphincter function and clinical presentation in patients with pelvic floor descent. Gastroenterology. 1983; https://doi.org/10.1016/S0016-5085(83)80231-5.
104. Atkin GK, Suliman A, Vaizey CJ. Patient characteristics and treatment outcome in functional anorectal pain. Dis Colon Rectum. 2011; https://doi.org/10.1007/DCR.0b013e318217586f.
105. Grant SR, Salvati EP, Rubin RJ. Levator syndrome: an analysis of 316 cases. Dis Colon Rectum. 1975; https://doi.org/10.1007/BF02587168.

Endoscopy

4

Matthew D. Zelhart and Brian R. Kann

Key Concepts

- Endoscopic examination is essential in the evaluation of patients with colorectal complaints and is a key component of a complete colorectal examination.
- Physical examination, anoscopy, rigid proctoscopy, and flexible sigmoidoscopy are components of the exam that can easily be performed in the office setting to evaluate complaints arising from the anus, rectum, and rectosigmoid colon.
- Colonoscopy allows for complete evaluation of the entire colon and rectum, as well as the terminal ileum.
- Multiple regimens for bowel preparation prior to colonoscopy exist, and the endoscopist should be aware of the differences. A split-dose prep has been shown to be more effective than a single-dose prep.
- The endoscopist should be familiar with sedation regimens for endoscopy, including possible adverse effects.
- A number of adjunctive maneuvers for difficult exams and alternative techniques to improve the quality of endoscopy can be employed.
- The endoscopist should be able to recognize and manage complications of endoscopic procedures and employ appropriate measures to prevent their occurrence.
- Quality measures to ensure adequacy of colonoscopic examinations include adenoma detection rate and withdrawal time.

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Introduction

The ability to safely and effectively visualize the lower gastrointestinal (GI) tract is a necessary skill for any physician caring for patients with colorectal disorders. Endoscopic evaluation of the lower gastrointestinal tract should be considered an essential extension of the physical exam. Colorectal surgeons should be both familiar and facile with all of the commonly utilized endoscopic diagnostic and therapeutic techniques.

Anorectal Examination

Prior to examining a patient with anorectal complaints, it is imperative to obtain a detailed history, as this will often lead to a presumptive diagnosis and help tailor the exam. Perhaps the most important part of the anorectal examination is to create an environment that preserves the patient's modesty and reduces anxiety. It is often preferable to speak with the new patient initially, obtain the history, establish rapport, and explain how the examination will proceed. The provider can then leave the room to have the patient disrobe and have a medical assistant/nurse position the patient appropriately before returning to the exam room.

It is essential that there be a chaperone in the room during the examination. The exam room should be well lit, ideally with a sink in the room, and have a toilet nearby (preferably in an adjoining room). A portable light source or head light should be available. Preparation and ensuring easy access to instrumentation is important, as searching or fumbling for equipment while the patient is already positioned for the exam can prove awkward.

Patient Positioning

The two most reliable positions in which to perform a thorough anorectal examination are prone jackknife and left lat-

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eral (Sim's position). The choice of position depends on availability of equipment/exam tables, patient factors such as age and mobility, and individual physicians' preference.

The prone jackknife position provides the best exposure for examination of the anorectum, but this requires a specialized proctoscopic table. The patient kneels on a padded ledge and leans forward, resting their chest and abdomen on the table; the table is then raised to an appropriate height for the examiner and angled forward, raising the buttocks upward. While sometimes awkward for the patient, this position provides for excellent visualization of the anorectum and easily facilitates office procedures such as anoscopy, proctoscopy, and hemorrhoid banding. This position should be avoided in certain situations, such as decreased mobility, recent abdominal surgery, morbid obesity, late pregnancy, and arthritic conditions affecting the knees, hips, and lower back.

The left lateral decubitus (Sim's) position is more suitable when a proctoscopic table is not available or if the aforementioned factors make the prone jackknife position difficult. The patient lies on their left side with their back close to the edge of the exam table and their hips and knees both flexed at 90°. The buttocks should extend out over the edge of the table for a short distance to allow for rotation of an anoscope if needed. Visualization is often not as good in this position as compared with the prone jackknife position, particularly in obese patients. Often, an assistant is required to retract the right buttock to improve visualization, especially in the anterior perineum.

Inspection and Palpation

Careful stepwise inspection of the perineum, anal margin, anal verge, and sacrococcygeal region should be performed before any other part of the examination. Adequate lighting is essential, and retraction of the buttocks by an assistant should be performed if necessary. Specific conditions to visually inspect for include pilonidal disease, lesions of the anal margin skin or anal verge, hemorrhoidal disease, skin irritation, maceration or excoriation, perianal dermatoses, erythema, ulceration, drainage sites, condyloma, scarring or evidence of prior anorectal surgery, purulence, fecal soiling, anal discharge, and prolapsing tissue. The appearance of the anal sphincter at rest should be noted, and an assessment of perineal body bulk in females should be performed. The presence of a patulous anus may indicate underlying incontinence or prolapse. The patient should then be asked to perform a Valsalva maneuver and assessment should be made of the degree of perineal descent and the presence of genitourinary or rectal prolapse. Lightly touching the perianal skin should provoke the anocutaneous reflex, or "anal wink." Palpation can reveal tenderness, induration, or fluctuance, which may be indicative of a suppurative process. Gentle effacement of the anal verge may reveal a fissure-in-ano. When documenting physical findings, describe the location in relation to anatomic position (anterior, posterior, right, left), as opposed to using clockface descriptors, as these depend on the position that the patient is in when examined.

Digital Rectal Examination

A great deal of information can be obtained from a properly performed digital rectal examination (DRE). Communication with the patient in regard to what to expect is key to easing any anxiety they may have about the procedure. When the patient is anxious and tense, they are more likely to be less cooperative and the exam tends to yield less useful information. Patients who are needlessly made to feel uncomfortable may be less willing to undergo future examinations. There are certain conditions in which a DRE may be omitted. These include anal fissure, thrombosed external hemorrhoids, nonreducible internal hemorrhoids, tight anal stricture, and a large anorectal mass. Common teaching has been that DRE should be avoided in the setting of neutropenia due to the risk of causing translocation of gut flora through the rectal mucosa. However, there is little data to support this, and therefore neutropenia is considered a relative contraindication to DRE.

Once there has been proper communication with the patient, a well-lubricated index finger is gently inserted past the anal verge into the anal canal. Gentle pressure on the anus prior to insertion may initiate sphincter relaxation. If resistance is met, the patient should be asked to bear down as if attempting to pass a stool, which should cause relaxation of the external anal sphincter and more easily enable insertion [1]. Once the finger is fully inserted, stepwise organized assessment should ensue. If there is stool present in the rectal vault, one should note its consistency. Assessment of resting sphincter tone should be noted upon insertion of the examining finger, and a subjective assessment of squeeze tone can be made by asking the patient to squeeze. Patients with underlying sphincter dysfunction often rely on compensatory mechanisms to maintain continence, and, when asked to squeeze, they will instinctively squeeze their buttocks and not their sphincter. In this instance, the patient often needs "coaching" in order to have them focus on squeezing their anal sphincter instead of the buttocks to make an accurate assessment of their squeeze pressure. Gentle sweeping of the finger circumferentially allows for the assessment of any intraluminal mass lesion. If a mass is present, note its size, mobility, firmness, and relationship to the anal verge, anorectal ring, and other surrounding structures. A presacral/retrorectal lesion may be palpated posteriorly. Anteriorly, assessment of the prostate gland should be performed in males, and the cervix is also often palpable in females.

Assessment for rectocele should also be performed anteriorly, and bimanual exam may be needed to fully assess the rectovaginal septum. Induration or fluctuance may be appreciated when there is infectious pathology present, and a firm "cord" may be palpated in the presence of an anal fistula. The presence of stenosis or stricturing should be noted, especially in patients who have undergone prior anorectal surgery or pelvic radiation. The patient should be asked to perform a Valsalva maneuver to allow more proximal lesions to descend to the reach of the examining finger.

Assessment of the pelvic floor can also be accomplished during DRE. Gentle pressure on the posterior anorectal ring at the level of the puborectalis may elicit discomfort, possibly indicating a pelvic pain disorder. The strength and function of these muscles can be assessed during a Valsalva maneuver and with voluntary contraction. When good function is present, the examiner should feel these muscles tighten with a voluntary contraction. When posterior pressure is placed on the puborectalis, the anal opening should "gape" before returning to a normal configuration, indicating an intact reflex pathway to the thoracolumbar spinal cord.

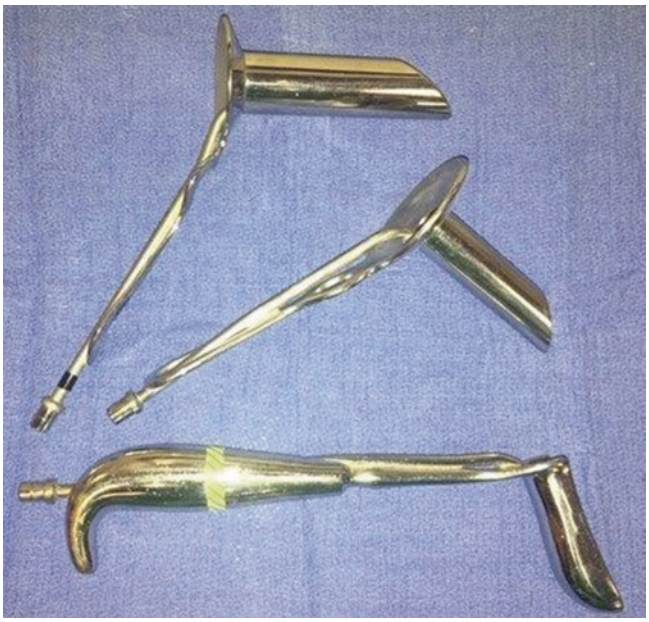

Fig. 4.1 Examples of anoscopes

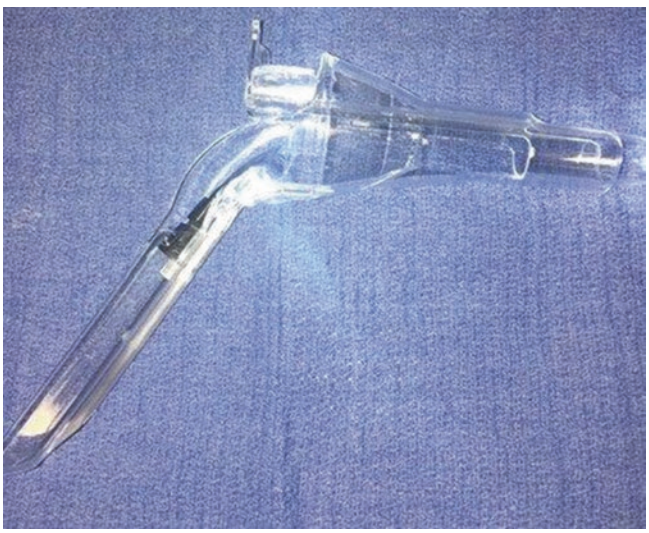

Fig. 4.2 Disposable anoscope with self-contained light source

Anoscopy

Anoscopy is a simple, inexpensive, and effective means of visualizing the anal canal and distal rectum and is an essential adjunct to the examination of the patient who presents with anorectal complaints. There may be certain clinical scenarios, such as in the presence of an anal fissure or thrombosed hemorrhoid, when anoscopy cannot be performed due to patient discomfort, but typically the procedure should be well tolerated by the patient when performed properly. The anoscope consists of the scope itself, an obturator, and a light source. Various sizes and configurations are available, both reusable and disposable (Fig. 4.1). The authors' preference is to use a disposable anoscope with a self-contained internal light source (Fig. 4.2), as opposed to an external light source connected to a reusable anoscope via a fiberoptic cord. An anoscope with a beveled or slotted end is preferred to facilitate hemorrhoidal ligation if indicated.

In most instances, having the patient prep with an enema prior to the procedure is not necessary, and sedation is not required. Once the patient has been properly positioned, and after DRE has been performed, the generously lubricated anoscope is gently inserted, using the thumb of the inserting hand to secure the obturator in place. If resistance is met, the scope should be completely withdrawn and reinserted at a slightly different angle. Once the scope has been fully advanced, the obturator is removed and visual inspection of the mucosa is performed. Prior to rotating the anoscope to inspect a new area, the obturator should be reinserted to avoid pinching or tearing the mucosa. Alternatively, the anoscope can be repeatedly removed and reinserted, moving to sequential quadrants of the anal canal, though this tends to be more uncomfortable for the patient. Pathology such as internal hemorrhoids, polyps, condyloma, mass lesions, mucosal inflammation, and hypertrophied anal papillae can be readily identified. Biopsies of abnormal mucosa or masses can be easily performed at the same setting, as can therapeutic procedures such as hemorrhoid banding or sclerotherapy. Complications of anoscopy are rare and include inadvertent tearing of the anoderm and bleeding, which usually results from a biopsy or therapeutic procedure and not the anoscopy itself.

Proctoscopy

Rigid proctoscopy is utilized for further evaluation of the anorectum up to the distal sigmoid colon and is particularly useful for determining the precise distance of a rectal lesion from the anal verge. Like anoscopy, it requires no sedation and can typically be performed in an office setting, though enemas are generally required to clear the rectum of residual stool. The standard proctoscope is 25 cm long with an outer diameter of 19 mm, though 15 mm and 11 mm scopes are also available (Fig. 4.3). The outer surface of the proctoscope is usually marked at 1 cm intervals to allow for measurements to be taken from the anal verge. An air bladder for insufflation and fiberoptic light source are required; though newer fully disposable proctoscopes have an internal self-contained light source.

Proctoscopy can be used to assess for a number of anorectal conditions, including rectal bleeding not explained by hemorrhoidal disease, proctitis, ulcers, and evaluation of rectal mass lesions. Diagnostic biopsies and simple polypectomies can be performed. Therapeutic procedures, such as topical formalin application for radiation proctitis, can also be performed, though these are typically not done in the office setting. Contraindications to proctoscopy include painful anorectal conditions such as fissure, thrombosed hemorrhoids, anal stenosis, and recent anorectal surgery. Unfortunately, with easier access to flexible endoscopy in recent years, the "art" of rigid proctoscopy has declined, and more recently trained colon and rectal surgeons are less comfortable with rigid proctoscopy.

After the patient is positioned in either the prone jackknife or left lateral decubitus position and DRE has been performed, the well-lubricated proctoscope and inner obturator are gently inserted while holding the obturator in place with the examiner's thumb, aiming the scope posteriorly toward the sacrum. Once the proctoscope passes the sphincter complex, the obturator is removed, the viewing window is closed, and air is gently insufflated to distend the rectal lumen. Direct visualization of the rectal lumen via the viewing window of the proctoscope allows for manipulation and redirection of the scope so that it can be slowly advanced. Deliberate communication with the patient is essential as the procedure is being performed. Withdrawal and redirection of the scope allow for straightening of angles and navigation around mucosal folds. Generally, the scope can be advanced to a distance of approximately 20 cm from the anal verge with minimal patient discomfort. Pain can sometimes be experienced if the tip of the scope gets caught on a mucosal fold, if the rectum becomes overdistended, or when attempting to navigate a sharp angulation. If any point the patient experiences excessive pain, the scope should be withdrawn.

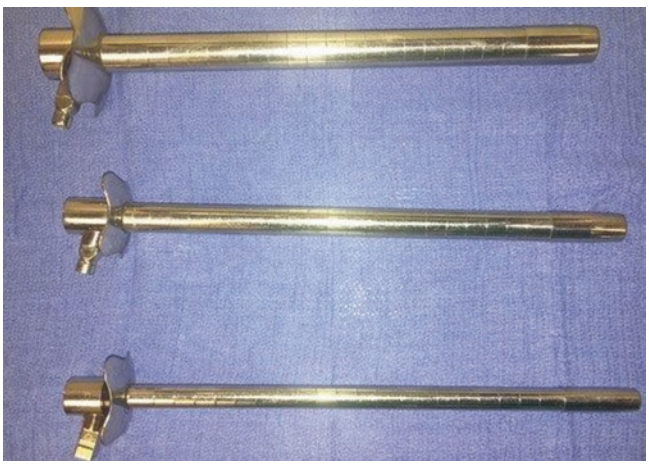

Fig. 4.3 Rigid proctoscopes

Once the proctoscope has been fully inserted, it is then slowly and deliberately withdrawn, sweeping it gently from side to side, using the tip of the scope to flatten out mucosal folds and the valves of Houston to permit thorough mucosal evaluation. Suction can be used via the proctoscope to remove residual stool or mucous. If a polyp or mass is identified, note the distance from the inferior edge of the lesion to the anal verge. Biopsies can be performed, and, with proper instrumentation, smaller lesions can be fulgurated or removed via snare polypectomy. Prior to removal of the proctoscope at the completion of the exam, the viewing window should be opened to allow for the release of any retained air.

Complications resulting from rigid proctoscopy are rare, and usually the result of an unexperienced or overaggressive endoscopist. Minor tears of the anal skin may cause pain and bleeding; mucosal trauma from the edge of the proctoscope can also result in rectal bleeding. Bleeding may occur after biopsy or polypectomy. Perforation is exceedingly rare.

Endoanal/Endorectal Ultrasound

Endoanal ultrasound (EAUS) and endorectal ultrasound (ERUS) are valuable adjuncts to the physical examination and endoscopic mucosal evaluation of the anorectum. This imaging modality allows for detailed evaluation of the anal sphincter complex, the pelvic floor, anorectal disease processes, and anorectal neoplasms. It is particularly useful in the evaluation of fecal incontinence, with sensitivity and specificity of locating a sphincter defect approaching 100% [2]. EAUS can be used to identify and characterize anal abscesses and fistulas, often with the use of hydrogen peroxide instilled via an external fistula opening [3]. ERUS is most commonly used for staging of rectal cancer, with an accuracy of 66–92% for tumor depth and 64–88% for regional nodal status [4]. In recent years, magnetic resonance imaging has largely replaced ERUS in the preoperative staging of rectal cancer [5], though ERUS may still have a role in the staging of superficial neoplasia.

Ultrasound transducers designed for transanal use allow for 360° circumferential assessment of the anal canal and distal rectum. Probes are available for two-dimensional imaging, which is generally used for evaluation of the anal sphincter, or three-dimensional imaging, which is typically used for rectal cancer staging. Transducer frequencies for transanal use range from 3 to 20 MHz. The use of higher frequencies produces a higher-resolution image but cannot penetrate deeper tissues, while lower frequencies allow for a greater depth of penetration, though the resulting image may not have the fine detail of one produced at higher frequencies.

The procedure is generally well tolerated, does not require sedation, and can easily be performed in an office or outpatient setting. An enema should be administered prior to the procedure to clear the rectum of residual waste. The patient is positioned in the left lateral decubitus position, and, after DRE is performed, the well-lubricated ultrasound probe is gently advanced to the desired depth of insertion, then withdrawn to image the distal rectum and anus. Newer transducers are held stationary while the crystal moves within the transducer housing via an automated program for image acquisition.

Highly reflective tissues with higher water content will appear hyperechoic (light) on ultrasonographic imaging, while poorly reflective tissues with less water content will appear hypoechoic (dark). When performing EAUS, the anal canal is divided into three levels based on anatomic landmarks. In the distal anal canal, only the hyperechoic external anal sphincter is visible (Fig. 4.4). In the mid-anal canal, both the hyperechoic external anal sphincter and the hypoechoic internal anal sphincter are present (Fig. 4.5). The upper anal canal is characterized by the U-shaped puborectalis muscle wrapping around the anal canal (Fig. 4.6).

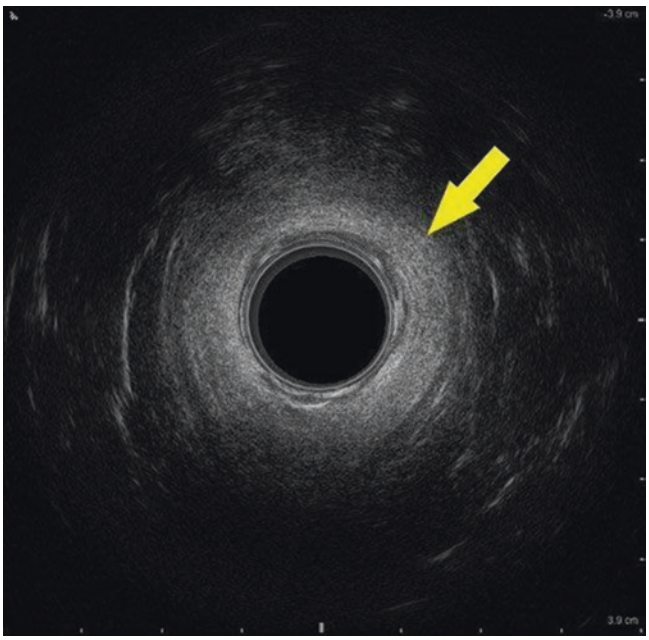

Fig. 4.4 Two-dimensional endoanal ultrasonographic appearance of the lower anal canal, highlighting the external anal sphincter (arrow)

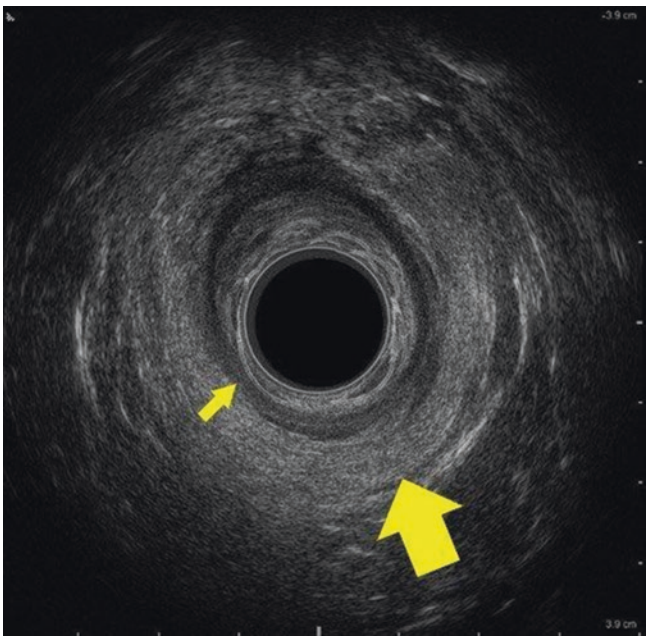

Fig. 4.5 Two-dimensional endoanal ultrasonographic appearance of the mid-anal canal, highlighting the external anal sphincter (large arrow) and the internal anal sphincter (small arrow)

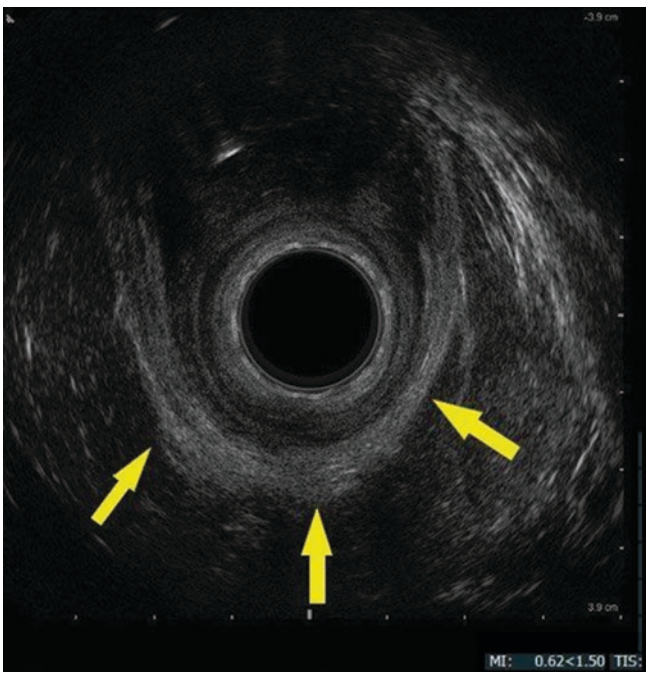

Fig. 4.6 Two-dimensional endoanal ultrasonographic appearance of the upper anal canal, highlighting the U-shaped puborectalis (arrows)

On ERUS, five distinct layers of the rectal wall can typically be seen. The innermost hyperechoic layer is the interface between the ultrasound probe and the mucosa. The next layer moving outward is the hypoechoic mucosal layer. The middle layer is the hyperechoic submucosa, followed by the hypoechoic muscularis propria. The final layer is the hyperechoic interface between the rectal wall and the perirectal fat. When a neoplasm is present, its relationship to the submucosal layer determines the ultrasonographic T-stage (uTx). A uT1 lesion invades the submucosa, whereas a uT2 lesion extends into but not through the muscularis propria. uT3 lesions extend through the muscularis propria into the perirectal fat, producing a characteristic "scalloped" appearance. uT4 lesions directly invade adjacent organs, such as the bladder or vagina.

Relative contraindications to EAUS/ERUS include anal stenosis and painful anorectal conditions. Complications are rare and usually a result of minor trauma to the anorectal mucosa or anoderm. The major advantages of EAUS/ERUS are that it is fast and easy to perform, relatively inexpensive (aside from the cost of acquiring the equipment), does not require sedation, and does not involve exposure to ionizing radiation exposure. The major disadvantage is that it is operator dependent, which raises concerns regarding reliability, reproducibility, and accuracy.

Flexible Endoscopy Techniques

A multitude of technical maneuvers are required to successfully perform flexible endoscopy. Like any invasive procedure, endoscopic technique is best "learned by doing" under the careful supervision of an experienced endoscopist. Mastery of the insertion techniques described below, used for both flexible sigmoidoscopy (FS) and colonoscopy, is essential in order to perform an efficient endoscopic examination while keeping patient discomfort and risk of harm to a minimum.

Torque

The twisting motion applied to the shaft of the scope by the endoscopist's right hand is called torque, an essential technique that allows for stiffening of the scope, changing the direction in which the angulation control knobs orient the tip of the scope. Torque can also increase the resistance of the scope to avoid formation of troublesome loops. "Gentle" torque can be used to keep the scope straight during scope advancement, and more "forceful" torque is used when removing or pushing through a loop.

Tip Deflection

Every effort should be made to keep the tip of the scope in the middle of the bowel lumen. As the scope is advanced and the tip of the scope moves away from the lumen, the endoscopist should return the tip to the center of the bowel lumen, manipulating the inner and outer directional control knobs with the left hand. Ideally, the endoscopist should be able to control and use both control knobs with only the thumb and index finger of the left hand. The goal should be to keep the right hand on the shaft of the scope and the left hand on the scope controls throughout the entire scope insertion.

Dithering/Jiggle

Rapid up-and-down, side-to-side, and to-and-fro movements of the shaft of the scope are often referred to as "dithering" or "jiggle." The objective of these maneuvers is to pleat or "accordion" the colon onto the shaft of the scope in order to shorten the length of the colon and keep the scope straight. This technique is especially useful when combined with rapid torqueing and rapid in-and-out movements of the scope.

Air Aspiration

As insufflated air accumulates in the colon during the procedure, the colon becomes distended and elongates, essentially pushing the "finishing line" further away. Judicious use of air insufflation is important during the procedure, but calculated aspiration/suction of air can be an important adjunct insertion technique. Aspiration of air can "pull" the tip of the scope around a turn of flexure without needing to push the scope forward and form a loop. Once the tip of the scope has passed the turn, advancement should be much easier due to the straightness of the colon.

Slide-By

The slide-by technique involves pushing blindly into a turn or bend with maximum tip deflection and without full visualization of the colon lumen, allowing the curvature of the bowel wall to guide the scope past the turn. This is a controversial maneuver due to the potential risk of bowel wall injury/perforation and should never be performed by unsupervised trainees or novice endoscopists. If significant resistance to forward advancement is experienced or the mucosa becomes blanched at the tip of the scope, the maneuver should be terminated immediately. In the non-sedated/minimally sedated patient, the slide-by maneuver can be very painful due to tension on the bowel mesentery. Once the slide-by maneuver has successfully passed an area of sharp angulation, the scope should be immediately straightened and any loops reduced.

Flexible Sigmoidoscopy

The use of flexible sigmoidoscopy (FS) allows for a greater length of the distal colon and rectum to be evaluated in the office setting and has become more popular due to its ease of use, improved magnification and optics, better patient tolerance, and higher yield of findings over conventional rigid proctoscopy [6]. Depending on the manufacturer, the length of the scope ranges from 60 to 71 cm and the outer diameter ranges from 12 to 14. When performed properly by an experienced endoscopist, FS has been shown to have an average depth of insertion of 40–50 cm, reaching the descending colon in 80% of examinations [7, 8], and is capable of detecting 65–75% of polyps and 50–65% of colorectal cancer [9–11]. It should be noted that FS is not an adequate substitute for screening colonoscopy, as it will not detect colonic polyps and/or neoplasms proximal to the distal transverse colon/splenic flexure.

While the flexible sigmoidoscope is easier to handle than a colonoscope and the technique is easier to learn than colonoscopy, it should only be performed by a properly trained endoscopist or a closely supervised trainee. Given that the patient is not sedated, often anxious, and bowel preparation can be suboptimal, the procedure can occasionally be challenging to perform in the office setting. The indications for FS in the office setting are numerous. FS can be used to evaluate rectal bleeding not explained by findings on anoscopy or to evaluate for suspected proctitis. It can be used to identify the level of a rectal or rectosigmoid tumor, though this is somewhat less reliable than rigid proctoscopy. FS is also an excellent tool in the evaluation of the response to neoadjuvant chemoradiation in patients with rectal cancer. Additionally, postoperative evaluation of distal anastomoses can rapidly be performed to evaluate for stricture or cancer recurrence. FS is also a useful means of monitoring for recurrence after local excision of a rectal neoplasm or in patients with a complete response to neoadjuvant chemoradiation who are in a "watch and wait" protocol.

It is advisable to give the patient one to two enemas prior to the procedure. Sedation is typically not needed, and the patient is best positioned in the left lateral decubitus position. After a proper DRE, the well-lubricated scope is gently inserted, and air should be gently insufflated to distend the rectum. As the scope is advanced, it is navigated around the valves of Houston to the rectosigmoid junction. The scope is then advanced into sigmoid colon, which sometimes requires torqueing of the scope either clockwise or counterclockwise. Care should be taken to clearly visualize the lumen of the bowel before advancing the scope. Blind "slide-by" maneuvers should be avoided in the non-sedated patient to minimize discomfort, and care should be taken to insufflate just enough air to distend the bowel enough for adequate visualization and safe advancement. The scope is then advanced under direct visualization as far as possible, generally to the level of the splenic flexure. Limitations to the depth of scope insertion include the volume of residual stool, patient discomfort, and significant sigmoid diverticular disease. Once the scope has been advanced to its fullest extent, it is then withdrawn carefully and deliberately to evaluate the entire mucosal surface. Any lesions that are identified can be biopsied. Small polyps can be removed with biopsy forceps, though removal of larger polyps may best be done during a subsequent colonoscopy when the patient has performed a full bowel preparation. Identification of polyps in the distal colon during FS should prompt the patient to undergo a full colonoscopy in order to assess for additional polyps in the proximal colon.

The most common complication after FS is abdominal pain and bloating due to overdistention and air trapping. Bleeding may occur after a biopsy or polypectomy. Fortunately, serious complications are exceedingly rare with FS. The perforation rate has been reported to be as low as 0.002% [12]. When perforation does occur, it is typically at the level of the distal sigmoid where it angulates from the fixed rectum at the sacral promontory.

Colonoscopy

Colonoscopy is essential in screening for colorectal cancer, surveillance of patients with history of colorectal neoplasia, and evaluation and management of patients with intestinal complaints. A well-performed colonoscopy allows the physician to evaluate the mucosa of the terminal ileum, colon, and rectum, with biopsy and photodocumentation of abnormal findings, as well as other therapeutic interventions. A survey of American Society of Colon and Rectal Surgeons (ASCRS) members found that more than 90% reported performing colonoscopy as part of their clinical practices, completing an average of 41 procedures per month [13]. The ability to perform a thorough colonoscopy is an essential skill for colorectal surgeons to possess, and training in colonoscopy remains an essential core component of colon and rectal surgery residency programs. The indications for colonoscopy are numerous and covered in the appropriate chapters elsewhere in this book.

Bowel Preparation

The necessity of an adequate bowel preparation prior to colonoscopy cannot be emphasized enough. Removal of all debris from the colonic lumen in order to thoroughly examine the mucosal surface remains a challenge for both the physician and the patient. Most patients describe the bowel prep prior to colonoscopy as the most unpleasant part of the pro-

cedure. The ideal bowel prep is one that is safe, highly effective and reliable, convenient, and tolerable enough that patients are not deterred from completing the prep or undergoing future procedures. Unfortunately, this has not yet been developed [14]. In spite of the development of "better tolerated" bowel preps, approximately one-quarter of colonoscopies performed in the United States and Western Europe are considered to have an inadequate quality preparation [15, 16]. Inadequate bowel preparations lead to lower adenoma detection rates (ADRs), longer colonoscopy times, repeated procedures, shorter surveillance intervals, increased cost of colorectal cancer prevention, and decreased patient satisfaction [17].

A number of commercially available bowel preparations are currently available (Table 4.1), and the choice of which agent is used is often practitioner dependent or directed by which agent a patient's health insurance will cover at the lowest cost. Currently available bowel preps fall into one of three categories: iso-osmotic, hypo-osmotic, and hyperosmotic agents.

Polyethylene glycol (PEG), an inert polymer of ethylene oxide that passes through the gastrointestinal tract without net absorption or secretion, is typically combined with electrolyte solutions to create iso-osmotic preparations. The use of such PEG-electrolyte lavage solutions (PEG-ELS) is one of the most common formulations for precolonoscopy bowel preparation and is the "gold standard" against which other bowel prep formulations are compared. Unfortunately, the large volume required to be ingested (4 L) and poor palatability limit patient compliance; up to 15% of patients are unable to complete the preparation fully [18]. A sulfate-free formulation of PEG-ELS has been developed in an attempt to improve the taste and smell, with similar efficacy and safety when compared with standard PEG-ELS [19]. Additionally, an FDA-approved low-volume (2 L) PEG-ELS prep combined with ascorbic acid has also been shown to have similar efficacy to the standard 4 L PEG-ELS with improved tolerance [20]. The "low-volume" nature of this preparation is misleading, however, as the patient is required to drink an additional 1 L of clear liquids in addition to the 2 L of prep.

The use of PEG-3350 (MiraLax®, Bayer, Whippany, NJ) combined with a commercially available electrolyte solution in the form of a sports drink (PEG-3350-SD) has been widely adopted due to its low cost and better tolerance, though it is not FDA approved for colonoscopy preparation. PEG-3350-SD, often combined with a stimulant laxative such as bisacodyl, results in intestinal catharsis through a hypo-osmotic effect. Studies comparing it with a standard 4 L PEG-ELS prep have shown conflicting results in terms of adenoma detection rates and quality of bowel prep [21–23]. One should also keep in mind that, unlike the electrolyte solutions used for prescription bowel preps, commercially available sports drinks are typically not osmotically balanced, and there have been reports of severe hyponatremia associated with the use of PEG-3350-SD as a bowel prep prior to colonoscopy.

Hyperosmotic agents, such as magnesium citrate, sodium sulfate, and sodium phosphate, are also used as components of oral bowel preparation prior to colonoscopy. Magnesium citrate is not FDA approved as a colonoscopy prep, as data regarding its effectiveness are limited, and there is significant potential for toxicity, especially in the elderly and those with kidney disease. Oral sodium sulfate has been shown to be equivalent to low-volume (2 L) PEG-ELS [24] and superior to 4 L sulfate-free PEG-ELS [25]. A major advantage of oral sodium sulfate is the lack of significant fluid and electrolyte shifts. Sodium phosphate preparations had previously been used widely and were very popular due to the smaller volume of fluid required. However, concern regarding electrolyte disturbance and acute renal failure in certain populations has limited its use. The aqueous formulation of sodium phosphate has been voluntarily withdrawn from the market. A tablet formulation of sodium phosphate is available by prescription, but this requires the patient to take 32 tablets with 2 L of water, which limits its attractiveness. An FDA box warning advises against its use in elderly patients and in those with gastrointestinal motility disorders, renal or liver disease, or congestive heart failure. Sodium phosphate has also been reported to cause mucosal inflammation and ulceration that can mimic the appearance of inflammatory bowel disease, so its use is not recommended in this patient population [26, 27]. Sodium picosulfate combined with magnesium citrate has more recently become a popular alternative as a low-volume bowel prep, combining both osmotic effects and laxative effects to cleanse the colon.

Regardless of the specific bowel preparation chosen, there is overwhelming evidence that a split-dose regimen, administering a portion (usually half) of the prep the day/evening prior to the procedure and the remaining portion of the prep the day of the procedure, results in a higher-quality prep [28–36]. A split-dose prep has also been shown to improve adenoma detection rates [37] as well as patient tolerance [32]. The second dose should be given 3–8 hours prior to the planned start of the procedure, but must be completed at least 2 hours prior to administering sedation to avoid potential aspiration, as recommended by the American Society of Anesthesiologists guidelines [38]. While 4 L PEG-ELS is FDA approved to be used in a single-dose fashion but not in a split-dose fashion, there is sufficient evidence to suggest that split-dose 4 L PEG-ELS produces the highest-quality preparations [39], and, per the Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE), is considered the current standard colonoscopy prep [39, 40].

Table 4.1 Partial list of commercially available bowel preparations

	PEG-ELS	SF-PEG-ELS	Low-volume PEG-ELS with ascorbic acid	Low-volume PEG-3350-SD	Oral sodium sulfate	Sodium picosulfate/ magnesium oxide/ anhydrous citric acid	Magnesium citrate	Sodium phosphate tablets
Brand name	GoLTYELY®	NuLYTELY®	Moviprep®	Miralax®	Suprep®	Prepopik®	Generic	Osmoprep®
Company	Braintree Laboratories (Braintree, MA)	Braintree Laboratories (Braintree, MA)	Salix Pharmaceuticals (Raleigh, NC)	Bayer (Whippany, NJ)	Braintree Laboratories (Braintree, MA)	Ferring Pharmaceuticals Inc. (Parsippany, NJ)	OTC	Salix Pharmaceuticals (Raleigh, NC)
Composition	PEG, sodium sulfate, sodium bicarbonate, sodium chloride, potassium chloride	PEG, sodium bicarbonate, sodium chloride, potassium chloride	PEG-3350, sodium sulfate, sodium chloride, ascorbic acid	PEG-3350	Sodium sulfate, potassium sulfate, magnesium sulfate	Sodium picosulfate, magnesium sulfate, anhydrous citric acid	Magnesium citrate	Sodium phosphate
Volume; recommended minimum additional fluid	4 L; None	4 L; None	2 L; 1 L clear fluid	238 g PEG-3350 in 2 L SD	12 oz; 2.5 L water	10 oz; 2 L water	20–30 oz; 2 L water	32 tablets; 2 L water
Dosing regimens[a]	*Split dose*: 2–3 L day before and 1–2 L day of procedure; *Single dose:* 4 L day before procedure	*Split dose:* 2–3 L day before and 1–2 L day of procedure; *Single dose:* 4 L day before procedure	*Split dose:* 1 L day before and 1 L day of procedure; *Single dose:* 2 L day before procedure	*Split dose:* 1 L day before and 1 L day of procedure; *Single dose:* 2 L day before procedure	*Split dose:* 6 oz OSS with 10 oz water + 32 oz water day before and 6 oz OSS with 10 oz water + 32 oz water day of procedure	*Split dose:* 5 oz Prepopik + 40 oz clear liquids day before and 5 oz Prepopik day before + 24 oz clear liquids day of procedure; *Single dose:* 5 oz Prepopik + 40 oz clear liquids the afternoon or early evening before the procedure and 5 oz Prepopik + 24 oz clear liquid 6 hours later	*Split dose:* 1–1.5 10-oz bottles day before and 1–1.5 10-oz bottles day of procedure	*Split dose:* 20 tablets day before and 12 tablets day of procedure
Comments	Poor taste; large volume; poorly tolerated; split-dose not FDA approved but considered criterion standard	More palatable than PEG-ELS	Poor taste; expensive; avoid in patients with glucose-6-phosphate dehydrogenase deficiency	Well tolerated; available OTC; not FDA approved as bowel prep; unbalanced ELS–electrolyte shifts may occur	Pleasant taste; less volume; well tolerated; expensive; avoid in patients with heart failure, renal insufficiency, end-stage liver disease, and electrolyte abnormalities	Less volume; well tolerated; expensive; avoid in patients with renal insufficiency	Avoid in patients with renal insufficiency and elderly; not FDA approved as bowel prep	Avoid in patients with heart or liver failure, renal insufficiency or risk factors for acute phosphate nephropathy, volume depletion, and patients taking ACEi or NSAIDs; not recommended for routine use

Adapted from Saltzman et al. [40] and Harrison and Hjelkrem [14]

PEG-ELS polyethylene glycol electrolyte solution, *SF* sulfate-free, *SD* sports drink, *OTC* over the counter, *OSS* oral sodium sulfate, *FDA* US Food & Drug Administration, *ACEi* Angiotensin-converting enzyme inhibitor, *NSAIDs* nonsteroidal anti-inflammatory drugs

[a]When utilizing split-dose regimen, second dose must be completed at least 2 hours prior to procedure

Special Considerations

Poor/Difficult Prep

It is not uncommon for patients to have a history of poor prior bowel preps for colonoscopy. Patients with a previous experience of inadequate preps or a history of chronic constipation are at particular risk for having a prep insufficient to undergo a thorough colonoscopy. It has been demonstrated that a low-quality bowel prep, defined as the inability to detect lesions <0.5 cm, should be followed up with an early repeat colonoscopy due to the risk of missed lesions [41]. In one study, split-dosage prep was superior to non-split prep in terms of completeness of prep and adenoma detection rates, while there was no difference between the patient having ingested a clear liquid diet and a low-residue diet prior to the prep [42].

Unfortunately, there is a paucity of literature prospectively addressing patients with a history of poor prep, leaving clinicians to individualize their practices based on clinical judgment. Many will start the prep and a clear liquid diet 2 days before the procedure. If the patient does not achieve clear bowel movements with this, then an additional osmotic or cathartic prep can still be administered the day before or the morning of the procedure. Patients with chronic constipation may also have coexisting gastroparesis or intestinal dysmotility, making it difficult to complete the bowel prep; the addition of an antiemetic agent can sometimes be helpful for this subset of patients. As a last resort, the patient can be admitted the day before the procedure to administer the prep through a nasogastric tube or endoscope.

Need for Antibiotics

Outside of scattered case reports, there is little data endorsing the need for routine prophylactic antibiotics in patients undergoing a colonoscopy. The updated 2015 ASGE guidelines recommend against the routine administration of antibiotic prophylaxis solely for prevention of infective endocarditis, as well as before GI endoscopic procedures for patients with synthetic vascular grafts, other nonvalvular cardiovascular devices, or orthopedic prosthesis. The guidelines do make the recommendation, based on low-level evidence, that patients with high-risk cardiac conditions and an established GI tract infection in which enterococci may be part of the infecting bacterial flora should receive antibiotic coverage [43].

Peritonitis in patients undergoing continuous ambulatory peritoneal dialysis can result from translocation across the bowel wall during GI endoscopic procedures. A retrospective study found that the risk of peritonitis after colonoscopy without antibiotic prophylaxis was 6.3% [44]. The ASGE guidelines suggest administration of antibiotic prophylaxis before endoscopy of the lower GI tract in patients undergoing continuous ambulatory peritoneal dialysis, though this is based on very low-level evidence [43]. The International Society for Peritoneal Dialysis (ISPD) recommends ampicillin (1 g) plus a single dose of an aminoglycoside, with or without metronidazole, given intravenously immediately before GI endoscopic procedures to lower the risk of peritonitis [45].

Anticoagulated Patient

The potential risk vs benefit of anticoagulation in a patient undergoing endoscopy can present a challenging situation for the clinician, and clinical decisions should be made in conjunction with the physician managing the anticoagulation. While procedure-related bleeding can be a tangible and often immediate event, therapeutic maneuvers can be utilized to mitigate the risk and manage post-colonoscopy bleeding. Conversely, thromboembolic events can have devastating and irreversible effects. Balancing the risks of bleeding and a thromboembolic event can be difficult.

A screening colonoscopy, even with a biopsy, is considered a low-risk procedure for bleeding and almost all anticoagulant agents can be continued. However, if a polypectomy needs to be performed, the procedure now becomes high risk. Unfortunately, this information is usually not known in advance. The ASGE recommends that for patients receiving anticoagulant therapy, the procedure should be postponed until the patient no longer has a need for anticoagulation, if it can be done safely [46].

Most guidelines do not suggest mandatory discontinuation of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) prior to diagnostic or therapeutic endoscopy, especially in patients at high risk for cardiovascular disease. If these agents are to be held, they should be discontinued at least 7 days before the procedure. Thienopyridines, such as clopidogrel, should be stopped 5–7 days before the procedure. Consideration can be given to continuing aspirin for patients on dual platelet therapy [47].

Warfarin should be discontinued 5 days prior to the procedure, and low-molecular-weight heparin should be discontinued 12 hours prior to the procedure. Factor Xa inhibitors and direct thrombin inhibitors should be discontinued 1–5 days prior to the procedure, depending on the half-life of the individual medication. When holding anticoagulant therapy, "bridging" with low-molecular-weight heparin is sometimes practiced, though one double-blinded trial demonstrated that forgoing bridging was noninferior to bridging with low-molecular-weight heparin for prevention of arterial thromboembolism, while bridging inferred a risk of major bleeding events three times that of not bridging [48].

Sedation

While there is ample literature demonstrating that colonoscopy can be performed safely and adequately in non-sedated patients [49–51], most patients who undergo colonoscopy in the Unites States are administered some form of sedation. Sedation is utilized for multiple reasons—patients prefer a favorable experience, endoscopists prefer reasonable technical conditions under which to work, and both prefer optimal patient safety and procedural outcomes [52]. Sedation can be administered by either the endoscopy team or by an anesthesia specialist, though one must keep in mind that adding anesthesia services adds substantially to the cost of these procedures. Historically, most patients received endoscopist-directed moderate sedation. However, a 2017 study using a combination of Medicare and commercial billing data demonstrated a steady increase in the utilization of anesthesia services for gastrointestinal endoscopy, rising from one-third of all patients in 2009 to about one-half of all patients in 2013 [53]. The authors estimated that this may cost as much as $1.5 billion annually in the United States. The main driver of this shift in sedation care is due to the use of propofol deep sedation.

Endoscopist-directed moderate sedation most commonly employs a combination of a benzodiazepine and an opiate. The main disadvantages of this regimen include the length of time needed to achieve adequate sedation, procedural recall, poor intra-procedural sedation, prolonged recovery, and post-procedural emesis. One study evaluating the actual depth of sedation in patients undergoing endoscopic procedures with a targeted moderate level of sedation found that 45% actually were at a level of deep sedation at least once during the procedure [54]. This demonstrates that moderate sedation is inadequate for some patients who are at risk for having a suboptimal experience or receive excessive sedation, leading to the potential for increased adverse effects. When employing moderate sedation, it is essential to have reversal agents readily available—naloxone for opioid reversal and flumazenil for benzodiazepine reversal.

Propofol is a hypnotic alkylphenol derivative that facilitates inhibitory neurotransmission mediated by gamma-aminobutyric acid (GABA), resulting in sedation, amnesia, and hypnosis. The use of propofol has proven to be more advantageous than moderate sedation in a number of variables, including rapid onset, rapid recovery, minimal post-procedural adverse effects, procedural amnesia, good procedural operating conditions, and excellent patient and provider satisfaction [55]. Propofol is traditionally reserved for use by trained anesthesia professionals for a number of reasons. It easily results in deep sedation, and patients often achieve a level of general anesthesia, defined as a lack of response to painful stimulation and frequent need for airway intervention.

Due to the increased cost associated with the requirement of an anesthesia provider to administer propofol, alternative delivery methods have been investigated. A meta-analysis published in 2015 found that the safety of non-anesthesia provider-administered propofol sedation for advanced endoscopic procedures compared favorably with anesthesia provider-administered propofol sedation, though it came at the cost of decreased patient and endoscopist satisfaction [56]. There is rapidly accumulating data to suggest that administration of propofol by registered nurses supervised by endoscopists can be performed safely [57], and there is a substantial evidence base to support the safety of endoscopist-delivered propofol protocols, demonstrating its cost-effectiveness compared with administration of propofol by anesthesia specialists. Although these protocols have been implemented successfully in some European countries, their use in the United States has been limited by financial considerations, medical–legal risk concerns, and what some feel to be nonevidence-based policies of governing organizations [58].

Instrumentation

Depending on the specific manufacturer and product specifications, colonoscopes vary in length from 133 to 170 cm (Fig. 4.7). The typical outer diameter of a standard adult colonoscope is 12.8–13.2 mm, though smaller-diameter pediatric (11.6–11.7 mm) and neonatal (9.7–9.8 mm) colonoscopes are also available. The basic colonoscope houses a suction channel, an air/water insufflation channel, fiberoptic bundles for light transmission, a biopsy port/working channel connected to the suction channel, and cables attached to the angulation control knobs (also called “wheels” or “dials”) used to deflect the tip of the colonoscope for direction change. There are specific models of colonoscopes with a

Fig. 4.7 Colonoscope

second working channel, which can be helpful for more advanced therapeutic procedures. Most modern colonoscopes also have a variable stiffness control that allows the endoscopist to vary the rigidity of the scope.

Colonoscopy Technique

Colonoscopy can be an extremely challenging skill to learn, requiring appropriate training, practice, patience, and attention to detail. A redundant/tortuous colon, angulation created by postoperative or inflammatory adhesions, and altered postoperative anatomy can create technical challenges in navigating the entire length of the colon for even the most experienced of endoscopists.

Once the patient has provided informed consent for the procedure (and separate consent for sedation if anesthesia services are being utilized) and appropriate cardiopulmonary monitoring has been instituted, he or she is positioned in the left lateral decubitus position. The colonoscope is brought from the procedure cart to the bed/stretcher, ensuring that there are no loops or twists in the scope, which will add additional tension to the inner cables. After an appropriate level of sedation is achieved, visual inspection of the anal margin/anal verge is performed, followed by DRE. The well-lubricated colonoscope is then advanced into the anus. It is helpful to double-glove the right hand, removing the outer glove after performing DRE and inserting the colonoscope, in order to avoid getting lubricant on the control body and angulation control knobs, which can make them difficult to maneuver.

Air is gently insufflated to distend the bowel lumen as the colonoscope is advanced into the rectum. There is a tendency for residual liquid to pool in the distal rectum. This should be suctioned prior to advancing the colonoscope to prevent forceful expulsion of the residual bowel contents should the patient begin coughing at any point in the procedure due to airway irritation. One should keep in mind that the suction port is located at the 5:00 position on the tip of the colonoscope. The colonoscope should be rotated so that the fluid being suctioned is located at the inferior aspect of the field of view, and the tip of the scope should be placed just above the air–fluid interface prior to suctioning. The force of suction is dependent upon how far the suction button is depressed. In order to prevent the mucosa from being drawn into the suction port and obstructing it, one should avoid full depression of the suction button for prolonged periods. Instead, repeated short periods of partial depression of the suction button followed by releasing it allows for re-distention of the lumen, preventing luminal collapse around the scope. Simultaneous air insufflation and suction can accomplish the same result.

The colonoscope is then advanced through the rectum, navigating around the valves of Houston (Fig. 4.8) to reach the rectosigmoid junction. Advancing the colonoscope past this point can be one of the more challenging areas of the colonoscopy. There is often an acute angle at this junction, especially if the sigmoid colon is redundant. If the patient has undergone prior pelvic surgery, especially hysterectomy, the sigmoid may become fixed, making negotiation of this angle even more difficult and often painful. As the colonoscope is advanced, it should be kept as straight as possible. A combination of short advancements/withdrawals with slight clockwise torque and appropriate tip deflection can help advance the scope into the sigmoid colon. Slide-by maneuvers should be avoided, if at all possible, as this is one of the most frequent sites of colonoscopic perforation.

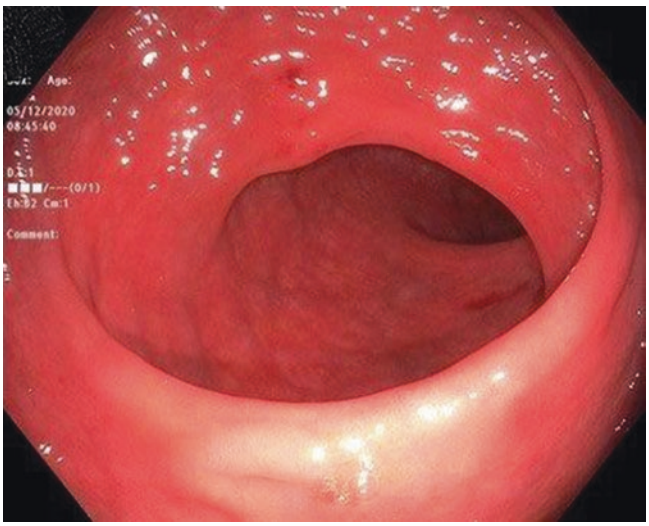

Fig. 4.8 Endoscopic appearance of the rectum, noting the three valves of Houston

Once the colonoscope is advanced into the sigmoid colon, any loops should be reduced, using tip deflection and torque. If loop reduction is not possible, the scope can be carefully inserted farther into the sigmoid, "pushing through the loop," as long as there is minimal resistance and it does not cause the patient excessive discomfort. Keep in mind that this may elicit a vasovagal response with bradycardia—if this occurs, the colonoscope should be withdrawn to reduce the loop.

The sigmoid colon is the most tortuous segment of the colon and is associated with high muscular tone, frequent spasm, and a higher incidence of diverticulosis (Fig. 4.9). The sigmoid colon lacks fixation and can be quite redundant and elongated. A number of techniques can be required to successfully navigate this portion of the colon, including insertion/pull back, jiggle, and torque (usually clockwise), allowing for the sigmoid colon to "accordion" over the scope, advancement of the scope, and prevention of further loop formation.

Large diverticula, when present, can be mistaken for the true bowel lumen. Careful advancement of the colonoscope through a sigmoid colon riddled with diverticula requires patient, frequent use of pull-back techniques to gain a better appreciation of the true colonic lumen. As the scope is

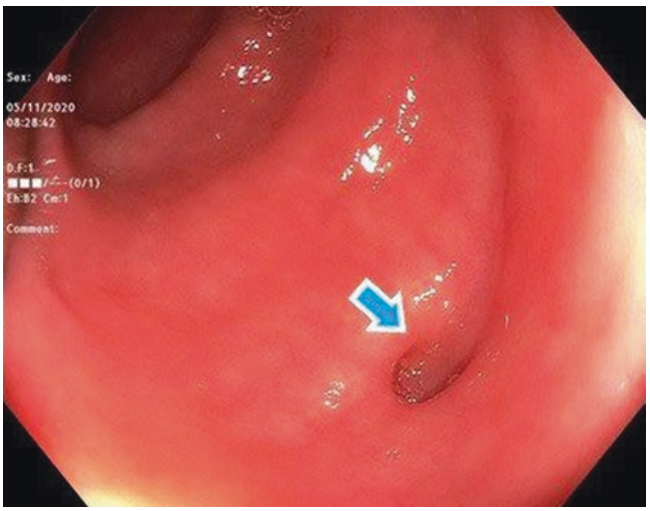

Fig. 4.9 Endoscopic appearance the sigmoid colon, noting diverticulum (arrow)

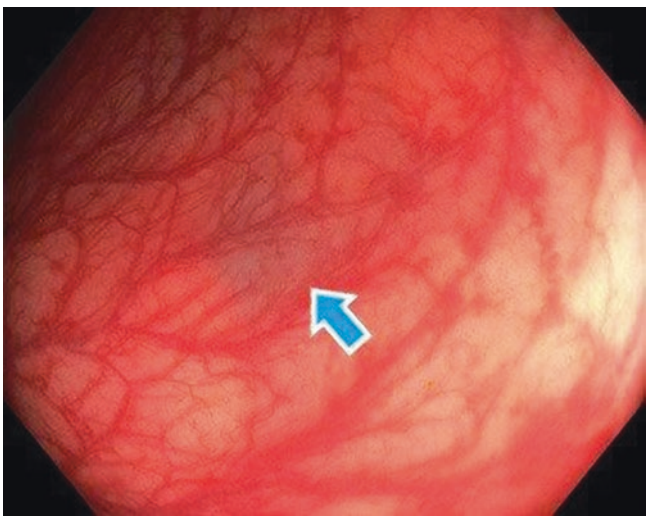

Fig. 4.10 Endoscopic appearance of the spleen (arrow) visible through the colonic wall at the splenic flexure

advanced, one should strive to keep it as straight as possible to prevent loop formation.

Passage of the colonoscope from the sigmoid colon into the descending colon is usually evident, as the descending colon is typically much straighter and less muscular than the sigmoid colon. Once the descending colon is reached, any remaining loops should be reduced with withdrawal and torqueing maneuvers. If there are no loops present, the colonoscope should be easily advanced from this point to the splenic flexure, which can sometimes be identified by the blue shadow of the spleen seen through the wall of the colon (Fig. 4.10) and/or pooling of fluid. Negotiating the splenic flexure is often a simple maneuver, requiring minimal tip deflection and torque. Other times, the splenic flexure may be a complex series of turns and twists in multiple planes, requiring tip deflection, torque, and push/pull techniques.

Once the colonoscope traverses the splenic flexure, the lumen of the transverse colon takes on a characteristic triangular appearance formed by the taenia coli (Fig. 4.11). The transverse colon can also be quite redundant, and the midpoint may descend down into the pelvis where it can become fixed by adhesions, especially following pelvic surgery. Loops are commonly created during this part of the exam, and external pressure on the abdominal wall assists advancement.

As the transverse colon is traversed, the hepatic flexure can be recognized by visualizing the blue shadow from the liver, especially in thinner patients (Fig. 4.12), as well as pooling of liquid. If the hepatic flexure is especially acute,

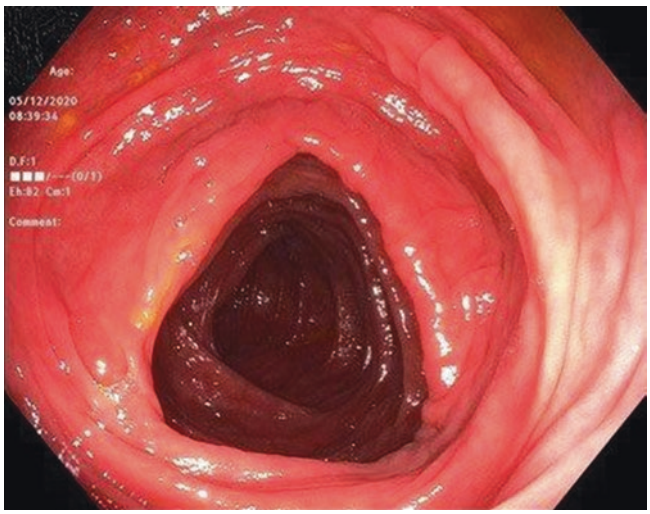

Fig. 4.11 Endoscopic appearance of the transverse colon, noting the triangular lumen

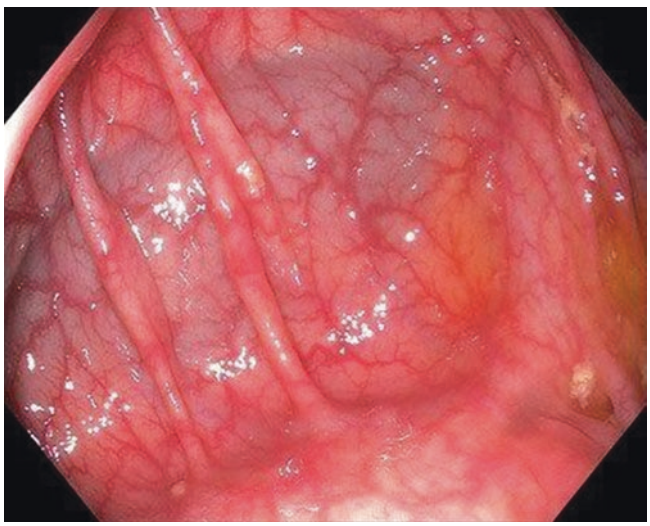

Fig. 4.12 Endoscopic appearance of the liver visible through the colonic wall at the hepatic flexure

the novice endoscopist often mistakes this "fool's cecum" for the true cecum. One should use tip deflection to negotiate this area of particularly sharp angulation. Occasionally, it is necessary to gently push through a loop to advance the colonoscope into the ascending colon and then reduce the loop, at which point withdrawing the scope often will result in paradoxical advancement of the tip of the colonoscope toward the cecum. Another maneuver is to use intermittent suction to draw the tip of the scope down toward the cecum once the colonoscope has made the initial turn around the hepatic flexure. Transitioning the patient from the lateral decubitus position to supine position and the use of external abdominal pressure can also be useful adjuncts in getting the colonoscope to advance to the cecum.

The ileocecal valve marks the junction between the ascending colon and the cecum. The appearance of the valve can be highly variable—it may be visible simply as a fold at the base of the ascending colon, as a polypoid-like yellowish mass with a lipomatous appearance, as a visible lumen opening into the terminal ileum, or it may be completely hidden (Fig. 4.13a–c). When the valve is not easily identified, the presence of gas bubbles or enteric contents flowing from it can assist with its identification.

A complete colonoscopic examination is ensured only when the cecum has been clearly and indisputably cannulated. This base of the cecum is characterized by a "crow's foot" appearance, caused by the muscular arrangement of the colonic wall coalescing around the appendiceal orifice (Fig. 4.14). Identification and photodocumentation of the ileocecal valve and appendiceal orifice (and terminal ileum if intubated) is mandatory for quality assurance of a complete examination. Trans-illumination of the scope through the right-lower-quadrant abdominal wall or endoscopic visualization of external pressure on the right-lower-quadrant abdominal wall is not a reliable indicator that the cecum has been cannulated and should never be used as a substitute for clear visualization of anatomic landmarks. Detailed evaluation of the entire cecum is essential, including the recess behind the ileocecal valve, where it is easy to miss small, flat lesions.

While intubation of the ileocecal valve to visualize the terminal ileum is an essential component of a colonoscopy in patients with inflammatory bowel disease or in a search for obscure gastrointestinal bleeding, the exact role of routine visualization of the terminal ileum during all colonoscopies is not clear. One study in which routine terminal ileal intubation was attempted in over 1300 consecutive patients found that it was successfully performed in 90.2% of cases, but clinically significant findings in asymptomatic patients were found in only 3.3% of cases [59]. Another retrospective study of over 6400 patients who had terminal ileal intubation performed at the time of screening colonoscopy found gross endoscopic abnormalities in 1% and pathologic abnormalities in 0.3%, calling into question the need for routine terminal ileal intubation [60]. Others have argued that, because asymptomatic small bowel lesions with potential for significant consequences such as terminal ileal carcinoid tumors can be identified, routine ileoscopy should be performed with all colonoscopies [61].

While the routine performance of routine ileocecal valve cannulation is somewhat controversial, it is a skill that all endoscopists must possess, and the ability to expertly per-

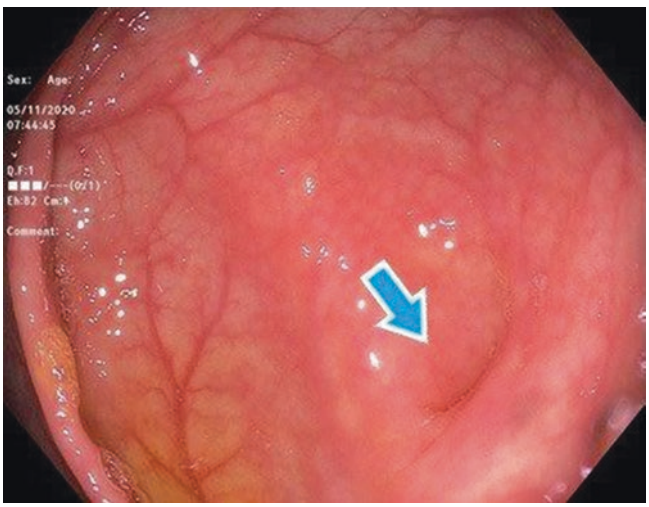

Fig. 4.14 Endoscopic appearance of the appendiceal orifice (arrow)

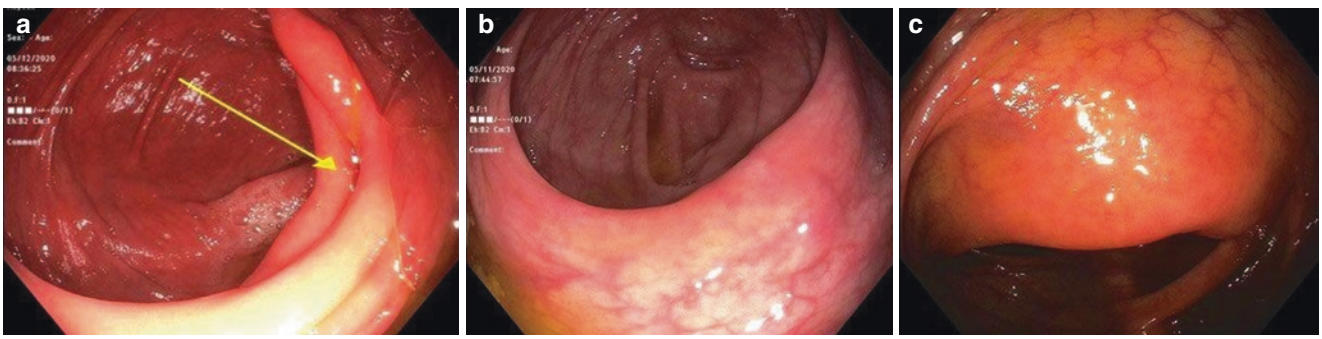

Fig. 4.13 (**a**–**c**) Varied endoscopic appearances of the ileocecal valve

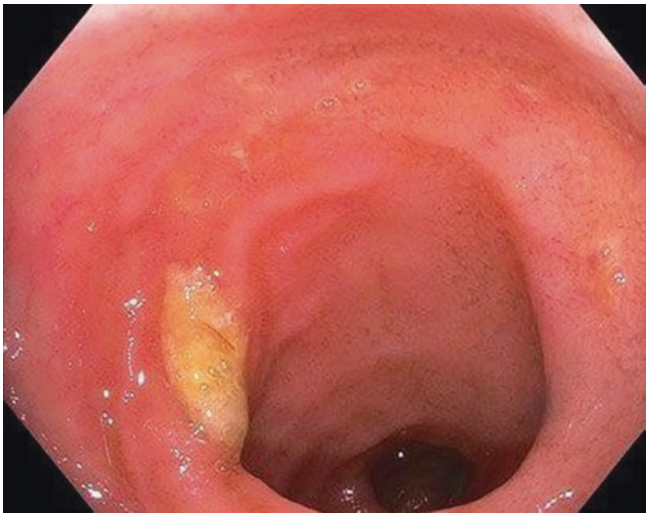

Fig. 4.15 Endoscopic appearance of the terminal ileum, noting the granular-appearing mucosa

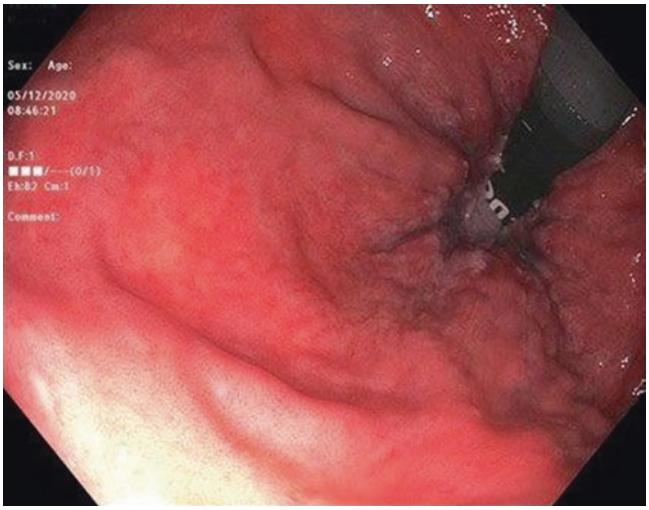

Fig. 4.16 Retroflexed view of the distal rectum

form the maneuver improves with practice. Before attempting to intubate the ileocecal valve, one must first ensure that all loops have been reduced. With a gentle curve in the end of the colonoscope, the edge of the ileocecal valve is then "hooked," and the scope is then gently advanced into the lumen of the terminal ileum. Terminal ileal intubation serves as additional confirmation of a complete colonoscopy in the rare instances where identification of the appendiceal orifice and ileocecal valve is ambiguous.

The terminal ileal mucosa has a much different appearance than colonic mucosa, easily recognizable by its granular appearance and its increased motility (Fig. 4.15). Multiple lymphoid follicles, especially in younger patients, may resemble small polyps. The scope should be advanced as far as it can be without difficulty, taking care to use minimal air insufflation in order to avoid overdistention of the small intestine. Biopsies should be obtained as clinically indicated.

Once the full extent of insertion has been reached, the colonoscope is then slowly and methodically withdrawn, taking care to fully examine the colon for mucosal lesions. It is sometimes helpful to lock one of the angulation control knobs to minimize extraneous movement of the tip of the colonoscope as it is withdrawn. Residual debris should be irrigated and pools of fluid should be suctioned. Care should be taken to evaluate behind mucosal folds when possible; the tip of the colonoscope can often be used to flatten out or splay mucosal folds to look behind them as the scope is withdrawn. There is some controversy as to the practice of routine retroflexion once the colonoscope has been withdrawn into the rectum (Fig. 4.16). Though it has been shown that the use of routine rectal retroflexion does not increase the detection of clinically important neoplasia [62], it can sometimes be helpful in evaluation for sources of anorectal bleeding. Retroflexion of the colonoscope can cause discomfort in incompletely sedated patients, superficial mucosal trauma resulting in post-procedural bleeding, and, in very rare cases, rectal perforation.

Alternative Techniques

Carbon Dioxide Insufflation

Carbon dioxide insufflation has rapidly gained popularity in the setting of endoscopy. Carbon dioxide is absorbed through the gut mucosa much faster than air and expelled through the respiratory system, offering several advantages [63]. Because of rapid absorption, the bowel does not remain distended for long periods of time. If a combined laparoscopic and endoscopic procedure is being performed, insufflated carbon dioxide will be absorbed quickly, allowing for less bowel distention and more working room for the surgical part of the procedure. This is especially evident in surgical procedures performed on patients with incompetent ileocecal valves, who would otherwise be prone to massive small bowel distention, which would limit the field of view during laparoscopy. Additionally, patient comfort during and after colonoscopy has been reported to be improved with the use of carbon dioxide insufflation [64–66].

Water Insufflation

Water insufflation can be another helpful adjunct during difficult colonoscopies. In this technique, water is instilled into the colonic lumen to distend it without the use of air insufflation. This technique has been shown to decrease pain and loop formation. It can also facilitate stabilization of the colon wall during endoscopic resection of large polyps.

However, there is a higher rate of incomplete colonoscopy with the utilization of this technique [67]. While data on water insufflation are mixed, a recent comparative study between carbon dioxide and water insufflation showed that the use of water insufflation was associated with a higher adenoma miss rate [68].

Chromoendoscopy

Chromoendoscopy utilizes a dye (typically 0.5–1% indigo carmine) injected through the colonoscope with the use of a spray catheter to coat the colonic mucosa in order to create more contrast and enhance the visualization of the mucosa [69]. This aids the endoscopist in delineating areas of dysplasia and improves assessment of glandular structure and pit patterns. This technique is especially beneficial in the setting of surveillance in patients with inflammatory bowel disease, where dysplastic lesions tend to be flatter and less conspicuous [70, 71]. The use of chromoendoscopy during screening colonoscopies has also shown improved detection of flat adenomas, though it comes at the expense of a longer procedure time [72].

Narrow Band Imaging

Narrow band imaging (NBI) uses a filter that narrows the green and blue wavelengths and eliminates the red wavelength from standard white light. This enhances the visualization of superficial mucosal structures, especially microcapillaries [73]. Adenomas demonstrate increased vascularity and appear brown against a blue-green background of normal mucosa. Serrated polyps, which are often hypovascular, appear pale against the background of normal mucosa under NBI [74]. The use of NBI has been shown to result in a higher adenoma detection rate when compared to normal white light endoscopy [73]. NBI has also been shown to demonstrate similar yield for detection of ulcerative colitis-associated neoplasia when compared with chromoendoscopy [75, 76].

Full-Spectrum Endoscopy

Full-spectrum endoscopy (FUSE) is a system with coupled lenses mounted to each side of the colonoscope tip, projected externally to multiple viewing screens next to each other. This permits observation up to a 330-angle field of view during colonoscopy in an effort to decrease adenoma miss rate. This was designed to be of particular benefit in areas that are typically difficult to fully visualize. Initial studies demonstrated a decreased adenoma miss rate [76], but subsequent studies have shown mixed results [77]. The cost of the system had been a significant rate-limiting factor in its adoption.

Difficult Exams

Occasionally, even the most experienced of endoscopists will encounter difficult exams that require the use of adjunctive maneuvers, such as abdominal pressure and positional changes. The use of overtubes has mostly ceased due to the advent of adjustable stiffness endoscopes. The most common reason for a difficult examination is the formation of a loop, which makes further advancement of the scope impossible, painful, and potentially harmful, and these adjunctive maneuvers are meant to reduce loop formation or to prevent loops from reforming once they have been reduced. When these techniques fail, one should consider withdrawing the scope back to the rectosigmoid and resuming the procedure.

Changing Patient Position

While colonoscopy typically begins in the left lateral decubitus position, transitioning to a supine position may sometimes ease the navigation of a difficult sigmoid colon. It can also aid in advancing the scope from the ascending colon to the cecum when there is significant backstream looping of the scope. Alternatively, if the patient begins supine, shifting to the left lateral decubitus position can help to achieve the same goal. While done rarely, turning the patient to their right side is another technique that can be useful when the examination has reached the ascending colon and it cannot be advanced into the cecum. Moving to a prone position can also be helpful, though this is difficult to perform in an already sedated patient and requires particular attention to patient safety.

Abdominal Pressure

The technique of applying external pressure via the abdominal wall by an assistant to splint redundant areas of the colon can assist significantly in reduction of loop formation. This technique is most effective when there is a known loop present and the endoscopist can properly guide the assistant to apply pressure at the correct location. The most common areas of looping are the sigmoid and transverse colon, though applying pressure to different areas of the abdominal wall can help determine where the problem lies. A loop in an extremely redundant loop of sigmoid may actually be located on the right side of the abdomen. The effectiveness of abdominal pressure is dependent on the skill of the assistant. Initial pressure aimed at the sigmoid colon should be applied superior and to the right of the umbilicus and directed toward the left lower quadrant. Abdominal pressure should be applied in a gradual fashion to avoid rapid changes in intra-abdominal pressure.

Rotating the Scope

During the navigation of a difficult or acute angulation of the bowel lumen, it may be helpful to change the entire angle of approach of the scope, which can be accomplished by torqueing the shaft and rotating it 180° while keeping the tip of the scope centered in the middle of the bowel lumen using the deflection knobs.

Incomplete Colonoscopy

Every effort should be made to complete a colonoscopy to the cecum to ensure the detection of right-sided lesions. However, rates of incomplete colonoscopy range from 4% to 25%, for a variety of reason [78]. After an incomplete colonoscopy, the patient still needs a complete examination of the portion of the colon that was not visualized, and the strategies for managing incomplete colonoscopies are varied.

Sometimes a colonoscopy cannot be completed simply due to an inadequate prep. If this is the case, the reasons for the poor prep should be elucidated, a strategy to ensure an adequate patient preparation should be formulated as discussed earlier, and repeat colonoscopy should be attempted. If feasible, the patient can be kept on a liquid diet following the failed colonoscopy, given additional prep that evening, and undergo an attempt at repeat colonoscopy the following day. In the setting of a poor prep, the imaging studies below are not likely to be of benefit; if the prep is not good enough to permit a colonoscopy, it certainly will not be sufficient for diagnostic imaging.

For patients who had an incomplete colonoscopy due to inability to achieve cecal intubation, multiple modalities can be applied. The means of sedation can be altered with the help of anesthesia, smaller- or larger-caliber colonoscopes can be used, and carbon dioxide or water insufflation can be utilized. For instances where there are difficult loop formations, fluoroscopy or a scope guidance system can be utilized to aid the endoscopist in the detection and prevention of loop formation [79]. Advancements in balloon endoscopy have been expanded to be used in colonoscopy to assist with difficult procedures [80]. In situations where one unexpectedly encounters an obstruction that cannot be traversed, further evaluation should ensue, understanding that patient will likely need surgery or some other intervention, at which time simultaneous colonoscopy to evaluate the proximal colon can be performed.

Traditionally, double-contrast barium enema (DCBE) was performed for patients who had an incomplete colonoscopy despite utilization of the above measures. The use of DCBE in this setting has been largely replaced by the use of computed tomography (CT) colonography (or "virtual colonoscopy"), which has been shown to be more sensitive than double-contrast barium enema [81]. CT colonography has been shown to have a sensitivity of 96% for detection of colorectal cancer, 67–94% for detection of advanced adenomas ≥1 cm, and 73–98% for detection of advanced adenomas ≥6 mm [82]. Disadvantages of CT colonography include the need for another bowel prep and distention of the colon with insufflated room air or carbon dioxide in a non-sedated patient, which can be uncomfortable. In a patient who is undergoing a difficult colonoscopy, aborting the colonoscopy and proceeding directly with CT colonography, if it is available, is a good strategy to save the patient from re-prepping. However, one recent study suggests that CT colonography for incomplete colonoscopy is suboptimal compared with having the patient undergo a repeat colonoscopy by an "expert endoscopist" [83]. Due to concerns about the risk of radiation exposure in patients who have undergone multiple CT scans, magnetic resonance (MR) colonography, previously used mainly in the evaluation of inflammatory bowel disease, is now also being utilized for polyp detection [84].

Complications

More than 15 million colonoscopies are done each year in the Unites States [85], the vast majority of which occur without complications. However, colonoscopy is an invasive procedure, one that is difficult to master, and complications that can impart significant harm on the patient are possible. Preprocedural discussion with the patient should address the specific risks involved, highlighting the fact that, in the vast majority of cases, the benefit of having the procedure performed far outweighs the risks. Complications can be related to the bowel preparation prior to the procedure, sedation during the procedure, or events that occur during the procedure itself.

Complications Due to Bowel Preparation

In the past, one of the most commonly encountered complications of bowel preparation was nephrocalcinosis and renal failure associated with the use of sodium phosphate preparations, resulting in their removal as an option [86]. The most common complication associated with the more commonly used PEG solutions is nausea and vomiting, which can on occasion be a sign of upper gastrointestinal pathology [87]. Aspiration is a risk in elderly patients and those with gastroparesis. As previously mentioned, electrolyte abnormalities can occur with the use of non-osmotically balanced electrolyte solutions, though these are rarely of clinical significance.

Complications Due to Anesthesia/Sedation

An administrative claims data review published in 2016 revealed that 34% of colonoscopies were conducted with

anesthesia services and that the use of anesthesia services was associated with a 13% risk of any complication within 30 days, including perforation, hemorrhage, abdominal pain, complications specific to anesthesia, and stroke [88]. Procedural sedation should be performed in a closely monitored setting, with continuous pulse oximetry and cardiac monitoring. Oversedation can lead to respiratory depression and hypoxia as well as hypotension. Patients with underlying cardiac conditions may be particularly sensitive. Propofol specifically has been shown to suppress cardiac output and can lead to systemic hypotension [89]. Vasovagal reactions can occur in up to 16% of cases [90], though this is typically due to overdistention of the bowel or traction of the bowel and mesentery due to looping of the colonoscope. Upon recognition of a vasovagal episode, air should be aspirated endoscopically from the colonic lumen, and loops should be reduced. Most vasovagal episodes are self-limited and require no specific pharmacologic management. True cardiac arrhythmias during colonoscopy are quite uncommon and usually result from electrolyte disturbances from bowel preparation and hypovolemia; the vast majority are self-limited and require no specific intervention [91].

While it has been shown that, with good technique, colonoscopy is associated with severe pain in only 10% of examinations [92], there is a tendency to be liberal with procedural sedation due to patient anxiety. Oversedation can mask suboptimal technique, leading to increased risk of procedural complications such as perforation, particularly in patients with redundant or tortuous colons or those who have adhesions from prior surgical intervention. Intra-procedural aspiration can also occur with oversedation due to the patient's inability to protect the airway; applying abdominal pressure or repositioning the patient supine may increase the risk of aspiration, and particular care should be undertaken with patients with known gastroparesis or gastrointestinal dysmotility. A large population-based cohort administrative database study from Canada showed that anesthesia assistance for outpatient colonoscopy was associated with an increased risk of aspiration pneumonia (odds ratio [OR], 1.63; 95% confidence interval [CI], 1.11–2.37) [93].

Procedural Complications

Perforation

While perforation during a colonoscopy is an extremely rare event, most endoscopists will unfortunately encounter this distressing complication at some point in their careers. Colonic perforation is probably the most serious of complications that can occur during colonoscopy and can impart devastating consequences on the patient. The impact on the endoscopist's psyche should not be underestimated as well. The exact incidence of colonoscopic perforation is difficult to estimate. Older studies have reported an incidence of 0.012–0.8% for diagnostic examinations and up to 5% for therapeutic colonoscopies [94, 95]. A more recent systematic review found the pooled prevalence of perforation during all colonoscopies to be 0.05% and the perforation rate of colonoscopy with polypectomy to be 0.08% [96].

Colonoscopic perforation can result from direct trauma from the colonoscope, overdistention and barotrauma, or as a result of a therapeutic intervention, such as polypectomy or dilation. The sigmoid colon is the most common site of perforation from direct trauma, accounting for 64–74% of perforations [97, 98]. Direct trauma rarely occurs from the tip of the scope actually puncturing the colon. This most commonly occurs during "slide-by" maneuvers when attempting to navigate severe angulations of the colon, particularly at the rectosigmoid junction, or if the scope is inadvertently and forcefully advanced through a diverticulum. Direct mechanical trauma from the colonoscope most commonly occurs from "sideways" pressure or "bowing" of the scope on the bowel wall far proximal to the end of the scope while trying to push through a redundant or fixed loop of colon. Risk factors for traumatic perforation during colonoscopy include severe diverticular disease with muscular hypertrophy and luminal narrowing, severe inflammatory bowel disease, colonic ischemia, and a history of prior abdominopelvic surgery. When these risk factors are present, care should be taken to ensure that colonoscope insertion is gentle and not rushed, that the lumen of the colon is clearly visualized before advancing the scope, and that loops are reduced; the use of a pediatric scope can also facilitate safe completion of the exam in high-risk patients.

Perforation due to overdistension and barotrauma accounts for up to 35% of colonoscopic perforations [99] and typically occurs in the more proximal, thin-walled ascending colon and cecum, often after prolonged attempts to navigate a difficult segment of colon. The more recent adoption of carbon dioxide insufflation is thought to be protective in terms of avoiding barotrauma due to its rapid absorption. Proximal barotrauma can also occur following colonoscopic stent placement for a near-obstructing distal lesion. In these instances, the proximal colon is already distended and potentially ischemic prior to the procedure. With attention on addressing the obstructing distal lesion, the endoscopist can easily lose sight of how much additional intraluminal air is being insufflated during a potentially prolonged procedure, putting the patient at risk for perforation.

Abandoning a difficult colonoscopy should not be looked upon as a "failure." While cecal intubation rates are scrutinized and looked upon as a quality measure, the consequences of a colonoscopic perforation cannot be overemphasized. Colonoscopists should have better acceptance of an incomplete examination [94] and not put the patient at unnecessary risk for the sake of pride or ego.

Identification of colonoscopic perforations may be evident during the procedure, as demonstrated by the appearance of a traumatic defect in the wall of the colon or visualization of extracolonic fat. Severe abdominal pain immediately following the procedure is a common presentation of perforation. When perforation is suspected, an upright abdominal film should be obtained immediately to evaluate for pneumoperitoneum, as an overdistended, non-perforated colon with significant air trapping can result in significant abdominal pain that can mimic peritonitis. If plain films are equivocal, computed tomography can be helpful. In general, perforations identified during or immediately after colonoscopy have a better prognosis than those with delayed recognition, less frequently requiring surgical intervention [100–102].

Management of colonoscopic perforation is determined by the etiology of the perforation and the patient's clinical condition. Diffuse peritonitis is clearly an indication for emergent exploration. If the patient requires operative intervention, laparoscopic exploration is generally felt to be safe unless there are specific contraindications. If the bowel prep for the colonoscopy was adequate, there is minimal peritoneal contamination, and the patient is hemodynamically stable intraoperatively, either open or laparoscopic primary repair of a small defect or resection with primary anastomosis is acceptable [97, 103, 104]. In the setting of a perforation complicating a therapeutic colonoscopy in which the patient does not have peritonitis and is clinically stable, attempted nonsurgical management with bowel rest and intravenous (IV) antibiotics is reasonable. Success rates with nonoperative management range from 33% to 90% [105]. Endoscopic treatment via placement of clips is possible when the perforation site is recognized intra-procedurally or in the immediate post-procedural period [106], with a success rate of 59–100% [107–110]. Of note, complication rates and lengths of hospital stay are significantly higher in patients who have undergone delayed surgery after failed conservative management than in patients who were initially treated with surgery [111].

Bleeding

Post-polypectomy bleeding is one of the most common serious complications following colonoscopy, occurring in 0.3–6.1% of cases [112, 113]. Bleeding after diagnostic colonoscopy is quite rare (0.3%) [114] and usually follows biopsy. Immediate post-polypectomy bleeding is usually evident and can typically be immediately managed endoscopically with the use of mechanical clips and/or direct cautery, with or without the use of dilute epinephrine injection [115, 116]. Delayed post-polypectomy bleeding can occur up to a week or longer post-procedure and can be quite alarming to the patient, highlighting the fact that patients should be given instructions outlining how to proceed if they do experience post-polypectomy bleeding.

Risk factors for post-polypectomy bleeding include polyp size (>2 cm), thick stalk, right colon location, resumption of antithrombotic/anticoagulant therapy, cardiovascular disease, and hypertension [116, 117]. Watabe et al. reported that polyps larger than 10 mm were at a 4.5-fold greater risk for post-polypectomy bleeding than smaller ones. They also found that the incidence of post-polypectomy bleeding was 0.4% for polyps smaller than 10 mm, 1.6% for those 10–19 mm, 3.8% for those 20–29 mm, and 5.3% for those larger than 29 mm [118]. Patients on anticoagulant therapy are at a higher risk for post-polypectomy bleeding, though this risk is not seen with aspirin, NSAIDs, or other antiplatelet therapies [119–121]. "Hot biopsy" utilizing electrocautery has been employed in order to minimize the risk of post-polypectomy bleeding. However, hot biopsy is felt to be just as likely, if not more likely, to result in post-polypectomy bleeding [113], as the zone of coagulation produced by hot biopsy cautery is directed downward into the submucosa, where it can damage the wall of submucosal arteries, leading to delayed bleeding [94].

Management of post-polypectomy bleeding begins with resuscitation if the patient has sustained significant hemorrhage and is unstable. If the bleeding continues, the patient should be given a rapid bowel prep and have repeat colonoscopy performed, during which endoscopic maneuvers as described above are typically employed. Alternatively, angiographic embolization may be employed [122]. Surgery is almost never required.

Post-polypectomy Syndrome

Post-polypectomy syndrome refers to a constellation of symptoms, including abdominal pain, fever, and leukocytosis, without radiographic evidence of colonic perforation, that occur following a colonoscopic polypectomy. The symptoms are thought to be caused by a transmural burn to the bowel wall, resulting from the use of electrocautery, with localized peritonitis without radiographic evidence of colonic perforation. The incidence of post-polypectomy syndrome ranges from 0.003% to 0.1% of all colonoscopies [123]. This rate increases to approximately 1% after endoscopic mucosal resection (EMR) and up to 7–8% after endoscopic submucosal dissection (ESD) [124].

Patients typically present 1–5 days following colonoscopy with fever and pain with localized peritoneal signs. The clinical picture often mimics perforation, aside from the absence of free air on radiographic studies. This entity is usually managed with IV fluids, broad-spectrum antibiotics, and bowel rest until symptoms subside [125]; surgical intervention is almost never necessary. In rare instances, the transmural burn can progress to a full-thickness perforation. On CT images, patients with post-polypectomy syndrome demonstrate severe mural thickening with a stratified enhancement pattern, a mural defect filled with fluid, surrounding infiltration, and the absence of extraluminal air [126].

Splenic Injury

Splenic injury during colonoscopy is surprisingly rare, especially given the sharp angulation of the splenic flexure and the close approximation of the colon to the spleen. The reported incidence is estimated at 1 in 100,000 procedures [127], though the true incidence is likely much higher due to unreported cases. A systematic review published in 2016 identified 172 reported cases [128]. This injury typically results from traction on the wall of the colon avulsing the splenocolic ligament. The most typical pattern of injury is a subcapsular hematoma [129], though splenic rupture with frank hemoperitoneum and hemorrhagic shock can be seen as well. In the aforementioned systematic review, splenic injuring during colonoscopy was seen more frequently in females (70.8% of reported cases) and in patients who had undergone prior abdominopelvic surgeries (63.8% of reported cases) [128]. While the tenets of nonsurgical management parallel those for blunt splenic injury in the surgical trauma literature, the majority of patients ultimately require operative intervention, though splenic artery embolization has been successfully employed and seems to be gaining favor in hemodynamically stable patients [128, 130, 131].

Infectious Complications

Colonoscopy has been associated with bacteremia in 2–4% of patients [132] and the risk of infectious complications is felt to be significantly less. Reports of infective endocarditis are exceedingly rare, and prophylaxis for "high-risk" cardiac conditions is recommended at the endoscopist's discretion [133]. The risk of introduction of an infectious agent via a contaminated colonoscope is estimated at 1 in 1.8 million [94]. The most commonly transmitted organisms are *Salmonella*, *Pseudomonas*, and *Mycobacterium* [134]. It is thought that the ability of these organisms to form biofilms on the inner channel surfaces contributes to their ability to persist in spite of decontamination [135]. Transmission of *Klebsiella*, *Enterobacter*, *Serratia*, and hepatitis B and hepatitis C has also been reported [136]. The endoscopist should have a working knowledge of the process of scope cleaning and processing, and endoscopy units should employ vigorous infection control measures.

The Endoscopy Unit

Endoscope Processing

Recent endoscopy-associated outbreaks of multidrug resistant organisms have infected patients and even resulted in death. While these have been associated mostly with contaminated duodenoscopes, it has renewed the focus on endoscope processing and cleaning [137]. In fact, the infection rate of 1 infection per 1.8 million procedures reported by the ASGE in 1993 is now felt to be closer to 1 in 276,000 [138]. Lapses in instrument reprocessing are felt to be one of the main contributing factors.

The Centers for Disease Control and Prevention (CDC) recommends a multistep process for reprocessing scopes. Precleaning should take place immediately after the procedure to prevent biofilm; testing for any leaks in the device should also be done at this time. Manual cleaning with a high-level disinfectant should then be performed to remove any organic debris. This includes brushing and flushing of all ports and channels. A final visual inspection should be completed prior to the instrument being properly stored. This cleaning process is most often facilitated by use of an automated endoscope processor. Surveillance culturing to monitor endoscopes after reprocessing is recommended by a majority of organizations [139].

A recent cost analysis showed that reprocessing and repair costs per colonoscopy range from $101 at high-volume centers to $280 at low-volume centers. Factoring in new infection concerns, repair costs, and high per procedure costs, multiple organizations have begun exploring the finances of disposable flexible endoscopes [140].

Efficiency

Resource allocation and staff scheduling are incredibly complex burdens for every hospital and endoscopy center. Over-utilization and under-utilization both increase lost revenue, patient dissatisfaction, and staff burnout. Managing endoscopy suite efficiency continues to gain importance as health care resources continue to become more strained and limited. Many strategies for assessment of individual endoscopy units have been promoted, but the most important factor appears to be implementation of at least one strategy to increase efficiency of individual units [141].

Discrete event simulation (DES) is a process that was originally developed for the manufacturing industry but is now used by multiple health care centers to evaluate and improve efficiency. One endoscopy center reported utilizing DES to improve efficiency by running multiple software scenarios using patent data from five randomly chosen days and found that for maximum efficiency, they needed eight pre-procedure rooms and nine recovery rooms for their five-suite endoscopy center [142].

DES has also been used to demonstrate the negative financial consequences of "no-show" patients. Berg et al. reported that, for a 24-slot appointment day in an outpatient endoscopy suite, perfect attendance would result in a net gain of $4433.32, while a no-show rate of 18% would contribute to a daily loss of $725.42; the authors suggested implementing a practice of overbooking to offset costs of no-shows [143]. Another study simply added a nursing

phone call to the patient 7 days prior to the procedure, which was found to decrease the no-show rate from 16.5% to 12.8%, saving the institution $43,173 annually after costs were subtracted [144].

Overall endoscopy suite efficiency can also be hampered when other specialists are needed for the procedure, notably anesthesia. It has been shown that scheduling individual blocks for particular cases that require anesthesia increased efficiency over utilization of a standard block for a designated period of the day, in which anesthesia was only utilized as needed [145].

Quality Measures

With the increase in the number of annually performed colonoscopies in the United States and an ever-increasing focus on quality of care, metrics for ensuring the quality of screening colonoscopies has become a topic of increased interest. Ideal quality measurements should include a feasibly measured, clinically significant endpoint that is difficult to artificially manipulate [146]. Current quality measures for colonoscopy include cecal intubation rate, photodocumentation, screening intervals, bowel preparation quality, withdrawal time, and adenoma detection rate (ADR). The majority of data collected regarding colonoscopic quality has been focused on withdrawal time and ADR.

Withdrawal Time

The US Multi-Society Task Force (USMSTF) first recommended withdrawal time as a quality metric in 2002, using a benchmark of at least 6 minutes for screening colonoscopies not requiring biopsy or other maneuvers [147]. More recent studies have suggested that a withdrawal time of 9 minutes increases detection of both adenomas and serrated lesions [148].

The main disadvantage with the use of withdrawal time as a quality metric is that it can be easily manipulated. There can be pressure to artificially prolong the withdrawal time by a number of manipulations so as to not have a quality fallout. These include incorrectly noting the time of cecal intubation and initiation of withdrawal, repeated evaluation of the same section of colon multiple times, or simply "parking" the scope in the rectum until the desired withdrawal time has been documented. These maneuvers clearly do not increase the endpoint of adenoma or malignancy detection, yet on paper maintain an illusion of quality.

Adenoma Detection Rate

Adenoma detection rate (ADR) is the fraction of patients who are 50 years or older undergoing first-time primary screening colonoscopies and who have one or more adenomas detected. It is an excellent quality measure due to lack of confounding factors and ease of data collection. Further, it is a better measure of quality of the actual endoscopist, as patient compliance and pathological disagreements are not a substantial factor. Current ADR benchmarks are ≥30% for male patients, ≥20% for female patients, and ≥25% for a mixed male/female population [149].

The use of ADR as a quality measure provides optimal features when compared to other pathological detection rates. The use of malignancy detection rates as a quality measure negates the screening potential of the colonoscopy and is a much less commonly seen entity on which to collect data. The use of polyp detection rates, which includes all polyps, not just adenomas, can be manipulated by retrieving benign polyps such as hyperplastic polyps or other mucosal abnormalities that do not contribute to colorectal malignancy.

The use of ADR as a quality measure does have some drawbacks. Currently there are strict criteria limiting the data collection to patients over 50 and including only the first colonoscopy. Some argue that expanding the criteria to all screening colonoscopies, regardless of patient age, and including subsequent screening colonoscopies at 10 years would increase the data available to create a better metric.

The use of ADR as a quality measure also can create some incentive to only collect one polyp per colonoscopy and to rush through the remainder of colonoscopy after the first polyp is detected. This, combined with the fact that endoscopists are typically only reimbursed for one polypectomy per colonoscopy, may potentially disincentivize the endoscopist to closely examine the entire colon after the first polypectomy is performed [150]. These drawbacks have pushed some to evaluate the use of adenomas per colonoscopy (APC) as a quality measure. This measurement would reward careful examination of the entire colon and help to eliminate factors that promote the aforementioned "one-and-done" behavior [151].

Leasing vs Purchasing Endoscopy Equipment

Many surgeons and hospital administrators struggle with the decision regarding whether to purchase or lease medical equipment. It is a complex decision that involves credit, cash-on-hand, contraction negotiations, and many other additional factors in addition to the actual equipment and physician preferences.

Purchasing equipment has some advantages. Equity is maintained in the equipment and the value after depreciation belongs to the owner. Over the long term, this can potentially translate to cost-savings. Additionally, the concept of a "one-and-done" negotiation can be much more appealing to unit directors than the prospect of renegotiating contracts every few years. Once the final purchase price has been negotiated

and paid, the transaction is complete. However, a major drawback to this approach is that the cost of expensive repairs will eventually fall upon the endoscopy unit once warrantees expire.

Leasing endoscopic equipment has become an increasingly popular alternative to many physicians and hospital administrators. Leasing contracts can be constructed for variable time periods, allowing endoscopy units to replace older equipment with newer, up-to-date equipment more regularly. For endoscopists just entering practice or newer endoscopy facilities, leasing contracts can also be set up so that there are no payments (or minimal payments) for a set time period to allow cash flow to build up.

While leasing has the distinct disadvantage of not maintaining equity, other advantages can make it an attractive option. Most busy endoscopists cannot afford for their medical equipment to be sent out for repairs, which can be costly, take significant time, and result in lost revenue. Most leasing contracts will bring in replacement equipment while repairs are being made, and maintenance of endoscopy equipment is typically built into the lease and warranty. Even more importantly, with the ever-increasing pace of change in endoscopic technology, the endoscopist can ensure that they are regularly upgrading to the most up-to-date equipment.

Clearly, there are a multitude of factors to consider when making a decision regarding procurement of new equipment. Rapidly changing technology and financial risks should be at the forefront of the thought process. However, long-term financials may not be as clear cut when weighing the two options, as uncertain procedural volumes, varied compensation by third-party payors, warranty lengths, unpredictable costs of repairs, and tax write-off considerations make long-term costs difficult to discern.

Training and Simulation

How to safely and adequately train medical personnel in endoscopy has been a topic of debate for some time. There has been an abundance of literature focused on the training of gastroenterology fellows, but until recently there has been a paucity of studies addressing endoscopy training and surgical residents. When comparing first- and third-year gastroenterology fellows, it has been shown that competence improved throughout training, but an independent completion rate of 90% was not obtained until after 500 colonoscopies were performed [152]. This volume of colonoscopies would be quite burdensome for the average surgical resident. Additionally, making comparisons between gastroenterology and surgery trainees regarding procedural competency volumes can be somewhat misleading, due to underlying differences between baseline procedural comfort and dexterity across the trainees in both specialties.

While colonoscopy has long been a part of the practice of colon and rectal surgeons, according to the American Board of Surgery (ABS), endoscopy is now becoming a much more common procedure for the average general surgeon in practice. An increasing focus has been put on training both general surgery and colon and rectal surgery residents in becoming proficient at endoscopy. It should be obvious to those involved in resident training that performance of an arbitrary number of procedures alone does not translate to proficiency [153]. To improve resident training in endoscopy, the ABS has created a Flexible Endoscopy Curriculum (FEC). Beginning with the 2017–2018 graduating year, before becoming board eligible in General Surgery, graduating residents are required to complete the ABS FEC, which includes Fundamentals of Endoscopic Surgery (FES) certification. The FES program, developed by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), is a comprehensive educational and assessment tool designed to teach and evaluate the fundamental knowledge, clinical judgment, and technical skills required in the performance of basic GI endoscopy [154]. Similar in design to the Fundamentals in Laparoscopic Surgery (FLS) Curriculum, it consists of a multiple-choice question exam and a five-part manual skills exam using a Virtual Reality endoscopy platform (GI Mentor II).

The changes in requirements have stimulated residency programs around the country to reevaluate how they provide training in endoscopy. The Accreditation Council for Graduate Medical Education (ACGME) residency review committee's minimum case requirement for colonoscopy for General Surgery is 50, and for colon and rectal surgery is 140, of which 30 must be interventional. Again, it should be emphasized that achieving the minimum case numbers is not synonymous with achieving proficiency.

While the use of simulation may help to add familiarity and comfort with the endoscopic equipment and develop baseline dexterity skills, it will never be able to replace experience on an actual patient. Teaching endoscopy is a challenge for many surgical educators as they are used to being able to "assist" in the operating room and to physically aid a trainee through a difficult step or situation. Teaching in endoscopy does not lend itself well to this type of teaching. When difficulty is encountered or patient safety is threatened, the supervisor must often take over the procedure, resulting in a lost learning opportunity for the trainee.

To combat these difficult hurdles in training, many surgical training programs have created dedicated endoscopic training blocks, comprised of both simulation and clinical experience. A standard scale has also been developed to help with evaluator and training variability. This Global Assessment of Gastrointestinal Endoscopic Skills (GAGES) scale can be used to provide specific feedback to trainees and track their improvement and proficiency throughout the training process (Fig. 4.17) [155].

GAGES - COLONOSCOPY SCORESHEET

GLOBAL **A**SSESSMENT OF **G**ASTROINTESTINAL **E**NDOSCOPIC **S**KILLS

SCOPE NAVIGATION **SCORE** ☐

Reflects navigation of the GI tract using tip deflection, advancement/withdrawal and torque

5 Expertly able to manipulate the scope in the GI tract autonomously
4
3 Requires verbal guidance to completely navigate the lower GI tract
2
1 Not able to achieve goals despite detailed verbal guidance requiring takeover

USE OF STRATEGIES **SCORE** ☐

Examines use of patient positions, abdominal pressure, insufflation, suction and loop reduction to comfortably complete the procedure

5 Expert use of appropriate strategies for advancement of the scope while optimizing patient comfort
4
3 Use of some strategies appropriately, but requires moderate verbal guidance
2
1 Unable to utilize appropriate strategies for scope advancement despite verbal assistance

ABILITY TO KEEP A CLEAR ENDOSCOPIC FIELD **SCORE** ☐

Utilization of insuffilation, suction and/or irrigation to maximize muscosal evaluation

5 Used insufflation, suction, and irrigation optimally to maintain clear view of endoscopic field
4
3 Requires moderate prompting to maintain clear view
2
1 Inability to maintain view despite extensive verbal cues

INSTRUMENTATION (if applicable; leave blank if not applicable) **SCORE** ☐

Random biopsy: targeting is assessed by asking the endoscopist to take another biopsy from the identical site. Targeted instrumentation: evaluation is based on ability to direct the instrument to the target.

5 Expertly directs instrument to desired target
4
3 Requires some guidance and/or multiple attempts to direct instrument to target
2
1 Unable to direct instrument to target despite coaching

QUALITY OF EXAMINATION **SCORE** ☐

Reflects attention to patient comfort, efficiency. and completeness of mucosal evaluation

5 Expertly completes the exam efficiently and comfortably
4
3 Requires moderate assistance to accomplish a complete and comfortable exam
2
1 Could not perform a satisfactory exam despite verbal and manual assistance requiring takeover of the procedure

Fig. 4.17 Global Assessment of Gastrointestinal Endoscopic Skills scoresheet. (Reused with permission from Vassiliou et al. [155])

Summary

The ability to perform a complete and thorough endoscopic evaluation of the patient with colorectal complaints is essential. This should be considered an extension of the physical exam and not a separate entity. The knowledge, techniques, and skills required to perform an endoscopic examination safely and competently should be within the armamentarium of the colon and rectal surgeon, and surgeons should continue to be actively engaged in the testing, training, and advancement of endoscopic techniques and technology.

References

1. Farmer KC, Church JM. Open sesame: tips for traversing the anal canal. Dis Colon Rectum. 1992;35(11):1092–3.
2. Deen KI, et al. Anal sphincter defects. Correlation between endoanal ultrasound and surgery. Ann Surg. 1993;218(2):201–5.
3. Navarro-Luna A, et al. Ultrasound study of anal fistulas with hydrogen peroxide enhancement. Dis Colon Rectum. 2004;47(1):108–14.
4. Schaffzin DM, Wong WD. Endorectal ultrasound in the preoperative evaluation of rectal cancer. Clin Colorectal Cancer. 2004;4(2):124–32.
5. MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. BMJ. 2006;333(7572):779.
6. Winnan G, et al. Superiority of the flexible to the rigid sigmoidoscope in routine proctosigmoidoscopy. N Engl J Med. 1980;302(18):1011–2.
7. Lehman GA, Buchner DM, Lappas JC. Anatomical extent of fiberoptic sigmoidoscopy. Gastroenterology. 1983;84(4):803–8.
8. Gillespie PE, et al. Colonic adenomas – a colonoscopy survey. Gut. 1979;20(3):240–5.
9. Tedesco FJ, et al. Diagnostic implications of the spatial distribution of colonic mass lesions (polyps and cancers). A prospective colonoscopic study. Gastrointest Endosc. 1980;26(3):95–7.
10. Lieberman DA, Smith FW. Screening for colon malignancy with colonoscopy. Am J Gastroenterol. 1991;86(8):946–51.
11. Johnson DA, et al. A prospective study of the prevalence of colonic neoplasms in asymptomatic patients with an age-related risk. Am J Gastroenterol. 1990;85(8):969–74.
12. Atkin WS, et al. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. Lancet. 2002;359(9314):1291–300.
13. Kann BR, et al. The importance of colonoscopy in colorectal surgeons' practices: results of a survey. Dis Colon Rectum. 2006;49(11):1763–7.
14. Harrison NM, Hjelkrem MC. Bowel cleansing before colonoscopy: balancing efficacy, safety, cost and patient tolerance. World J Gastrointest Endosc. 2016;8(1):4–12.
15. Harewood GC, Sharma VK, de Garmo P. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. Gastrointest Endosc. 2003;58(1):76–9.
16. Froehlich F, et al. Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: the European Panel of Appropriateness of Gastrointestinal Endoscopy European multicenter study. Gastrointest Endosc. 2005;61(3):378–84.
17. Cohen LB. Advances in bowel preparation for colonoscopy. Gastrointest Endosc Clin N Am. 2015;25(2):183–97.
18. Marshall JB, et al. Prospective, randomized trial comparing sodium phosphate solution with polyethylene glycol-electrolyte lavage for colonoscopy preparation. Gastrointest Endosc. 1993;39(5):631–4.
19. DiPalma JA, Marshall JB. Comparison of a new sulfate-free polyethylene glycol electrolyte lavage solution versus a standard solution for colonoscopy cleansing. Gastrointest Endosc. 1990;36(3):285–9.
20. Ell C, et al. Randomized trial of low-volume PEG solution versus standard PEG + electrolytes for bowel cleansing before colonoscopy. Am J Gastroenterol. 2008;103(4):883–93.
21. Hjelkrem M, et al. MiraLAX is not as effective as GoLytely in bowel cleansing before screening colonoscopies. Clin Gastroenterol Hepatol. 2011;9(4):326–332 e1.
22. McKenna T, et al. Colonoscopy preparation: polyethylene glycol with Gatorade is as safe and efficacious as four liters of polyethylene glycol with balanced electrolytes. Dig Dis Sci. 2012;57(12):3098–105.
23. Shieh FK, et al. MiraLAX-Gatorade bowel prep versus GoLytely before screening colonoscopy: an endoscopic database study in a community hospital. J Clin Gastroenterol. 2012;46(10):e96–e100.
24. Di Palma JA, et al. A randomized clinical study evaluating the safety and efficacy of a new, reduced-volume, oral sulfate colon-cleansing preparation for colonoscopy. Am J Gastroenterol. 2009;104(9):2275–84.
25. Rex DK, et al. A randomized clinical study comparing reduced-volume oral sulfate solution with standard 4-liter sulfate-free electrolyte lavage solution as preparation for colonoscopy. Gastrointest Endosc. 2010;72(2):328–36.
26. Zwas FR, et al. Colonic mucosal abnormalities associated with oral sodium phosphate solution. Gastrointest Endosc. 1996;43(5):463–6.
27. Rejchrt S, et al. A prospective, observational study of colonic mucosal abnormalities associated with orally administered sodium phosphate for colon cleansing before colonoscopy. Gastrointest Endosc. 2004;59(6):651–4.
28. Abdul-Baki H, et al. A randomized, controlled, double-blind trial of the adjunct use of tegaserod in whole-dose or split-dose polyethylene glycol electrolyte solution for colonoscopy preparation. Gastrointest Endosc. 2008;68(2):294–300; quiz 334, 336.
29. Aoun E, et al. A randomized single-blind trial of split-dose PEG-electrolyte solution without dietary restriction compared with whole dose PEG-electrolyte solution with dietary restriction for colonoscopy preparation. Gastrointest Endosc. 2005;62(2):213–8.
30. Cohen LB. Split dosing of bowel preparations for colonoscopy: an analysis of its efficacy, safety, and tolerability. Gastrointest Endosc. 2010;72(2):406–12.
31. El Sayed AM, et al. A randomized single-blind trial of whole versus split-dose polyethylene glycol-electrolyte solution for colonoscopy preparation. Gastrointest Endosc. 2003;58(1):36–40.
32. Kilgore TW, et al. Bowel preparation with split-dose polyethylene glycol before colonoscopy: a meta-analysis of randomized controlled trials. Gastrointest Endosc. 2011;73(6):1240–5.
33. Marmo R, et al. Effective bowel cleansing before colonoscopy: a randomized study of split-dosage versus non-split dosage regimens of high-volume versus low-volume polyethylene glycol solutions. Gastrointest Endosc. 2010;72(2):313–20.
34. Matro R, et al. Efficacy of morning-only compared with split-dose polyethylene glycol electrolyte solution for afternoon colonoscopy: a randomized controlled single-blind study. Am J Gastroenterol. 2010;105(9):1954–61.
35. Park JS, et al. Quality and effect of single dose versus split dose of polyethylene glycol bowel preparation for early-morning colonoscopy. Endoscopy. 2007;39(7):616–9.
36. Park SS, et al. Efficacy and tolerability of split-dose magnesium citrate: low-volume (2 liters) polyethylene glycol vs. single- or split-dose polyethylene glycol bowel preparation for morning colonoscopy. Am J Gastroenterol. 2010;105(6):1319–26.
37. Gurudu SR, et al. Increased adenoma detection rate with system-wide implementation of a split-dose preparation for colonoscopy. Gastrointest Endosc. 2012;76(3):603–8. e1
38. American Society of Anesthesiologists Committee. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. Anesthesiology. 2011;114(3):495–511.
39. Enestvedt BK, et al. 4-Liter split-dose polyethylene glycol is superior to other bowel preparations, based on systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2012;10(11):1225–31.

40. Saltzman JR, et al. Bowel preparation before colonoscopy. Gastrointest Endosc. 2015;81(4):781–94.
41. Clark BT, Rustagi T, Laine L. What level of bowel prep quality requires early repeat colonoscopy: systematic review and meta-analysis of the impact of preparation quality on adenoma detection rate. Am J Gastroenterol. 2014;109(11):1714–23; quiz 1724.
42. Tariq H, et al. Evaluation of the combined effect of factors influencing bowel preparation and adenoma detection rates in patients undergoing colonoscopy. BMJ Open Gastroenterol. 2019;6(1):e000254.
43. Khashab MA, et al. Antibiotic prophylaxis for GI endoscopy. Gastrointest Endosc. 2015;81(1):81–9.
44. Yip T, et al. Risks and outcomes of peritonitis after flexible colonoscopy in CAPD patients. Perit Dial Int. 2007;27(5):560–4.
45. Piraino B, et al. ISPD position statement on reducing the risks of peritoneal dialysis-related infections. Perit Dial Int. 2011;31(6):614–30.
46. Zuckerman MJ, et al. ASGE guideline: the management of low-molecular-weight heparin and nonaspirin antiplatelet agents for endoscopic procedures. Gastrointest Endosc. 2005;61(2):189–94.
47. Feagins LA. Management of anticoagulants and antiplatelet agents during colonoscopy. Am J Med. 2017;130(7):786–95.
48. Douketis JD, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. N Engl J Med. 2015;373(9):823–33.
49. Cataldo PA. Colonoscopy without sedation. Dis Colon Rectum. 1996;39(3):257–61.
50. Takahashi Y, et al. Sedation-free colonoscopy. Dis Colon Rectum. 2005;48(4):855–9.
51. Yörük G, et al. Colonoscopy without sedation. Turk J Gastroenterol. 2003;14(1):59–63.
52. Trummel JM, Chandrasekhara V, Kochman ML. Anesthesia for colonoscopy and lower endoscopic procedures. Anesthesiol Clin. 2017;35(4):679–86.
53. Predmore Z, et al. Anesthesia service use during outpatient gastroenterology procedures continued to increase from 2010 to 2013 and potentially discretionary spending remained high. Am J Gastroenterol. 2017;112(2):297–302.
54. Patel S, et al. Deep sedation occurs frequently during elective endoscopy with meperidine and midazolam. Am J Gastroenterol. 2005;100(12):2689–95.
55. Singh H, et al. Propofol for sedation during colonoscopy. Cochrane Database Syst Rev. 2008;(4):CD006268.
56. Goudra BG, et al. Safety of non-anesthesia provider-administered propofol (NAAP) sedation in advanced gastrointestinal endoscopic procedures: comparative meta-analysis of pooled results. Dig Dis Sci. 2015;60(9):2612–27.
57. Chen SC, Rex DK. Review article: registered nurse-administered propofol sedation for endoscopy. Aliment Pharmacol Ther. 2004;19(2):147–55.
58. Rex DK. Endoscopist-directed propofol. Gastrointest Endosc Clin N Am. 2016;26(3):485–92.
59. Meral M, et al. Is ileocecal valve intubation essential for routine colonoscopic examination? Eur J Gastroenterol Hepatol. 2018;30(4):432–7.
60. Kennedy G, et al. Routine ileal intubation during screening colonoscopy: a useful maneuver? Surg Endosc. 2008;22(12):2606–8.
61. Ten Cate EM, et al. Post-surgical surveillance of locally advanced ileal carcinoids found by routine ileal intubation during screening colonoscopy: a case series. J Med Case Rep. 2014;8:444.
62. Saad A, Rex DK. Routine rectal retroflexion during colonoscopy has a low yield for neoplasia. World J Gastroenterol. 2008;14(42):6503–5.
63. Kim SY, et al. Comparison of carbon dioxide and air insufflation during consecutive EGD and colonoscopy in moderate-sedation patients: a prospective, double-blind, randomized controlled trial. Gastrointest Endosc. 2017;85(6):1255–62.
64. Memon MA, et al. Carbon dioxide versus air insufflation for elective colonoscopy: a meta-analysis and systematic review of randomized controlled trials. Surg Laparosc Endosc Percutan Tech. 2016;26(2):102–16.
65. Sajid MS, et al. Carbon dioxide insufflation vs conventional air insufflation for colonoscopy: a systematic review and meta-analysis of published randomized controlled trials. Color Dis. 2015;17(2):111–23.
66. Wu J, Hu B. The role of carbon dioxide insufflation in colonoscopy: a systematic review and meta-analysis. Endoscopy. 2012;44(2):128–36.
67. Rabenstein T, Radaelli F, Zolk O. Warm water infusion colonoscopy: a review and meta-analysis. Endoscopy. 2012;44(10):940–51.
68. Anderson JC, et al. Comparing adenoma and polyp miss rates for total underwater colonoscopy versus standard CO2: a randomized controlled trial using a tandem colonoscopy approach. Gastrointest Endosc. 2019;89(3):591–8.
69. Ribeiro MD, Soares J. Chromoendoscopy. Endoscopy. 2009;41(1):93.
70. Har-Noy O, et al. Chromoendoscopy, narrow-band imaging or white light endoscopy for neoplasia detection in inflammatory bowel diseases. Dig Dis Sci. 2017;62(11):2982–90.
71. Iannone A, et al. Chromoendoscopy for surveillance in ulcerative colitis and Crohn's disease: a systematic review of randomized trials. Clin Gastroenterol Hepatol. 2017;15(11):1684–1697.e11.
72. Kahi CJ, et al. High-definition chromocolonoscopy vs. high-definition white light colonoscopy for average-risk colorectal cancer screening. Am J Gastroenterol. 2010;105(6):1301–7.
73. Atkinson NSS, et al. Narrow-band imaging for detection of neoplasia at colonoscopy: a meta-analysis of data from individual patients in randomized controlled trials. Gastroenterology. 2019;157(2):462–71.
74. Rastogi A, et al. High accuracy of narrow band imaging without magnification for the real-time characterization of polyp histology and its comparison with high-definition white light colonoscopy: a prospective study. Am J Gastroenterol. 2009;104(10):2422–30.
75. Bisschops R, et al. Chromoendoscopy versus narrow band imaging in UC: a prospective randomised controlled trial. Gut. 2018;67(6):1087–94.
76. Gralnek IM, et al. Standard forward-viewing colonoscopy versus full-spectrum endoscopy: an international, multicentre, randomised, tandem colonoscopy trial. Lancet Oncol. 2014;15(3):353–60.
77. Hassan C, et al. Full-spectrum (FUSE) versus standard forward-viewing colonoscopy in an organised colorectal cancer screening programme. Gut. 2017;66(11):1949–55.
78. Ridolfi TJ, Valente MA, Church JM. Achieving a complete colonic evaluation in patients with incomplete colonoscopy is worth the effort. Dis Colon Rectum. 2014;57(3):383–7.
79. Chen Y, et al. Magnetic endoscopic imaging vs standard colonoscopy: meta-analysis of randomized controlled trials. World J Gastroenterol. 2013;19(41):7197–204.
80. Teshima CW, et al. Single-balloon-assisted colonoscopy in patients with previously failed colonoscopy. Gastrointest Endosc. 2010;71(7):1319–23.
81. Johnson CD, et al. Accuracy of CT colonography for detection of large adenomas and cancers. N Engl J Med. 2008;359(12):1207–17.
82. Pickhardt PJ. Imaging and screening for colorectal cancer with CT colonography. Radiol Clin N Am. 2017;55(6):1183–96.
83. Parsa N, Vemulapalli KC, Rex DK. Performance of radiographic imaging after incomplete colonoscopy for nonmalignant causes in clinical practice. Gastrointest Endosc. 2020;91(6):1371–7.
84. Shin LK, Poullos P, Jeffrey RB. MR colonography and MR enterography. Gastrointest Endosc Clin N Am. 2010;20(2):323–46.

85. Joseph DA, et al. Colorectal cancer screening: estimated future colonoscopy need and current volume and capacity. Cancer. 2016;122(16):2479–86.
86. Markowitz GS, et al. Renal failure due to acute nephrocalcinosis following oral sodium phosphate bowel cleansing. Hum Pathol. 2004;35(6):675–84.
87. Church JM. Pre-colonoscopy bowel preparation intolerance: a sign of upper gastrointestinal pathology. Aust N Z J Surg. 1991;61(10):796–7.
88. Wernli KJ, et al. Risks associated with anesthesia services during colonoscopy. Gastroenterology. 2016;150(4):888–94; quiz e18.
89. Bilotta F, et al. Cardiovascular effects of intravenous propofol administered at two infusion rates: a transthoracic echocardiographic study. Anaesthesia. 2001;56(3):266–71.
90. Herman LL, et al. Risk factors associated with vasovagal reactions during colonoscopy. Gastrointest Endosc. 1993;39(3):388–91.
91. Eckardt VF, et al. Complications and adverse effects of colonoscopy with selective sedation. Gastrointest Endosc. 1999;49(5):560–5.
92. Wang D, et al. The use of propofol as a sedative agent in gastrointestinal endoscopy: a meta-analysis. PLoS One. 2013;8(1):e53311.
93. Bielawska B, et al. Anesthesia assistance in outpatient colonoscopy and risk of aspiration pneumonia, bowel perforation, and splenic injury. Gastroenterology. 2018;154(1):77–85 e3.
94. Church J. Complications of colonoscopy. Gastroenterol Clin N Am. 2013;42(3):639–57.
95. Shi X, et al. Lower rate of colonoscopic perforation: 110,785 patients of colonoscopy performed by colorectal surgeons in a large teaching hospital in China. Surg Endosc. 2014;28(8):2309–16.
96. Reumkens A, et al. Post-colonoscopy complications: a systematic review, time trends, and meta-analysis of population-based studies. Am J Gastroenterol. 2016;111(8):1092–101.
97. Luning TH, et al. Colonoscopic perforations: a review of 30,366 patients. Surg Endosc. 2007;21(6):994–7.
98. Alsowaina KN, et al. Management of colonoscopic perforation: a systematic review and treatment algorithm. Surg Endosc. 2019;33(12):3889–98.
99. Loffeld RJ, Engel A, Dekkers PE. Incidence and causes of colonoscopic perforations: a single-center case series. Endoscopy. 2011;43(3):240–2.
100. Iqbal CW, et al. Surgical management and outcomes of 165 colonoscopic perforations from a single institution. Arch Surg. 2008;143(7):701–6; discussion 706–7.
101. Levy I, Gralnek IM. Complications of diagnostic colonoscopy, upper endoscopy, and enteroscopy. Best Pract Res Clin Gastroenterol. 2016;30(5):705–18.
102. Park JY, et al. The outcomes of management for colonoscopic perforation: a 12-year experience at a single institute. Ann Coloproctol. 2016;32(5):175–83.
103. Martinez-Perez A, et al. Laparoscopic vs. open surgery for the treatment of iatrogenic colonoscopic perforations: a systematic review and meta-analysis. World J Emerg Surg. 2017;12:8.
104. Di Saverio S, et al. Minimally invasive laparoscopic management of colonoscopic perforation avoiding laparotomy and colostomy: when and how to perform primary repair - a video vignette. Color Dis. 2016;18(8):817–8.
105. Lohsiriwat V. Colonoscopic perforation: incidence, risk factors, management and outcome. World J Gastroenterol. 2010;16(4):425–30.
106. Paspatis GA, et al. Diagnosis and management of iatrogenic endoscopic perforations: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy. 2014;46(8):693–711.
107. Magdeburg R, et al. Endoclipping of iatrogenic colonic perforation to avoid surgery. Surg Endosc. 2008;22(6):1500–4.
108. Kim JS, et al. Endoscopic clip closure versus surgery for the treatment of iatrogenic colon perforations developed during diagnostic colonoscopy: a review of 115,285 patients. Surg Endosc. 2013;27(2):501–4.
109. Cho SB, et al. Therapeutic options for iatrogenic colon perforation: feasibility of endoscopic clip closure and predictors of the need for early surgery. Surg Endosc. 2012;26(2):473–9.
110. Taku K, et al. Iatrogenic perforation associated with therapeutic colonoscopy: a multicenter study in Japan. J Gastroenterol Hepatol. 2007;22(9):1409–14.
111. An SB, et al. Decision-making in the management of colonoscopic perforation: a multicentre retrospective study. Surg Endosc. 2016;30(7):2914–21.
112. Committee, A.S.o.P., et al. Complications of colonoscopy. Gastrointest Endosc. 2011;74(4):745–52.
113. Sorbi D, et al. Postpolypectomy lower GI bleeding: descriptive analysis. Gastrointest Endosc. 2000;51(6):690–6.
114. Kavic SM, Basson MD. Complications of endoscopy. Am J Surg. 2001;181(4):319–32.
115. Guo SB, et al. Application of endoscopic hemoclips for nonvariceal bleeding in the upper gastrointestinal tract. World J Gastroenterol. 2009;15(34):4322–6.
116. Strate LL, Gralnek IM. ACG clinical guideline: management of patients with acute lower gastrointestinal bleeding. Am J Gastroenterol. 2016;111(5):755.
117. Jaruvongvanich V, et al. Risk factors for delayed colonic postpolypectomy bleeding: a systematic review and meta-analysis. Int J Color Dis. 2017;32(10):1399–406.
118. Watabe H, et al. Risk assessment for delayed hemorrhagic complication of colonic polypectomy: polyp-related factors and patient-related factors. Gastrointest Endosc. 2006;64(1):73–8.
119. Hui AJ, et al. Risk of colonoscopic polypectomy bleeding with anticoagulants and antiplatelet agents: analysis of 1657 cases. Gastrointest Endosc. 2004;59(1):44–8.
120. Sawhney MS, et al. Risk factors for severe delayed postpolypectomy bleeding. Endoscopy. 2008;40(2):115–9.
121. Shalman D, Gerson LB. Systematic review with meta-analysis: the risk of gastrointestinal haemorrhage post-polypectomy in patients receiving anti-platelet, anti-coagulant and/or thienopyridine medications. Aliment Pharmacol Ther. 2015;42(8):949–56.
122. Rossetti A, et al. Transarterial embolization in acute colonic bleeding: review of 11 years of experience and long-term results. Int J Color Dis. 2013;28(6):777–82.
123. Ko CW, Dominitz JA. Complications of colonoscopy: magnitude and management. Gastrointest Endosc Clin N Am. 2010;20(4):659–71.
124. Hirasawa K, et al. Coagulation syndrome: delayed perforation after colorectal endoscopic treatments. World J Gastrointest Endosc. 2015;7(12):1055–61.
125. Kim HW. What is different between postpolypectomy fever and postpolypectomy coagulation syndrome? Clin Endosc. 2014;47(3):205–6.
126. Shin YJ, et al. CT findings of post-polypectomy coagulation syndrome and colonic perforation in patients who underwent colonoscopic polypectomy. Clin Radiol. 2016;71(10):1030–6.
127. Piccolo G, et al. Presentation and management of splenic injury after colonoscopy: a systematic review. Surg Laparosc Endosc Percutan Tech. 2014;24(2):95–102.
128. Jehangir A, et al. A systematic review of splenic injuries during colonoscopies: Evolving trends in presentation and management. Int J Surg. 2016;33 Pt A:55–9.
129. Michetti CP, Smeltzer E, Fakhry SM. Splenic injury due to colonoscopy: analysis of the world literature, a new case report, and recommendations for management. Am Surg. 2010;76(11):1198–204.

130. Stein DF, Myaing M, Guillaume C. Splenic rupture after colonoscopy treated by splenic artery embolization. Gastrointest Endosc. 2002;55(7):946–8.
131. Holubar S, et al. Splenic rupture: an unusual complication of colonoscopy. Am Surg. 2007;73(4):393–6.
132. Low DE, et al. Prospective assessment of risk of bacteremia with colonoscopy and polypectomy. Dig Dis Sci. 1987;32(11):1239–43.
133. Wilson W, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007;116(15):1736–54.
134. Spach DH, Silverstein FE, Stamm WE. Transmission of infection by gastrointestinal endoscopy and bronchoscopy. Ann Intern Med. 1993;118(2):117–28.
135. Kovaleva J, et al. Transmission of infection by flexible gastrointestinal endoscopy and bronchoscopy. Clin Microbiol Rev. 2013;26(2):231–54.
136. Nelson DB, et al. Technology status evaluation report. Transmission of infection by gastrointestinal endoscopy. May 2001. Gastrointest Endosc. 2001;54(6):824–8.
137. Epstein L, et al. New Delhi metallo-beta-lactamase-producing carbapenem-resistant Escherichia coli associated with exposure to duodenoscopes. JAMA. 2014;312(14):1447–55.
138. Ofstead CL, et al. Re-evaluating endoscopy-associated infection risk estimates and their implications. Am J Infect Control. 2013;41(8):734–6.
139. Shin SP, Kim WH. Recent update on microbiological monitoring of gastrointestinal endoscopes after high-level disinfection. Clin Endosc. 2015;48(5):369–73.
140. Larsen S, Kalloo A, Hutfless S. The hidden cost of colonoscopy including cost of reprocessing and infection rate: the implications for disposable colonoscopes. Gut. 2020;69(2):197–200.
141. Yong E, et al. Efficiency of an endoscopy suite in a teaching hospital: delays, prolonged procedures, and hospital waiting times. Gastrointest Endosc. 2006;64(5):760–4.
142. Sauer BG, et al. Efficiency of endoscopy units can be improved with use of discrete event simulation modeling. Endosc Int Open. 2016;4(11):E1140–5.
143. Berg BP, et al. Estimating the cost of no-shows and evaluating the effects of mitigation strategies. Med Decis Mak. 2013;33(8):976–85.
144. Childers RE, et al. The role of a nurse telephone call to prevent no-shows in endoscopy. Gastrointest Endosc. 2016;84(6):1010–1017 e1.
145. Tsai MH, et al. Changing anesthesia block allocations improves endoscopy suite efficiency. J Med Syst. 2019;44(1):1.
146. Rex DK. Detection measures for colonoscopy: considerations on the adenoma detection rate, recommended detection thresholds, withdrawal times, and potential updates to measures. J Clin Gastroenterol. 2020;54(2):130–5.
147. Barclay RL, et al. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. N Engl J Med. 2006;355(24):2533–41.
148. Shaukat A, et al. Longer withdrawal time is associated with a reduced incidence of interval cancer after screening colonoscopy. Gastroenterology. 2015;149(4):952–7.
149. Rex DK, et al. Quality indicators for colonoscopy. Gastrointest Endosc. 2015;81(1):31–53.
150. Wang HS, et al. Adenoma detection rate is necessary but insufficient for distinguishing high versus low endoscopist performance. Gastrointest Endosc. 2013;77(1):71–8.
151. Zhao S, et al. Magnitude, risk factors, and factors associated with adenoma miss rate of tandem colonoscopy: a systematic review and meta-analysis. Gastroenterology. 2019;156(6):1661–1674 e11.
152. Spier BJ, et al. Colonoscopy training in gastroenterology fellowships: determining competence. Gastrointest Endosc. 2010;71(2):319–24.
153. Weis JJ, et al. FES exam outcomes in year two of a proficiency-based endoscopic skills curriculum. Surg Endosc. 2020;34(2):961–6.
154. Mizota T, et al. Development of a fundamentals of endoscopic surgery proficiency-based skills curriculum for general surgery residents. Surg Endosc. 2020;34(2):771–8.
155. Vassiliou MC, et al. Global Assessment of Gastrointestinal Endoscopic Skills (GAGES): a valid measurement tool for technical skills in flexible endoscopy. Surg Endosc. 2010;24(8):1834–41.

Endoscopic Management of Polyps and Endolumenal Surgery

5

William Forrest Johnston and Emre Gorgun

Abbreviations

ESGE	European Society of GI Endoscopy
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
CELS	Combined endoscopic-laparoscopic surgery
ELS	Endolumenal surgery

Key Concepts

- Endolumenal surgery is the forefront of minimally invasive surgery and is rapidly developing.
- Colon and rectal surgeons should be involved in the progression of endolumenal surgery as it will offer benefit to patients.
- New endolumenal techniques can be used to address large polyps that once required resection and treat malignant large bowel obstructions.

Introduction

Colonoscopy was initially described as a way to screen patients for mucosal abnormalities in the colon and has been adopted as the standard for colorectal cancer screening and prevention. However, when retrograde colonoscopy was first described in 1969, "there were some who said it couldn't be done, shortly followed by those who said it couldn't be done safely, followed by those who declared that it required a tricky skill which few would be able to acquire" [1]. Time has proved otherwise. Colonoscopic polypectomy has been demonstrated to decrease the incidence of colorectal cancer and has been widely adopted by the medical community [2]. With advances in technology, colonoscopy has progressed dramatically, and flexible colonoscopy is now used with various platforms that enable advanced endoscopic surgical procedures to be effectively completed. Endolumenal surgery is a rapidly progressive field in gastrointestinal surgery performed by both surgeons and gastroenterologists that offers the benefits of non-invasive surgery done in an outpatient setting. However, endolumenal surgeons are confronted with the challenge of operating through a flexible scope in a confined space that is frequently moving. Similar to opponents of early colonoscopy, there are many physicians in various stages of opposition. Due to the benefits to the patient, endoscopic surgery has the potential to be the next leap forward in minimally invasive surgery. This chapter will discuss the technical aspects of endolumenal surgery, ranging from forceps polypectomy to endoscopic submucosal dissection and colonic stenting.

Forceps

There are three commonly available options for forceps polypectomy: cold biopsy forceps, jumbo cold biopsy forceps, and hot biopsy forceps. For cold biopsy, the standard forceps open to 6 mm, and jumbo cold forceps open to 8.6 mm. Jumbo biopsy forceps have been shown to be superior to standard cold forceps for complete resection [3]. Historically, hot biopsy forceps were commonly used for polyp resection with the theoretical benefit of fulgurating any remaining dysplastic tissue around the polyp. However, this theoretical advantage has been refuted. A retrospective review of 62 hot biopsy polypectomies demonstrated a 17% rate of persistent polypoid tissue on repeat endoscopy 1–2 weeks after the original treatment [4].

Additionally, hot biopsy is associated with an increased risk of delayed hemorrhage compared to cold biopsy [5].

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Furthermore, hot biopsy alters the polyp morphology and creates more histological architectural distortion and fragmentation than cold biopsy [6]. For the aforementioned reasons, the European Society of GI Endoscopy (ESGE) has recommended against the use of hot biopsy forceps [7].

Cold biopsy forceps have also been described as an adjunct to difficult to remove large spreading polyps. While these polyps are typically removed with snare (described below), some polyps will not allow snare resection as the snare will slide over the polyp. In these situations, cold forceps are used to methodically avulse all visible polypoid tissue. Following avulsion of the mucosa, the submucosa and margins can be treated with soft coagulation from the tip of a hot snare. This technique, deemed CAST for Cold-forceps Avulsion with adjuvant Snare-Tip soft coagulation, has been reported as an effective and safe strategy for the management of non-lifting large laterally spreading (LST) colonic lesions [8]. CAST is easy to use, does not require additional equipment, and is useful adjunctive technique for organ sparing.

Snare

Endoscopic snare allows resection of larger lesions and more tissue compared to forceps. Incomplete resection of polyps by any method is associated with interval development of colorectal cancer in patients undergoing colonoscopy [9]. In removal of polyps <6 mm, snare excision has a higher rate of complete resection compared to forceps removal (93% for cold snare vs. 76% for cold biopsy forceps, $p < 0.001$) [10].

Snares vary in size, shape, and ability for coagulation. Hot snares are the traditional method for endoscopic snaring but have waned in popularity over recent years due to complications including increased risk of delayed bleeding and thermal injury. Use of a cold snare without electrocautery is associated with lower rate of post-polypectomy hemorrhage and shorter time for polypectomy and colonoscopy [11, 12]. Complete resection rates with cold snare are equivalent to hot snare [13]. Dedicated cold snares have been further improved with use of a thinner wire that more easily cuts tissue. Compared to traditional snares used without cautery, dedicated thin-wire cold snares have a higher rate of complete resection, especially with polyps 8–10 mm in size or sessile polyps [14]. The 2017 guidelines from ESGE recommend cold snare polypectomy as the preferred method for polyps <5 mm in size and strongly favor cold snare polypectomy for polyps 6–9 mm in size [7]. Hot snare polypectomy has been reserved for sessile polyps 10–19 mm in size after submucosal injection has been used to decrease the risk of thermal injury. Hot snare is also recommended for pedunculated polyps to decrease the rate of bleeding.

Bleeding after polypectomy is infrequent but may result in hospitalization, repeat colonoscopy, and poor patient experience. The rate of bleeding after polypectomy is approximately 1–2 per 1000 patients and is 10 times the rate of bleeding compared to colonoscopy without polypectomy [15]. Bleeding after cold snare polypectomy tends to be immediate and can be addressed at the time of initial colonoscopy, while bleeding after hot snare is often delayed and not apparent at the initial colonoscopy. Bleeding after hot snare occurs 0.1–0.7% of polypectomies and can occur up to 30 days after the procedure [16]. Prophylactic clip placement after routine polypectomy does not decrease the risk of delayed bleeding [17], and this practice should be avoided as it drastically increases the cost of the procedure without substantial benefit. Selective use of endoscopic clips is discussed later in the chapter.

Tips for Optimal Snaring

Polypectomy is required in 30–40% of all colonoscopies. To make polypectomy easier, the polyp should be positioned at the bottom half of the screen because the instrument channel on the colonoscope exits the scope at the 5 o'clock position. Occasionally, the lesion cannot be placed in the inferior aspect of the screen due to tortuosity of the colon or location behind a prominent fold. In those situations, working with the scope tip further away from the lesion may facilitate polypectomy by producing a favorable angle of attack to the polyp. Additionally, jumbo forceps removal may be technically easier for polyps in a challenging location if the size is small. If a snare is applicable, lesions are more easily grasped with dedicated cold snares, since they have a thinner wire that can grip the tissue better than an electrocautery compatible snare. If a hot snare is used after a lift for a larger lesion, consideration should be given for use of a non-oval-shaped snare. Snares with some angulation, like a hexagonal snare, tend to grasp tissue better as well as have a greater proximal opening compared to standard oval or round snares. Figure 5.1 shows different type of snares.

Care should be taken during polypectomy to ensure that complete resection of the polyp has been performed. In a prospective study of over 1400 patients, there was a 10% rate of incomplete resection for polyps 5–20 mm. Risk factors for incomplete resection included larger size and sessile serrated polyps vs. adenoma [18]. Any remaining polyp tissue after snare polypectomy can be removed with repeat snare excision or cold forceps avulsion.

Lifting

Flat lesions may require submucosal lift to separate the desired tissue for resection from the underlying colonic muscular wall and decrease the risk of full-thickness mechanical

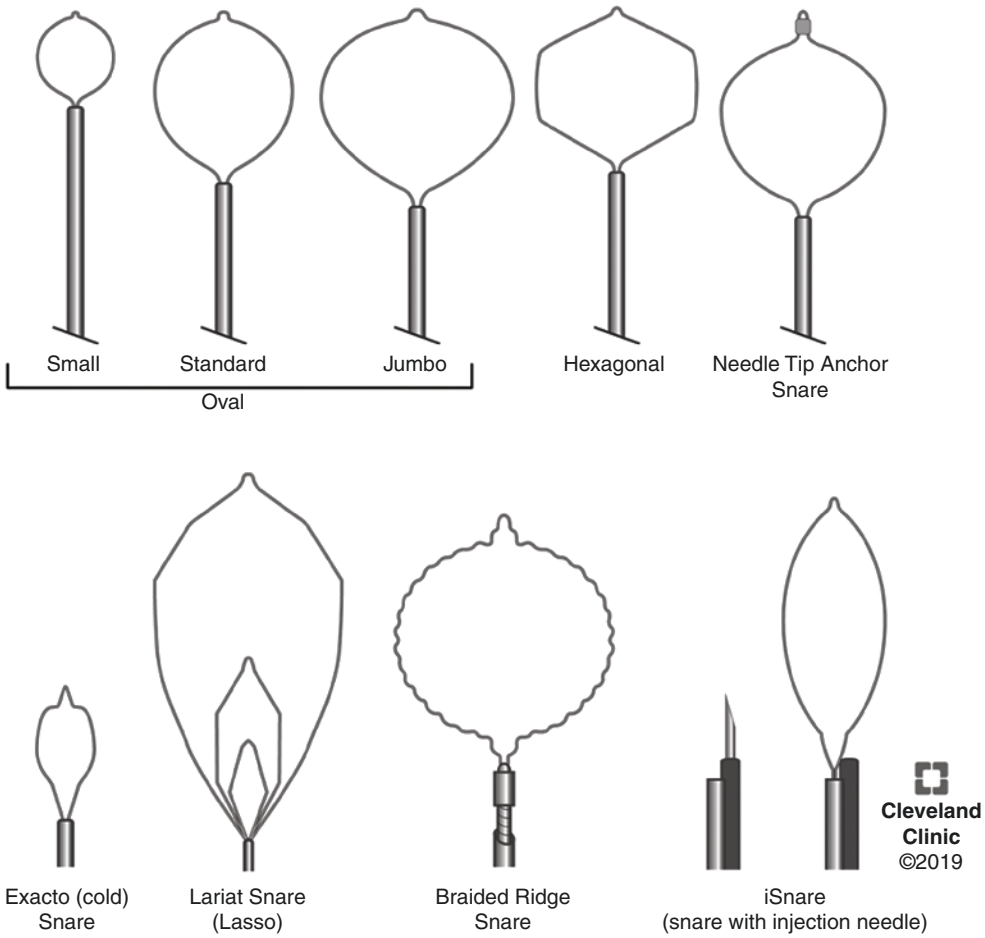


Fig. 5.1 Different types of snares (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2020. All Rights Reserved)

disruption or thermal injury from a hot snare. Common submucosal lifting agents include saline, hyaluronic acid, glycerol, dilute albumin, and proprietary gels. For most polyps, submucosal saline injection suffices and provides a lift that lasts approximately 3 minutes [19]. Normal saline has proven equivalent to other lifting solutions in terms of complete resection rate, post-procedural bleeding, and post-polypectomy syndrome or perforation [20]. For more complex lesions requiring a longer resection time, a more durable solution is desirable. Viscous solutions are often more durable and provide a more localized lift with less lateral diffusion. Multiple solutions exist, ranging from hydroxyethyl starch (hetastarch) to more expensive proprietary solutions like Eleview® (Medtronic, Dublin, Ireland) and ORISE® (Boston Scientific, Marlborough, MA) that can last for over 40 minutes [21].

Adequate lift is critical to allow for advanced endoscopic techniques. Ideal injections are submucosal, but endoscopic injections can be easily misplaced in deeper layers (subserosal or intramuscular). Addition of colored dye to the injected solution can help delineate the submucosal layer as the overlying mucosa is thin and the color of the solution will be readily appreciated. Correctly placed submucosal injections tend to create more focal and taller lifts, while subserosal or intramuscular injections will create a less prominent and broader lift [22]. Submucosal injection can be facilitated by starting to inject solution prior to putting the needle into the mucosa so that the injectant will push away submucosal layers once penetrating the overlying mucosa. Alternatively, the needle can be placed into the colon wall and then gently withdrawn back into the submucosal layer. It is easier to create a lift when injecting in a tangential direction to the bowel wall and avoiding injecting perpendicular to the bowel wall. Techniques for submucosal injection are also applicable to endoscopic tattoo placement to avoid tattoo dispersing throughout the abdomen. If a larger area is needed to lift, injections should be directed at the border of the prior submucosal cushion to stay in the submucosal plane (Fig. 5.2).

Submucosal lift injections can be performed in a dynamic technique to make a taller lift. The needle placement in the submucosa is confirmed with a small amount of injection to demonstrate an adequate lift plane followed by a large-volume rapid injection. During the large-volume injection, the needle and scope can be re-directed within the submucosa to generate a tall and long-lasting lift [23]. For lesions that are on a fold, submucosal injection should start on the

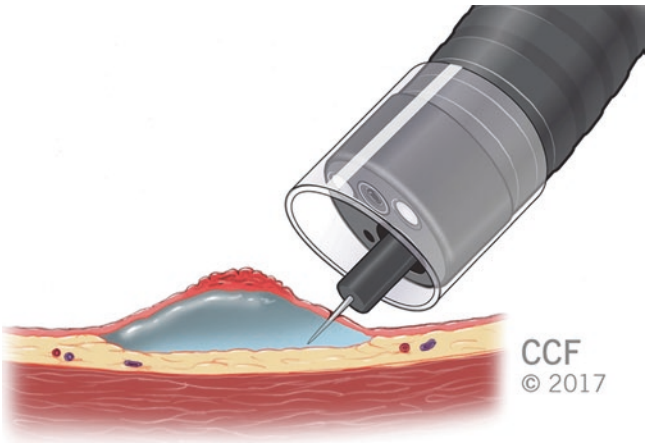


Fig. 5.2 To perform a submucosal injection, the injection needle should be tangential (parallel) to the mucosa. Fluid is injected as the needle is advanced to push away the muscularis and create and submucosal expansion to lift the overlying tissue (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2020. All Rights Reserved)

proximal/oral part of the bowel to lift the lesion toward the scope. Lesions that do not lift may be due to entry into the incorrect plane, scarring from past attempts at injection or polypectomy, or related to more advanced lesions that have invaded into the submucosa.

Endoscopic Mucosal Resection

Lesions that are too large for simple polypectomy can be treated with endoscopic mucosal resection (EMR). EMR is regularly used for polyps ranging from 20 mm to 50 mm in size. EMR is a technique designed for sessile or flat lesions that are confined to the superficial layer of the colon wall. The most common EMR method is the lift and cut technique, in which the lesion is lifted with a submucosal injection followed by snare polypectomy. With expansion of the submucosal space, the polyp can be removed without injury to the muscular layer of the bowel. The goal is to completely remove the polyp with as few snare excisions as possible [7]. EMR is started with a submucosal injection to lift the lesion to create space for resection. Since lesions with EMR are often larger than simple polypectomy, a solution with a longer durability than saline is desired. The ESGE recommends the addition of a staining dye (e.g., methylene blue or indigo carmine) to the submucosal injection to help identify lesion margins and deep tissue injury. The submucosal lift protects the underlying muscularis propria while decreasing resistance in the desired resection plane. The lesion is then resected with snare in as few pieces as possible with care to make sure that the entire lesion is removed. A normal margin of 2–3 mm of healthy-appearing tissue should be included to ensure complete removal. To decrease the risk of leaving islands of polyp tissue, piecemeal snaring should be done sequentially with the snare aligned along the margin of the prior resection. If there are any small remaining amounts of polypoid tissue, these can be ablated with electrocautery or removed with forceps. Following resection, clips can be selectively placed for tissue approximation (Fig. 5.3). Hot snare is commonly used during EMR. However, cold snare has also been shown to be effective for piecemeal resection after submucosal lift for polyps up to 55 mm with a low rate of recurrent disease or complication [24].

The major drawback of EMR is that larger lesions cannot be excised in *en bloc* fashion. EMR has been shown to be safe and effective for lesions smaller than 20 mm [25]. Lesions greater than 2 cm are often excised in piecemeal fashion, which limits the pathologic assessment of the polyp. Piecemeal resection can theoretically allow small amounts of polypoid tissue to remain that would result in recurrent polyp growth. While early experience with EMR indicated recurrent polyp formation on follow-up colonoscopy in 30% of patients [26], a recent prospective multicenter trial of 1000 EMR procedures demonstrated a lower recurrence rate (17% overall). For smaller polyps (20 mm in size), recurrence rate was 5% [27]. Risk factors for recurrence were increased size (OR = 8.2 for polyp >40 mm vs. 20 mm), APC usage (OR = 2.4), and bleeding (OR = 1.6). APC usage likely results in superficial ablation of the polyp, but does not eradicate the polyp tissue. The lack of efficacy of APC has been confirmed with other studies evaluating APC versus avulsion for the treatment of small amounts of residual polyp tissue after EMR. Avulsion with hot biopsy forceps was associated with a significantly lower adenoma recurrence rate compared to ablation with APC (10% recurrence with avulsion vs. 59% recurrence with APC on follow-up colonoscopy in 1 study of 278 patients with EMR of colon lesion >2 cm) [28].

Clip

While routine use of prophylactic clips after polypectomy is discouraged due to cost, endoscopic clips can be used selectively to re-approximate mucosa after EMR or be placed on bleeding vessels in an effort to increase hemostasis. Risk factors for post-polypectomy bleeding include large polyp size, proximal location, use of anticoagulant or antiplatelet agents, and the presence of multiple comorbidities [29]. In a recent multicenter randomized control trial, endoscopic clip application to close the mucosal defects of polypectomies for non-pedunculated polyps larger than 20 mm was associated with a decreased rate of post-polypectomy bleeding [30]. The benefit of clip application was most pronounced in the proximal colon with an absolute risk reduction of 6.3% (9.6% bleed without clips vs. 3.3% bleed with clips, $p < 0.001$). Clip application for large polyps in the distal

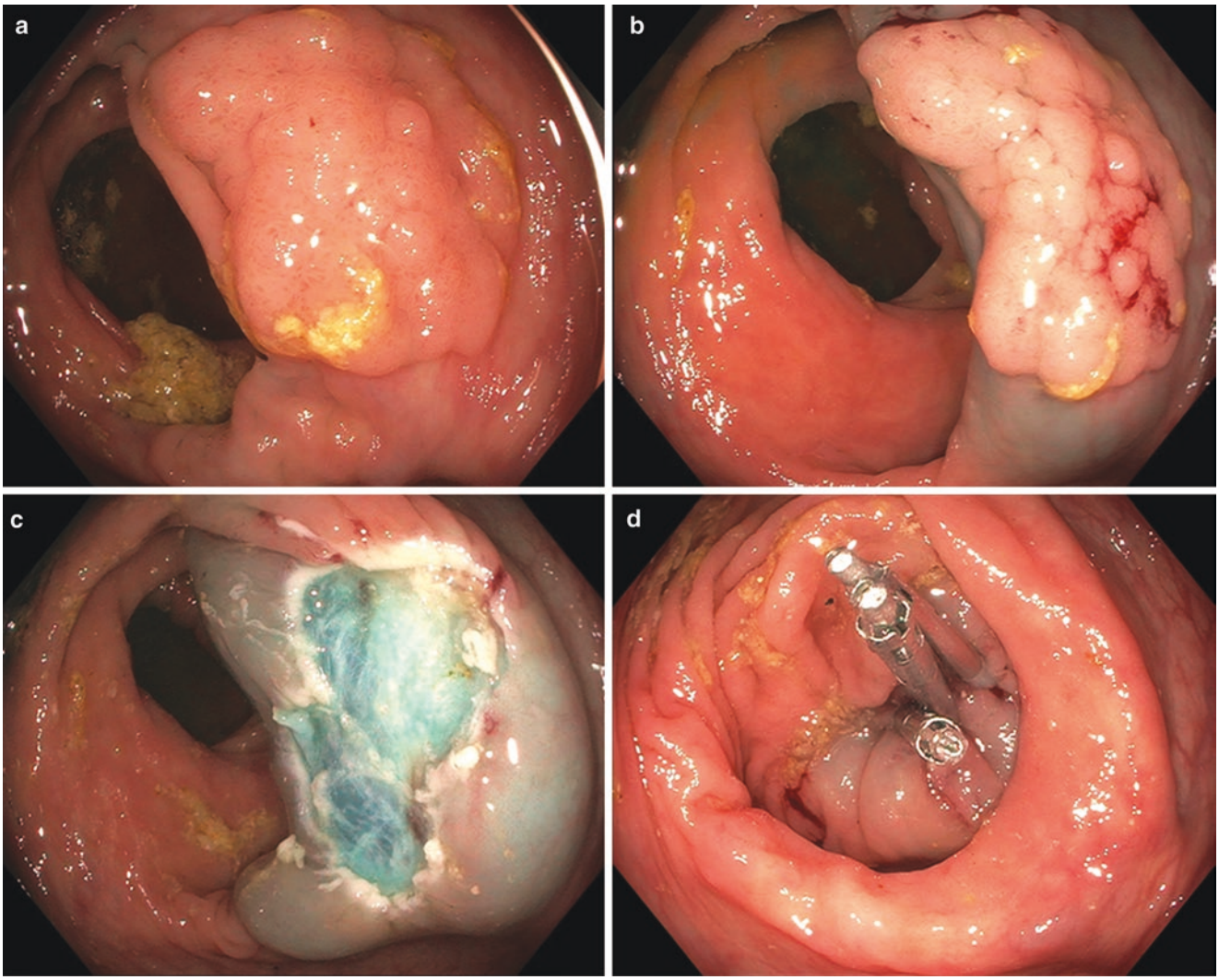


Fig. 5.3 EMR technique. (**a**) Large flat lesion in the right colon. (**b**) Lift with submucosal injection. (**c**) Piecemeal EMR resection with snare. (**d**) Endoscopic clip placement for closure

colon did not affect the rate of post-polypectomy bleeding. Application of clips has also been shown to decrease the rate of delayed bleeding even if complete mucosal re-approximation could not be accomplished [31]. Therefore, consideration should be given for selective use of clips following endoscopic resection of large polyps (>2 cm), particularly in the proximal colon.

Underwater EMR

Underwater EMR was described in 2012 as a method to avoid submucosal injection during resection of large polyps with EMR [32]. As described above, submucosal injection may be in the wrong layer leading to intramuscular injection. Furthermore, submucosal injection may make snare application more challenging as the snare may slip over the distended mucosa and not grasp the polyp. To perform underwater EMR, the air is evacuated and the lumen is filled with 500 mL to 1 L sterile water. The edges of the polyp are marked with APC. The polyp is removed in piecemeal fashion with a snare on cutting current to include all of the prior APC marks. Any small remnant tissue is treated hot biopsy coagulation. It is hypothesized that the water distends and flattens the colon to prevent the muscularis from being brought into the snare excision. When compared to traditional EMR, selective groups have demonstrated that underwater EMR allows increased complete macroscopic resection and decreased recurrence rates [33]. Additionally, underwater EMR has been used to increase rates of salvage endoscopic resection for recurrent polyps after past attempts at endoscopic resection [34].

Underwater techniques have also been applied to endoscopic submucosal dissection (ESD) [35]. Polyp resection while submerged in water can allow the edge of mucosa to float away from the submucosa and therefore improve the

endoscopic view of the dissection plane. Additionally, submerging the process of ESD in fluid allows greater heat dissipation, which theoretically decreases thermal injury. Potential benefits of underwater endoscopic resection must be balanced against the increased time requirement for water instillation.

Endoscopic Submucosal Dissection

Whereas EMR is limited in terms of size of en bloc excision, ESD is useful for larger lesions where complete histological evaluation is desired. ESD was first popularized in Japan in the 1990s for treatment of early gastric cancer. The gastric wall is thick and therefore allows for safe submucosal dissection with a margin for error. Colonic ESD was first described in the early 2000s [36]. The thin wall of the colon makes colonic ESD more challenging due to increased risk of full-thickness injury. However, the benefit of ESD is a more complete resection with lower recurrence rate. In a retrospective study of over 350 patients comparing colonic ESD and EMR, colonic ESD has a sevenfold lower recurrence rate. However, the complete resection of ESD comes at the cost of a nearly fivefold increased rate of perforation (6.2% ESD perforation vs. 1.3% EMR perforation) [37].

Colonic ESD allows resection of large benign lesions that traditionally required surgical resection. Dissection is performed in the submucosal layer under the lesion using a dedicated electrosurgical knife. Recent studies have shown that only 20% of polyps that were deemed endoscopically unresectable and referred to a surgeon for resection have invasive malignancy on final pathology [38, 39]. The rate of malignancy is even lower when carefully evaluating polyp morphology (see patient selection for ESD below). Large polyps that appeared benign to the endoscopist have less than 10% cancer rate [40]. This data suggests that the vast majority of patients with large benign-appearing colonic polyps can be treated adequately with endoscopic resection, saving these patients the morbidity of a larger colon resection. Comparing ESD to laparoscopic formal resection, patients treated with ESD had a significantly shorter hospital stay and decreased hospital financial cost [41]. Complication rates were similar, but the severity of complications was less in the patients treated with ESD compared to surgical resection.

ESD Complications

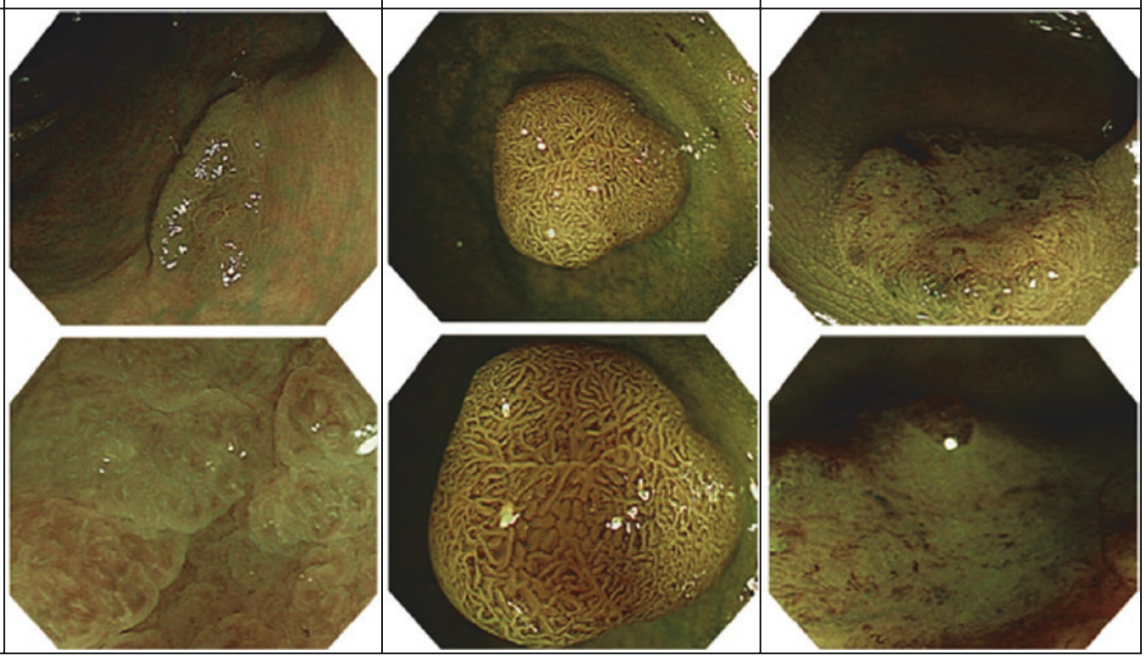
Prior to considering any intervention, one must be aware of the potential complications. Similar to most endoscopic polypectomy techniques, the most common complications after ESD are abdominal pain, bleeding, perforation, and tumor recurrence. Post-ESD electrocoagulation syndrome is similar to post-polypectomy syndrome and can be seen in up to 40% of patients [42]. Post-ESD bleeding occurs in approximately 2–7% of patients [43, 44]. ESD is also associated with a 5–20% perforation rate [45]. Risk of perforation is associated with increased tumor size and the presence of fibrosis. Perforation during ESD of lesions that are malignant can result in potential tumor seeding of the abdomen, as evidenced from the more robust gastric cancer literature. In a review of 22 perforations during gastric ESD, 2 patients (9%) had peritoneal seeding [46]. Lastly, endoscopic methods at resection carry the potential for recurrence. Local recurrence after ESD is remarkably low (approximately 1%) [43]. Furthermore, none of the recurrences contained invasive cancer and all were adequately managed with repeat endoscopic resection in this series.

Patient Selection for ESD

Careful selection of patients for attempted EMR and ESD is key. Procedural selection is based on the size of the tumor and the risk of underlying carcinoma. If the lesion is <2 cm, EMR is often favored. ESD is typically reserved for lesions >2 cm without features of malignancy. For patients where the diagnosis is unclear, ESD is an acceptable technique for excisional biopsy of lesions that have an increased risk of carcinoma but should be used with caution as the risk of full-thickness injury may be increased due to distortion of the submucosa from malignant invasion or fibrosis.

When doing a colonoscopy or preparing for ESD, the potential for underlying malignancy can be assessed by endoscopic characterization of the polyp appearance. Appearance of the lesion is critical and can be evaluated with one of several available classification systems, including Paris, Kudo pit pattern, or Narrow-band Imaging International Colorectal Endoscopic (NICE) classification. The gross morphology of the lesion is described by the Paris pattern, which divides lesions into polypoid vs. non-polypoid appearance. The non-polypoid superficial lesions are then divided based on their level of protrusion into the lumen (slightly elevated, flat, slightly depressed, and excavated). There is a clear inverse relationship between superficial lesion protrusion and the risk of submucosal invasion [47]. However, there is significant inter-observer variability in the classification of polyps according to the Paris system, suggesting that a simpler three-category classification of pedunculated, elevated, or depressed may be more widely applicable [48]. Depressed lesions have an increased rate of malignancy.

Pit patterns are based on the specific arrangement of glands in different lesions and can help determine hyperplastic vs. adenomatous vs. malignant lesions [49]. Narrow-band imaging (NBI) is commonly available technology that filters light into specific blue and green waveforms that will highlight vessels and mucosal tissue. NBI can be used to

	Type 1	Type 2	Type 3
Color	Same or lighter than background	Browner relative to background (verify color arises from vessels)	Brown to dark brown relative to background; sometimes patchy whiter areas
Vessels	None, or isolated lacy vessels coursing across the lesion	Brown vessels surrounding white structurs**	Has area(s) of disrupted or missing vessels
Surface Pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Ova, tubular or branched white structure surrounded by brown vessels**	Amorphous or absent surface pattern
Most likely pathology	**Hyperplastic**	**Adenoma*** **	**Deep submucosal invasive cancer**
Examples			

* Can be applied using colonoscopes with or without optical (zoom) magnification

** These structures (regular or irregular) may represent the pits and the epithelium of the crypt opening.

*** Type 2 consists of Vienna classification types 3,4 and superficial 5 (all adenomas with either low or high grade dysplasia, or with superficial submucosal carcinoma). The presence of high grade dyslasia or superficial submucosal carcinoma may be suggested by an irregular vessel or surface pattern, and is often associated with atypical morphology (e.g., depressed area).

Fig. 5.4 NICE classification. NICE, NBI International Colorectal Endoscopic; NBI narrow-band imaging (Reused with permission from Hayashi et al. [50]. Copyright © Elsevier 2013)

classify the polyp as hyperplastic, adenomatous, or malignant based on lesion color, vascular pattern, and surface pattern according to the NICE classification (Fig. 5.4) [50]. Accurate endoscopic assessment allows appropriate selection of polyps for EMR/ESD and avoidance of polyps that are better treated with resection due to concern for underlying malignancy.

The ability of the polyp to lift after submucosal injection has also been used to assess the potential for invasive malignancy. If tumor extends into the submucosa, the submucosa will not expand with injection. In a study of over 270 lesions, non-lifting sign had an overall accuracy of 95% for detecting an invasive malignancy, with a sensitivity of 62%, specificity of 98%, positive predictive value of 80%, and negative predictive value of 95% [51]. Furthermore, inadequate lift dramatically increases the likelihood of full-thickness injury as the submucosal layer is not expanded and there is consequently no buffer. Lesions may not lift well if there is fibrosis from prior attempts at resection or if the injection is too deep in the colon wall. The multiple reasons why a polyp will not adequately lift may explain why endoscopic assessment is more sensitive than the non-lifting sign for detecting invasion in flat or depressed lesions. Thus, in patients where the polyp does not lift well, there remains a role for ESD as long as the polyp has a benign morphologic appearance.

ESD Technique

Ideal polyps for ESD are polyps larger than 2 cm where invasion is not suspected. These are frequently laterally spreading tumors (LST) or polyps. For ESD, the mucosa is first marked outside of the edge of the lesion. This should be done with 2–3 mm normal mucosal margin. Although this step is not critical, it can be helpful for visualizing the borders. Submucosal injection should be performed outside of the coagulation marks so that there is a cushion under the endoscopic knife to decrease the risk of perforation. Once the lift is started, future injections should be directed at the edge of the prior lift to stay in the same plane and avoid the underlying muscularis propria. Once a submucosal lift has been established, the distal (anal) border of the mucosa around the lesion is incised in semicircular fashion with an endoscopic knife (Fig. 5.5). Complete circumferential incision will result in increased leak of submucosal fluid with greater difficulty of subsequent lift. After partial incision, further dissection proceeds tangential (parallel) to the submucosa to prevent injuring the colon wall by getting out of plane. Visualization is aided with a clear cap distal attachment to allow the endoscope to elevate the overlying mucosa and create traction. Additionally, positioning the patient in a manner that uses gravity to allow the polyp tissue to fall away from the colon wall will also improve exposure. Vessels are easily seen from the addition of a blue dye to the injection and are coagulated for hemostasis. As dissection continues, repeat submucosal injection is periodically used to expand the submucosa in front of the dissection.

Occasionally, a hybrid method with ESD and EMR can be useful and time efficient. ESD techniques are used to define the resection borders, perform the lift, and get the dissection started. Afterward, the remaining central dissection can be done with a large snare in an effort to save time. Hybrid ESD can be performed with similar en bloc resection rates and shorter procedural time [52]. However, the recurrence rate following hybrid ESD is higher than conventional ESD alone [53].

Following resection, routine colonoscopic review of the resection bed should be performed to look for any full-thickness defect or exposed vessels. Small defects can be closed with clips or endoscopic suturing techniques (below). Larger perforations can be closed with an over-the-scope clip. Over-the-scope clips involve pulling the defect into a specially designed cap and then releasing a large multi-pronged clip over the defect to approximate the edges. Exposed vessels can be treated with minimum coagulation to decrease the risk of bleeding. The lesion is then placed in a net for removal and stretched onto a board with pins for histology.

As would be expected of any new procedure, there is a learning curve with ESD. ESD has been pioneered out of Japan due to the high incidence of gastric cancer treated with gastric ESD. The infrequency of early gastric cancer in the Western hemisphere limits the training opportunity for ESD

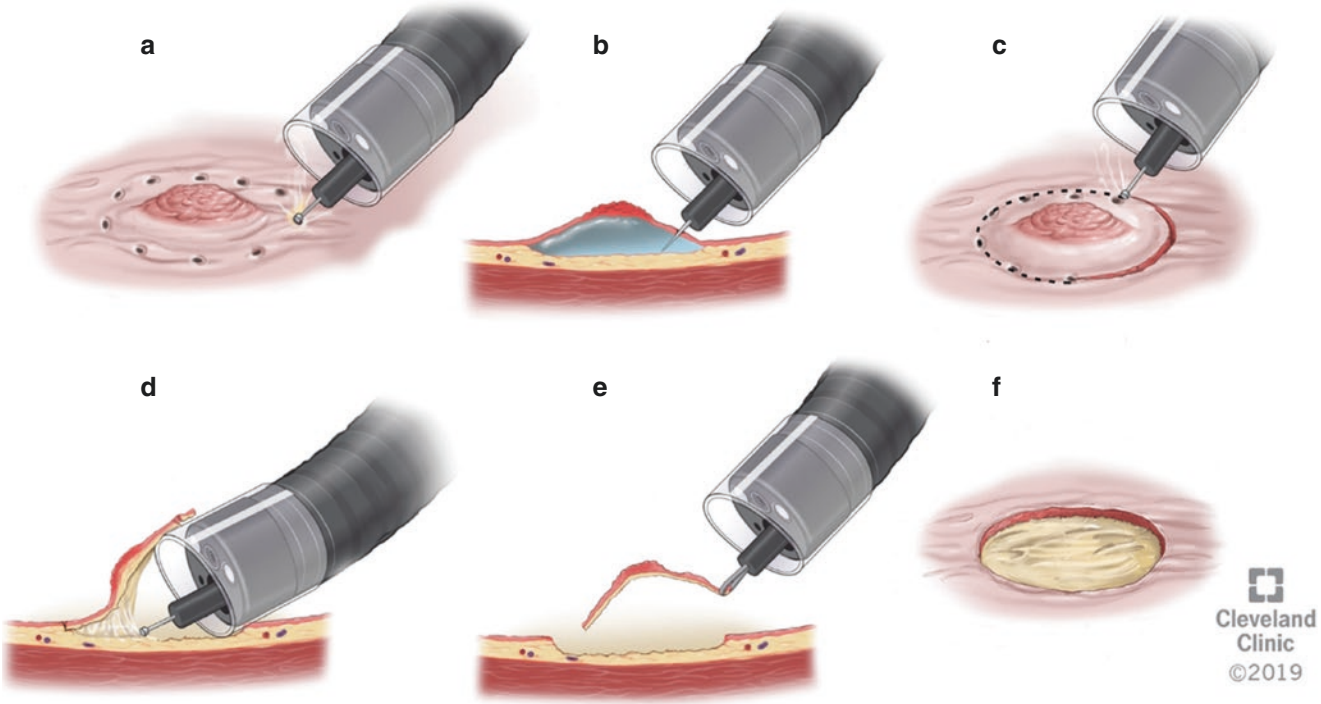


Fig. 5.5 ESD procedural steps (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2020. All Rights Reserved). (**a**) 2-3 mm margin is marked followed by (**b**) submucosal injection. (**c**) Endoscopic knife dissection of the distal (anal) portion of the lesion. (**d**) Careful submucosal dissection with repeated submucosal injection as needed. (**e**) Removal of the polyp intact to allow complete pathologic analysis. Polyp can be pinned on a corkboard for orientation. (**f**) Final dissection. Vessels can be seen and coagulated. Selective closure is used

techniques. Basic skills can be achieved through practice on ex vivo models. When transitioning to patient care, rectal lesions are in a more forgiving location due to the presence of the mesorectum, which will cover inadvertent full-thickness injuries. Even in high-volume centers, endoscopists may require up to 30 supervised cases prior to achieving technical proficiency of colonic ESD [54]. Endoscopists should expect a continued learning curve that may take years to master. In a single-center experience of 200 colonic ESD procedures, the perforation rate decreased from 12% during the first 100 cases to 2% in the second 100 cases [55]. Additionally, the en bloc resection rate increased from 80% to 92% over the 200 cases. Prior to developing an ESD program, one should achieve familiarity with methods of endoscopic closure and hemostasis to develop an arsenal of tools that can alleviate common complications.

Postoperative Care

As with most colonoscopy, patients treated with EMR can go home the same day. Patients treated with ESD may benefit from overnight observation. There is no need for prophylactic antibiotics. Abdominal x-rays are frequently used after a difficult dissection to look for the presence of free air. No dietary restrictions are necessary afterward.

Controversies with ESD Versus EMR

Critics of ESD may argue that en bloc resection of large, endoscopically benign-appearing colonic lesions is unnecessary as the rate of malignancy is <10% and that those lesions can be adequately treated with EMR [40]. Whereas ESD often involves advanced training and greater technical proficiency, EMR techniques are readily available with no specific setup and minimal additional training. Even though EMR has a higher recurrence rate, recurrences are usually detected with follow-up surveillance endoscopy and can be treated with repeat endoscopic interventions [27]. The downside of EMR is the piecemeal excision, which can be detrimental in polyps with carcinoma. In comparison, ESD can be curative for superficial carcinomas that invade upper 1/3 of the submucosa or <1000 μm (Sm1), as these lesions carry a low rate of lymph node metastasis [56]. However, this is a narrow population window for treatment. In comparing ESD and EMR, patients treated with ESD had a similar or higher rate of requiring subsequent surgery as patients treated with EMR [57]. In a study of over 1100 patients treated with colorectal ESD, the prevalence of invasive cancer was 19% [58]. Half of those were Sm2 and required surgical resection. Therefore, only 10% of patients treated with ESD had the benefit of complete resection of a superficial malignancy and avoidance of surgery. However, most would agree that there are certain patients with high-risk tumors that would benefit from en bloc resection to allow complete histologic analysis and potentially avoid major surgery. As a result of this potential benefit, ESD techniques are likely to continue to progress.

Endoscopic Suturing

Closure of large defects after ESD or EMR is challenging with traditional clip placement. In 2006, an over-the-scope endoscopic suturing platform was developed (OverStitch®, Apollo Endosurgery Inc., Austin, TX). The device requires a dual-channel endoscope and employs an endoscopic grasper to hold the oral side of the mucosa to pass the suture. The suture is then passed through the distal (anal) side of the mucosa to close the defect. Partial-thickness or full-thickness bites with the suture can be done to close the defect. The suture can be used in interrupted fashion or run as one long suture for more advanced endoscopists. Once facile with the device, endoscopic suturing is a time-efficient way to close large defects and may prevent the need for overnight observation [59]. Endoscopic suturing has been also used to effectively close full-thickness defects without the need for trans-abdominal operative intervention [60].

Stabilization Platforms

Advanced endoscopy can be challenging due to the lumenal folds and intra-procedural motion of the colon. Multiple stabilization platforms have been developed in an effort to allow more complex endoscopic surgery.

The DiLumen® (Lumendi Ltd., London, UK) is a double-balloon platform that fits over any colonoscope. The device is advanced over the scope to the desired location. The after-balloon is inflated, and then the fore-balloon is advanced beyond the target and inflated to create a therapeutic zone that is flat and smooth. The fore-balloon can also be used to create counter traction during ESD by attaching two small circles with suture to the balloon and then clipping the edge of the polyp resection to the circles [61]. When the fore-balloon is advanced, the edge of the resected mucosa is elevated to provide traction.

The ORISE Tissue Retractor System® (Boston Scientific, Marlborough, MA, USA) platform combines a stabilization cage along with two working channels to pass additional angled graspers to create counter tension. The flexible system is advanced over any colonoscope with a current working length of 40 cm. The lesion is placed at the 6 o'clock position and cage is then expanded to create a stable platform for surgery. Special graspers can be advanced to grasp tissue

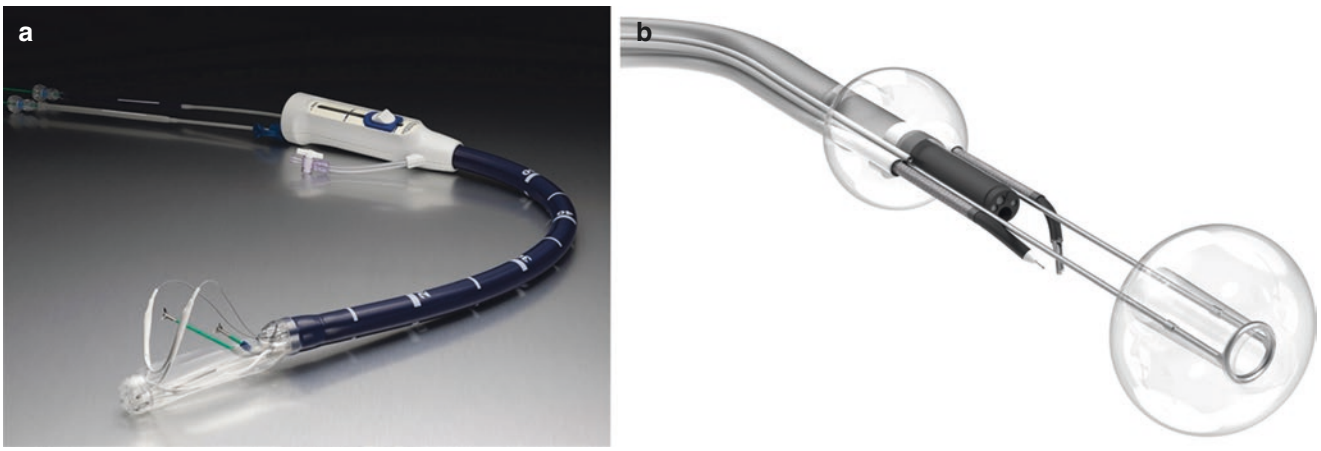


Fig. 5.6 Examples of endoscopic surgical platforms that create a therapeutic working zone with creation of counter traction to aid in dissection. (**a**) The ORISE TRS platform by Boston Scientific (Marlborough, MA) has a stabilization cage with two available retractors to provide counter tension. Image provided by Boston Scientific Corporation. (**b**) The DiLumen C2 platform by Lumendi (Westport, CT) has a fore and aft balloon to straighten and stabilize the colon with two available retractors to create tension (Reused with permission from Lumendi, LLC)

and then elevate the tissue to make dissection easier (Fig. 5.6) [62]. Endolumenal surgical platforms are rapidly progressing to simplify endoscopic resection techniques and allow resection of more complex lesions.

Approach to Referral for Unresectable Polyp

Surgeons are frequently referred large polyps that are considered endoscopically challenging for consideration for colectomy. Historically, colectomy was performed with only a 20% malignancy rate, suggesting that 80% of patients were over-treated with colectomy [38]. Patients often come with photos from their endoscopy, and it is a challenge to determine if the polyp will be endoscopically resectable.

Colored endoscopy photos and the pathology must be closely evaluated. If the photos are good quality, the lesion can be closely evaluated for ulceration, contour of the mucosal surface of the polyp, and vascular pattern. Similar to the above section on patient selection, features of malignancy should prompt colectomy instead of endoscopic attempts at resection. If the photographs are poor, repeat colonoscopy with attempts for ESD or EMR should be performed. If the colonoscopy is done in the operating room, a step-up approach of progressively more invasive techniques can be performmed. Resection can be attempted with endolumenal surgery and if unsuccessful, the patient can have combined endoscopic and laparoscopic surgery (CELS) or laparoscopic colectomy if warranted. The patient is consented for all three procedures prior to starting. The least invasive technique is attempted first followed by progressively more invasive techniques to remove the polyp. The benefit to the patient is that the polyp is removed at one sitting. The downfall of this approach relates to scheduling constraints. However, as one masters the ESD technique and preoperative assessment, selected cases can be easily scheduled in endoscopy units either with conscious sedation or monitored anesthesia care to avoid utilizing an operating room.

Colonic Stenting

Endolumenal advances have also been made in the treatment of large bowel obstruction. Historically, large bowel obstructions have been treated with abdominal surgery and formation of an ostomy due to dilation of the bowel, inability to prep, and emergent indication. Self-expanding metallic stents delivered endoscopically offer a minimally invasive solution to large bowel obstruction. Colonic self-expanding metal stents are uncovered to allow tissue ingrowth and prevent migration. Outcomes following stent placement have been controversial [63]. Colonic stenting is currently utilized in two situations: (1) a bridge to surgery in left-sided colonic obstructions and (2) palliation of malignant large bowel obstruction. There is no role for prophylactic stenting.

As a bridge to surgery in left-sided obstructions, stenting can avoid the need for stoma formation if the obstruction can be relieved and then colonic edema resolves to allow primary anastomosis. Patients treated with colonic stenting as a bridge to resection have a fivefold decreased likelihood of permanent stoma formation with a significant increase in primary anastomosis and decrease in wound infection rates [64]. However, stent placement does have complications, including perforation rate of 5%, migration rate of 4–10%, and repeat obstruction in 30% [65]. Due to stent related complications, two randomized controlled trials of colonic stents were closed early [66, 67]. Concerns about the oncologic safety of stenting as a bridge to surgery exist [68, 69]. The

only published guidelines on intraluminal colonic stents as a bridge to surgery are from the ESGE from 2014 and are based on meta-analyses showing increased rates of local recurrence without differences in overall survival [70]. These guidelines state that colonic stenting should not be the preferred method of treatment for left-sided obstructions in an otherwise healthy patient but could be considered in patients with a higher anesthetic risk (ASA ≥3 or age >70). At least two systematic reviews/meta-analyses published since then have concluded that the use of stenting as a bridge to surgery is oncologically safe with a similar 5-year survival, disease-free survival, and local recurrence rates as emergent surgery [71, 72]. Therefore, the use of stents in this setting is currently at the discretion of the individual surgeon based on experience and an assessment of the risks and benefits for a given patient's unique clinical presentation.

In the palliative setting, endoscopic stenting has been recommended by the ESGE as the preferred method of treatment [70]. According to a recent meta-analysis, stent placement for palliation has a similar mortality rate to emergent surgery with a shorter hospital stay and decreased stoma rate [73]. A separate study showed that long-term stent placement allowed 95% of patients to avoid stoma formation [74].

Prior to considering any colonic stenting, water-soluble contrast enema should be performed to evaluate the relevant anatomy. For obstructions, it is important to map out the location of the tumor, length of stenosis, and the lumen caliber. Alternatively, CT with rectal contrast can provide similar information while also demonstrating potential extrinsic causes and metastatic potential. If no contrast makes it across the lesion, stenting is less likely to be successful as it will be very challenging to pass a guidewire and increase risk of false passage of the guidewire resulting in potential perforation.

Based on personal experience, stenting colonic obstructions secondary to extrinsic causes (i.e., intra-abdominal metastatic disease resulting in colonic luminal narrowing or obstruction) is associated with an increased rate of migration and perforation, likely because the colon wall is not thickened and the mucosa is normal and does not allow stent ingrowth. Therefore, palliative stent placement is usually reserved for intrinsic obstructing lesions. Patients are counseled regarding the risks of stent placement. Either inability to place the stent or procedural complication is followed by emergent surgery with diverting colostomy formation [75].

Stenting Technique

Contrasted enema study is performed (either under fluoroscopy or in CT) to develop a roadmap. Fluoroscopy is used to guide placement. A guidewire is placed across the lesion. Confirmation of location can be done by exchanging the guidewire for a catheter to inject contrast and air to confirm intraluminal location. Haustrations should be seen with double-contrast injection. The appropriate size stent is selected, with favor given to the largest diameter and longest stent available. Shorter stents are chosen for rectal lesions to avoid stent placement within 5 cm of the anus, which may

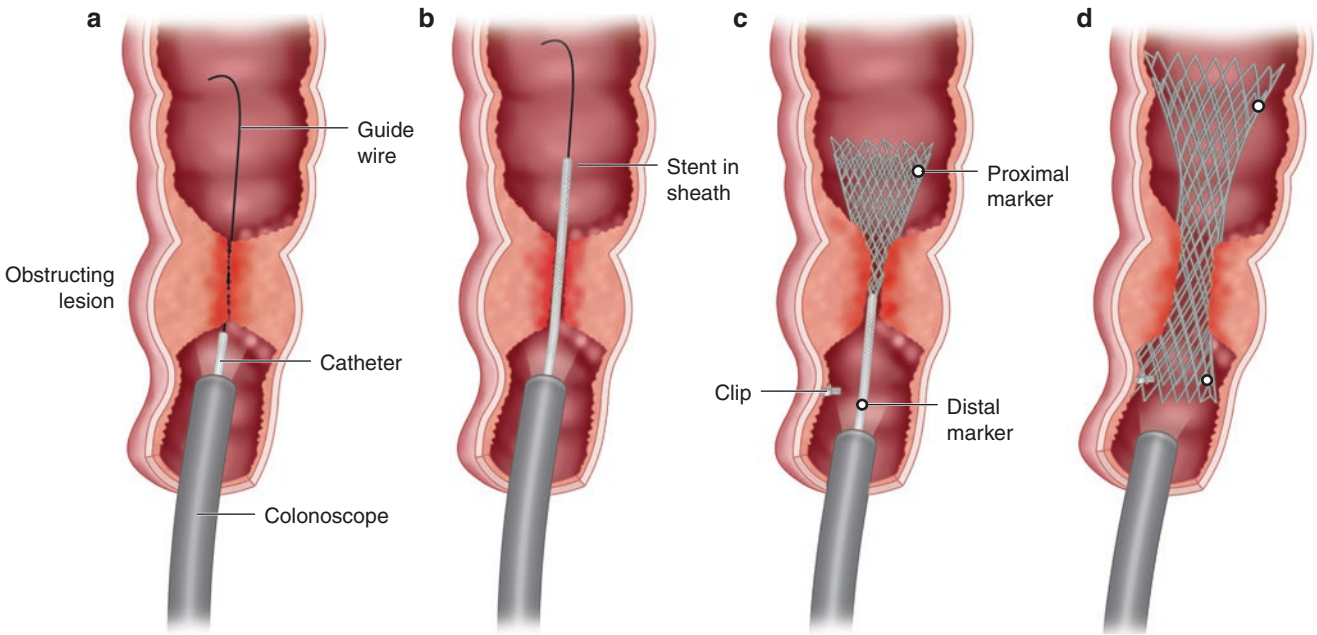


Fig. 5.7 Endoscopic stent placement of obstructing colon lesion. A guidewire is used to cross the lesion (**a**). Catheter can be advanced to instill contrast and air to confirm luminal location proximally. The sheathed stent is then advanced over the guidewire under fluoroscopy guidance (**b**). A clip can be placed 5 cm distal to the lesion to align with the distal marker on the stent, and then the sheath is withdrawn to deploy the stent under fluoroscopy (**c**). The stent will straddle the lesion and expand over the following 48 hours (**d**). Note that the clip and the distal marker are aligned

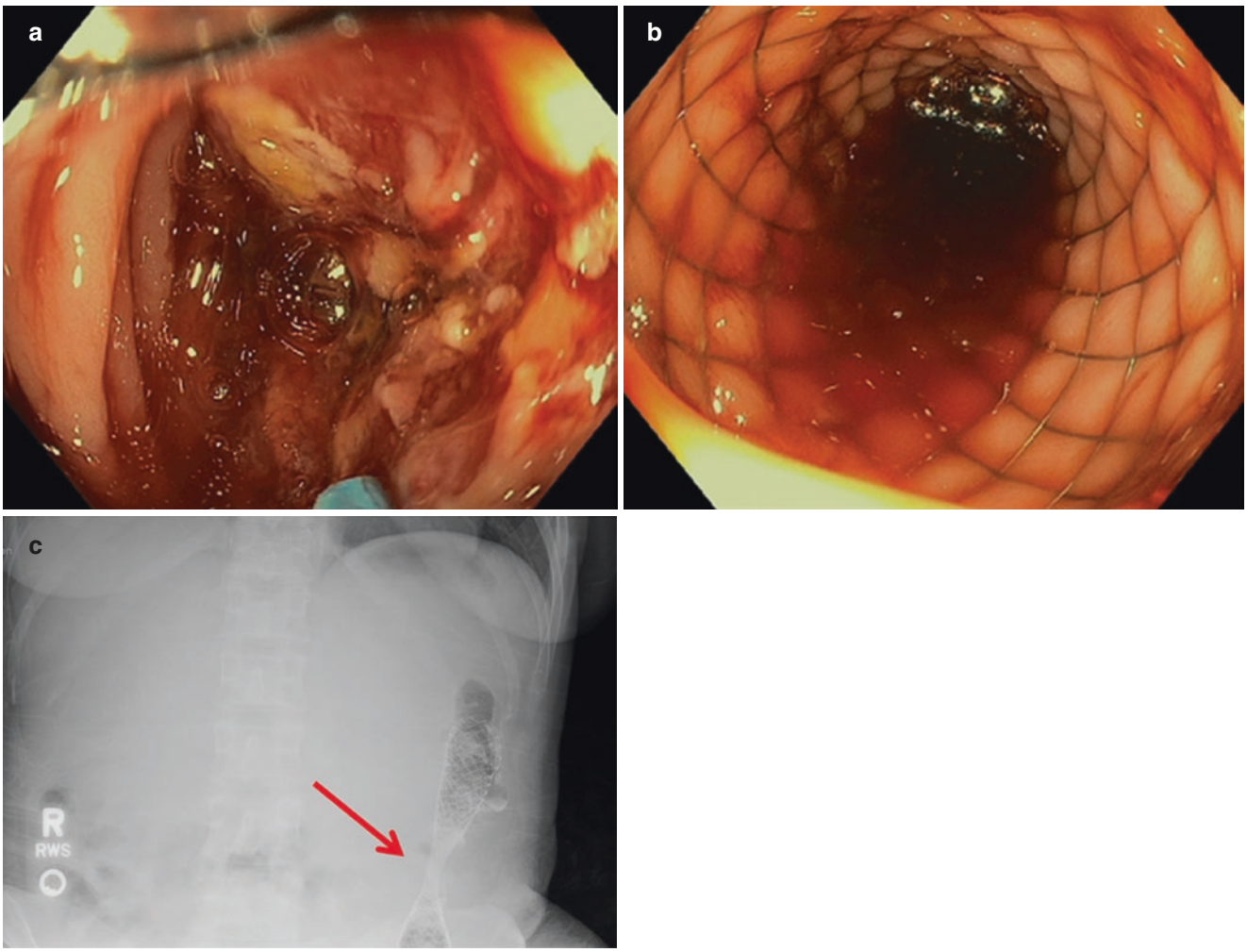


Fig. 5.8 Endoscopic stent placement. (**a**) The lumen in the obstructing mass is carefully selected and a guidewire is passed. Guidewire is exchanged for a catheter to inject contrast and air to confirm location. (**b**) Self-expanding metallic stent is then deployed. (**c**) Postoperative x-ray shows waist (red arrow) in the stent corresponding to the tumor location

result in significant tenesmus. The stent is passed under fluoroscopy guidance. A metallic clip can be placed 5 cm distal to the lesion as a radio-opaque marker for the landing zone of the distal aspect of the stent (Fig. 5.7)**.** Balloon dilation of the stent is not recommended. The scope is not passed through the stent after placement to avoid potential stent dislodgement. Abdominal x-rays are performed in recovery to confirm location and rule out obvious free air (Fig. 5.8)**.** Stent expansion will occur over the next 48 hours and the patient is monitored closely afterward for clinical result. Stool softeners are prescribed to help avoid fecal obstruction of the stent.

Stenting Anastomotic Leaks

Esophageal covered stents have been used in the colon and rectum to treat contained anastomotic leaks with case reports documenting success [76, 77]. The stent will block further extravasation of stool and may allow healing of the sinus. However, there is a high rate of stent migration, which may require stent replacement. In reported small cohort studies, covered stents are left in place without fecal diversion ranging from 20 to 50 days. Following removal, repeat water-soluble enema study is performed. Successful closure was seen in 80–100% of patients.

Conclusion

Endolumenal approaches to surgery are rapidly advancing and offer patients a minimally invasive approach that can result in a shorter hospital stay and more rapid return to normal activity with less morbidity. Surgeons are the ideal provider for endolumenal procedures. Patients can be stepped up from endolumenal surgery to CELS to formal resection based on the nature of the colonic lesions. Additionally, sur-

geons have a firm understanding of the anatomic constraints and the ability to repair potential complications. Although endolumenal surgery is considered challenging at present, it will likely continue to progress and gain more popularity over time with increased patient benefits. Advancing technology and flexible endorobotics will undoubtedly facilitate this evolution.

References

1. Wolff WI. Colonoscopy: history and development. Am J Gastroenterol. 1989;84(9):1017–25.
2. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, Schapiro M, Bond JH, Panish JF, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med. 1993;329(27):1977–81.
3. Aslan F, Cekic C, Camci M, Alper E, Ekinci N, Akpinar Z, Alpek S, Arabul M, Unsal B. What is the most accurate method for the treatment of diminutive colonic polyps?: standard versus jumbo forceps polypectomy. Medicine (Baltimore). 2015;94(15):e621.
4. Peluso F, Goldner F. Follow-up of hot biopsy forceps treatment of diminutive colonic polyps. Gastrointest Endosc. 1991;37(6):604–6.
5. Weston AP, Campbell DR. Diminutive colonic polyps: histopathology, spatial distribution, concomitant significant lesions, and treatment complications. Am J Gastroenterol. 1995;90(1):24–8.
6. Monkemuller KE, Fry LC, Jones BH, Wells C, Mikolaenko I, Eloubeidi M. Histological quality of polyps resected using the cold versus hot biopsy technique. Endoscopy. 2004;36(5):432–6.
7. Ferlitsch M, Moss A, Hassan C, Bhandari P, Dumonceau JM, Paspatis G, Jover R, Langner C, Bronzwaer M, Nalankilli K, Fockens P, Hazzan R, Gralnek IM, Gschwantler M, Waldmann E, Jeschek P, Penz D, Heresbach D, Moons L, Lemmers A, Paraskeva K, Pohl J, Ponchon T, Regula J, Repici A, Rutter MD, Burgess NG, Bourke MJ. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2017;49(3):270–97.
8. Tate DJ, Bahin FF, Desomer L, Sidhu M, Gupta V, Bourke MJ. Cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST) is an effective and safe strategy for the management of non-lifting large laterally spreading colonic lesions. Endoscopy. 2018;50(1):52–62.
9. Leung K, Pinsky P, Laiyemo AO, Lanza E, Schatzkin A, Schoen RE. Ongoing colorectal cancer risk despite surveillance colonoscopy: the Polyp Prevention Trial Continued Follow-up Study. Gastrointest Endosc. 2010;71(1):111–7.
10. Lee CK, Shim JJ, Jang JY. Cold snare polypectomy vs. Cold forceps polypectomy using double-biopsy technique for removal of diminutive colorectal polyps: a prospective randomized study. Am J Gastroenterol. 2013;108(10):1593–600.
11. Shinozaki S, Kobayashi Y, Hayashi Y, Sakamoto H, Lefor AK, Yamamoto H. Efficacy and safety of cold versus hot snare polypectomy for resecting small colorectal polyps: systematic review and meta-analysis. Dig Endosc. 2018;30(5):592–9.
12. Yamashina T, Fukuhara M, Maruo T, Tanke G, Marui S, Sada R, Taki M, Ohara Y, Sakamoto A, Henmi S, Sawai Y, Saito S, Nishijima N, Nasu A, Komekado H, Sekikawa A, Asada M, Tumura T, Kita R, Kimura T, Osaki Y. Cold snare polypectomy reduced delayed postpolypectomy bleeding compared with conventional hot polypectomy: a propensity score-matching analysis. Endosc Int Open. 2017;5(7):E587–94.
13. Kawamura T, Takeuchi Y, Asai S, Yokota I, Akamine E, Kato M, Akamatsu T, Tada K, Komeda Y, Iwatate M, Kawakami K, Nishikawa M, Watanabe D, Yamauchi A, Fukata N, Shimatani M, Ooi M, Fujita K, Sano Y, Kashida H, Hirose S, Iwagami H, Uedo N, Teramukai S, Tanaka K. A comparison of the resection rate for cold and hot snare polypectomy for 4–9 mm colorectal polyps: a multicentre randomised controlled trial (CRESCENT study). Gut. 2018;67(11):1950–7.
14. Horiuchi A, Hosoi K, Kajiyama M, Tanaka N, Sano K, Graham DY. Prospective, randomized comparison of 2 methods of cold snare polypectomy for small colorectal polyps. Gastrointest Endosc. 2015;82(4):686–92.
15. Rabeneck L, Paszat LF, Hilsden RJ, Saskin R, Leddin D, Grunfeld E, Wai E, Goldwasser M, Sutradhar R, Stukel TA. Bleeding and perforation after outpatient colonoscopy and their risk factors in usual clinical practice. Gastroenterology. 2008;135(6):1899–906, 1906 e1.
16. Singaram C, Torbey CF, Jacoby RF. Delayed postpolypectomy bleeding. Am J Gastroenterol. 1995;90(1):146–7.
17. Nishizawa T, Suzuki H, Goto O, Ogata H, Kanai T, Yahagi N. Effect of prophylactic clipping in colorectal endoscopic resection: a meta-analysis of randomized controlled studies. United European Gastroenterol J. 2017;5(6):859–67.
18. Pohl H, Srivastava A, Bensen SP, Anderson P, Rothstein RI, Gordon SR, Levy LC, Toor A, Mackenzie TA, Rosch T, Robertson DJ. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. Gastroenterology. 2013;144(1):74–80 e1.
19. Fujishiro M, Yahagi N, Kashimura K, Mizushima Y, Oka M, Enomoto S, Kakushima N, Kobayashi K, Hashimoto T, Iguchi M, Shimizu Y, Ichinose M, Omata M. Comparison of various submucosal injection solutions for maintaining mucosal elevation during endoscopic mucosal resection. Endoscopy. 2004;36(7):579–83.
20. Ferreira AO, Moleiro J, Torres J, Dinis-Ribeiro M. Solutions for submucosal injection in endoscopic resection: a systematic review and meta-analysis. Endosc Int Open. 2016;4(1):E1–E16.
21. Castro R, Libanio D, Pita I, Dinis-Ribeiro M. Solutions for submucosal injection: what to choose and how to do it. World J Gastroenterol. 2019;25(7):777–88.
22. Sandhu J, Winkler C, Yan X, Sharabi A, Grimes Z, Shantha Kumara HMC, Cekic V, Whelan R. Sclerotherapy needle injections can expand the subserosal and muscularis propria layers and cause a stable mucosal lift in ESD/EMR patients. Surg Endosc. 2019;33(3):949–58.
23. Sanchez-Yague A, Kaltenbach T, Raju G, Soetikno R. Advanced endoscopic resection of colorectal lesions. Gastroenterol Clin N Am. 2013;42(3):459–77.
24. Piraka C, Saeed A, Waljee AK, Pillai A, Stidham R, Elmunzer BJ. Cold snare polypectomy for non-pedunculated colon polyps greater than 1 cm. Endosc Int Open. 2017;5(3):E184–9.
25. Repici A, Pellicano R, Strangio G, Danese S, Fagoonee S, Malesci A. Endoscopic mucosal resection for early colorectal neoplasia: pathologic basis, procedures, and outcomes. Dis Colon Rectum. 2009;52(8):1502–15.
26. Buchner AM, Guarner-Argente C, Ginsberg GG. Outcomes of EMR of defiant colorectal lesions directed to an endoscopy referral center. Gastrointest Endosc. 2012;76(2):255–63.
27. Moss A, Williams SJ, Hourigan LF, Brown G, Tam W, Singh R, Zanati S, Burgess NG, Sonson R, Byth K, Bourke MJ. Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. Gut. 2015;64(1):57–65.
28. Holmes I, Kim HG, Yang DH, Friedland S. Avulsion is superior to argon plasma coagulation for treatment of visible residual neoplasia during EMR of colorectal polyps (with videos). Gastrointest Endosc. 2016;84(5):822–9.
29. Albeniz E, Fraile M, Ibanez B, Alonso-Aguirre P, Martinez-Ares D, Soto S, Gargallo CJ, Ramos Zabala F, Alvarez MA, Rodriguez-Sanchez J, Mugica F, Nogales O, Herreros de Tejada A, Redondo

E, Pin N, Leon-Brito H, Pardeiro R, Lopez-Roses L, Rodriguez-Tellez M, Jimenez A, Martinez-Alcala F, Garcia O, de la Pena J, Ono A, Alberca de Las Parras F, Pellise M, Rivero L, Saperas E, Perez-Roldan F, Pueyo Royo A, Eguaras Ros J, Zuniga Ripa A, Concepcion-Martin M, Huelin-Alvarez P, Colan-Hernandez J, Cubiella J, Remedios D, ICX B, Lopez-Viedma B, Cobian J, Gonzalez-Haba M, Santiago J, Martinez-Cara JG, Valdivielso E, Guarner-Argente C, Endoscopic Mucosal Resection Endoscopic Spanish Society G. A scoring system to determine risk of delayed bleeding after endoscopic mucosal resection of large colorectal lesions. Clin Gastroenterol Hepatol. 2016;14(8):1140–7.

30. Pohl H, Grimm IS, Moyer MT, Hasan MK, Pleskow D, Elmunzer BJ, Khashab MA, Sanaei O, Al-Kawas FH, Gordon SR, Mathew A, Levenick JM, Aslanian HR, Antaki F, von Renteln D, Crockett SD, Rastogi A, Gill JA, Law RJ, Elias PA, Pellise M, Wallace MB, Mackenzie TA, Rex DK. Clip closure prevents bleeding after endoscopic resection of large colon polyps in a randomized trial. Gastroenterology. 2019;157(4):977–984 e3.
31. Albeniz E, Alvarez MA, Espinos JC, Nogales O, Guarner C, Alonso P, Rodriguez-Tellez M, Herreros de Tejada A, Santiago J, Bustamante-Balen M, Rodriguez Sanchez J, Ramos-Zabala F, Valdivielso E, Martinez-Alcala F, Fraile M, Elosua A, Guerra Veloz MF, Ibanez Beroiz B, Capdevila F, Enguita-German M. Clip closure after resection of large colorectal lesions with substantial risk of bleeding. Gastroenterology. 2019;157(5):1213–21. e4
32. Binmoeller KF, Weilert F, Shah J, Bhat Y, Kane S. "Underwater" EMR without submucosal injection for large sessile colorectal polyps (with video). Gastrointest Endosc. 2012;75(5):1086–91.
33. Schenck RJ, Jahann DA, Patrie JT, Stelow EB, Cox DG, Uppal DS, Sauer BG, Shami VM, Strand DS, Wang AY. Underwater endoscopic mucosal resection is associated with fewer recurrences and earlier curative resections compared to conventional endoscopic mucosal resection for large colorectal polyps. Surg Endosc. 2017;31(10):4174–83.
34. Kim HG, Thosani N, Banerjee S, Chen A, Friedland S. Underwater endoscopic mucosal resection for recurrences after previous piecemeal resection of colorectal polyps (with video). Gastrointest Endosc. 2014;80(6):1094–102.
35. Yoshii S, Akasaka T, Hayashi Y, Tsujii Y, Nagai K, Higashino K, Ishihara R, Iijima H, Takehara T. "Underwater" endoscopic submucosal dissection: a novel method for resection in saline with a bipolar needle knife for colorectal epithelial neoplasia. Surg Endosc. 2018;32(12):5031–6.
36. Yamamoto H, Kawata H, Sunada K, Sasaki A, Nakazawa K, Miyata T, Sekine Y, Yano T, Satoh K, Ido K, Sugano K. Successful en-bloc resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood. Endoscopy. 2003;35(8):690–4.
37. Saito Y, Fukuzawa M, Matsuda T, Fukunaga S, Sakamoto T, Uraoka T, Nakajima T, Ikehara H, Fu KI, Itoi T, Fujii T. Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection. Surg Endosc. 2010;24(2):343–52.
38. Bertelson NL, Kalkbrenner KA, Merchea A, Dozois EJ, Landmann RG, De Petris G, Young-Fadok TM, Etzioni DA. Colectomy for endoscopically unresectable polyps: how often is it cancer? Dis Colon Rectum. 2012;55(11):1111–6.
39. Alder AC, Hamilton EC, Anthony T, Sarosi GA Jr. Cancer risk in endoscopically unresectable colon polyps. Am J Surg. 2006;192(5):644–8.
40. Gorgun E, Benlice C, Church JM. Does cancer risk in colonic polyps unsuitable for polypectomy support the need for advanced endoscopic resections? J Am Coll Surg. 2016;223(3):478–84.
41. Gamaleldin M, Benlice C, Delaney CP, Steele S, Gorgun E. Management of the colorectal polyp referred for resection: a case-matched comparison of advanced endoscopic surgery and laparoscopic colectomy. Surgery. 2018;163(3):522–7.
42. Jung D, Youn YH, Jahng J, Kim JH, Park H. Risk of electrocoagulation syndrome after endoscopic submucosal dissection in the colon and rectum. Endoscopy. 2013;45(9):714–7.
43. Gorgun E, Benlice C, Abbas MA, Steele S. Experience in colon sparing surgery in North America: advanced endoscopic approaches for complex colorectal lesions. Surg Endosc. 2018;32(7):3114–21.
44. Saito Y, Sakamoto T, Nakajima T, Matsuda T. Colorectal ESD: current indications and latest technical advances. Gastrointest Endosc Clin N Am. 2014;24(2):245–55.
45. Kim ES, Cho KB, Park KS, Lee KI, Jang BK, Chung WJ, Hwang JS. Factors predictive of perforation during endoscopic submucosal dissection for the treatment of colorectal tumors. Endoscopy. 2011;43(7):573–8.
46. Hirao M, Yamada T, Michida T, Nishikawa K, Hamakawa T, Mita E, Mano M, Sekimoto M. Peritoneal seeding after gastric perforation during endoscopic submucosal dissection for gastric cancer. Dig Surg. 2018;35(5):457–60.
47. Kudo S, Lambert R, Allen JI, Fujii H, Fujii T, Kashida H, Matsuda T, Mori M, Saito H, Shimoda T, Tanaka S, Watanabe H, Sung JJ, Feld AD, Inadomi JM, O'Brien MJ, Lieberman DA, Ransohoff DF, Soetikno RM, Triadafilopoulos G, Zauber A, Teixeira CR, Rey JF, Jaramillo E, Rubio CA, Van Gossum A, Jung M, Vieth M, Jass JR, Hurlstone PD. Nonpolypoid neoplastic lesions of the colorectal mucosa. Gastrointest Endosc. 2008;68(4 Suppl):S3–47.
48. van Doorn SC, Hazewinkel Y, East JE, van Leerdam ME, Rastogi A, Pellise M, Sanduleanu-Dascalescu S, Bastiaansen BA, Fockens P, Dekker E. Polyp morphology: an interobserver evaluation for the Paris classification among international experts. Am J Gastroenterol. 2015;110(1):180–7.
49. Kudo S, Rubio CA, Teixeira CR, Kashida H, Kogure E. Pit pattern in colorectal neoplasia: endoscopic magnifying view. Endoscopy. 2001;33(4):367–73.
50. Hayashi N, Tanaka S, Hewett DG, Kaltenbach TR, Sano Y, Ponchon T, Saunders BP, Rex DK, Soetikno RM. Endoscopic prediction of deep submucosal invasive carcinoma: validation of the narrow-band imaging international colorectal endoscopic (NICE) classification. Gastrointest Endosc. 2013;78(4):625–32.
51. Kobayashi N, Saito Y, Sano Y, Uragami N, Michita T, Nasu J, Matsuda T, Fu KI, Fujii T, Fujimori T, Ishikawa T, Saito D. Determining the treatment strategy for colorectal neoplastic lesions: endoscopic assessment or the non-lifting sign for diagnosing invasion depth? Endoscopy. 2007;39(8):701–5.
52. Bae JH, Yang DH, Lee S, Soh JS, Lee S, Lee HS, Lee HJ, Park SH, Kim KJ, Ye BD, Myung SJ, Yang SK, Byeon JS. Optimized hybrid endoscopic submucosal dissection for colorectal tumors: a randomized controlled trial. Gastrointest Endosc. 2016;83(3):584–92.
53. Milano RV, Viale E, Bartel MJ, Notaristefano C, Testoni PA. Resection outcomes and recurrence rates of endoscopic submucosal dissection (ESD) and hybrid ESD for colorectal tumors in a single Italian center. Surg Endosc. 2018;32(5):2328–39.
54. Sakamoto T, Saito Y, Fukunaga S, Nakajima T, Matsuda T. Learning curve associated with colorectal endoscopic submucosal dissection for endoscopists experienced in gastric endoscopic submucosal dissection. Dis Colon Rectum. 2011;54(10):1307–12.
55. Hisabe T, Nagahama T, Hirai F, Matsui T, Iwashita A. Clinical outcomes of 200 colorectal endoscopic submucosal dissections. Dig Endosc. 2012;24 Suppl 1:105–9.
56. Burgess NG, Bourke MJ. Endoscopic resection of colorectal lesions: the narrowing divide between East and West. Dig Endosc. 2016;28(3):296–305.
57. Fujiya M, Tanaka K, Dokoshi T, Tominaga M, Ueno N, Inaba Y, Ito T, Moriichi K, Kohgo Y. Efficacy and adverse events of EMR and endoscopic submucosal dissection for the treatment of colon neoplasms: a meta-analysis of studies comparing EMR and endoscopic submucosal dissection. Gastrointest Endosc. 2015;81(3):583–95.

58. Saito Y, Uraoka T, Yamaguchi Y, Hotta K, Sakamoto N, Ikematsu H, Fukuzawa M, Kobayashi N, Nasu J, Michida T, Yoshida S, Ikehara H, Otake Y, Nakajima T, Matsuda T, Saito D. A prospective, multicenter study of 1111 colorectal endoscopic submucosal dissections (with video). Gastrointest Endosc. 2010;72(6):1217–25.
59. Kantsevoy SV, Bitner M, Mitrakov AA, Thuluvath PJ. Endoscopic suturing closure of large mucosal defects after endoscopic submucosal dissection is technically feasible, fast, and eliminates the need for hospitalization (with videos). Gastrointest Endosc. 2014;79(3):503–7.
60. Kantsevoy SV, Bitner M, Hajiyeva G, Mirovski PM, Cox ME, Swope T, Alexander K, Meenaghan N, Fitzpatrick JL, Gushchin V. Endoscopic management of colonic perforations: clips versus suturing closure (with videos). Gastrointest Endosc. 2016;84(3):487–93.
61. Kantsevoy SV, Wagner A, Mitrakov AA, Thuluvath AJ, Berr F. Rectal reconstruction after endoscopic submucosal dissection for removal of a giant rectal lesion. VideoGIE. 2019;4(4):179–81.
62. Kantsevoy SV, Bitner M, Piskun G. New endoscopic platform for endoluminal en bloc tissue resection in the gastrointestinal tract (with videos). Surg Endosc. 2016;30(7):3145–51.
63. Cirocchi R, Farinella E, Trastulli S, Desiderio J, Listorti C, Boselli C, Parisi A, Noya G, Sagar J. Safety and efficacy of endoscopic colonic stenting as a bridge to surgery in the management of intestinal obstruction due to left colon and rectal cancer: a systematic review and meta-analysis. Surg Oncol. 2013;22(1):14–21.
64. Huck K, Hanenberg H, Gudowius S, Fenk R, Kalb R, Neveling K, Betz B, Niederacher D, Haas R, Gobel U, Kobbe G, Schindler D. Delayed diagnosis and complications of Fanconi anaemia at advanced age–a paradigm. Br J Haematol. 2006;133(2):188–97.
65. Han SH, Lee JH. Colonic stent-related complications and their management. Clin Endosc. 2014;47(5):415–9.
66. Pirlet IA, Slim K, Kwiatkowski F, Michot F, Millat BL. Emergency preoperative stenting versus surgery for acute left-sided malignant colonic obstruction: a multicenter randomized controlled trial. Surg Endosc. 2011;25(6):1814–21.
67. van Hooft JE, Bemelman WA, Oldenburg B, Marinelli AW, Lutke Holzik MF, Grubben MJ, Sprangers MA, Dijkgraaf MG, Fockens P, Collaborative Dutch Stent-In Study G. Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction: a multicentre randomised trial. Lancet Oncol. 2011;12(4):344–52.
68. Sagar J. Role of colonic stents in the management of colorectal cancers. World J Gastrointest Endosc. 2016;8(4):198–204.
69. Maruthachalam K, Lash GE, Shenton BK, Horgan AF. Tumour cell dissemination following endoscopic stent insertion. Br J Surg. 2007;94(9):1151–4.
70. van Hooft JE, van Halsema EE, Vanbiervliet G, Beets-Tan RG, JM DW, Donnellan F, Dumonceau JM, Glynne-Jones RG, Hassan C, Jimenez-Perez J, Meisner S, Muthusamy VR, Parker MC, Regimbeau JM, Sabbagh C, Sagar J, Tanis PJ, Vandervoort J, Webster GJ, Manes G, Barthet MA, Repici A, European Society of Gastrointestinal E. Self-expandable metal stents for obstructing colonic and extracolonic cancer: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2014;46(11):990–1053.
71. Cao Y, Gu J, Deng S, Li J, Wu K, Cai K. Long-term tumour outcomes of self-expanding metal stents as 'bridge to surgery' for the treatment of colorectal cancer with malignant obstruction: a systematic review and meta-analysis. Int J Color Dis. 2019;34(11):1827–38.
72. Amelung FJ, Burghgraef TA, Tanis PJ, van Hooft JE, Ter Borg F, Siersema PD, Bemelman WA, Consten ECJ. Critical appraisal of oncological safety of stent as bridge to surgery in left-sided obstructing colon cancer; a systematic review and meta-analysis. Crit Rev Oncol Hematol. 2018;131:66–75.
73. Ribeiro IB, Bernardo WM, Martins BDC, de Moura DTH, Baba ER, Josino IR, Miyahima NT, Coronel Cordero MA, Visconti TAC, Ide E, Sakai P, de Moura EGH. Colonic stent versus emergency surgery as treatment of malignant colonic obstruction in the palliative setting: a systematic review and meta-analysis. Endosc Int Open. 2018;6(5):E558–67.
74. Repici A, Fregonese D, Costamagna G, Dumas R, Kahler G, Meisner S, Giovannini M, Freeman J, Petruziello L, Hervoso C, Comunale S, Faroux R. Ultraflex precision colonic stent placement for palliation of malignant colonic obstruction: a prospective multicenter study. Gastrointest Endosc. 2007;66(5):920–7.
75. Gunnells D, Whitlow C. Malignant bowel obstructions. Semin Colon Rectal Surg. 2019;30(3):100684.
76. DiMaio CJ, Dorfman MP, Gardner GJ, Nash GM, Schattner MA, Markowitz AJ, Chi DS, Gerdes H. Covered esophageal self-expandable metal stents in the nonoperative management of postoperative colorectal anastomotic leaks. Gastrointest Endosc. 2012;76(2):431–5.
77. Cooper CJ, Morales A, Othman MO. Outcomes of the use of fully covered esophageal self-expandable stent in the management of colorectal anastomotic strictures and leaks. Diagn Ther Endosc. 2014;2014:187541.

Preoperative Evaluation in Colorectal Patients

6

Ron G. Landmann and Todd D. Francone

Key Concepts

- Patients undergoing elective abdominal colorectal operations are in the "intermediate" risk group for perioperative morbidity and mortality.
- Recognition and optimization of concomitant patient pathophysiology are paramount in minimizing sepsis (anastomotic leak, surgical site infection), complications, and overall morbidity.
- These include cardiopulmonary, renal, metabolic, and endocrine physiology and other pathophysiologic risk factors and derangements (such as frailty and immunosuppression).
- Implementation of ACC/AHA guidelines and evidence-based medical management leads to improved efficiencies with minimization of extraneous testing and delays, while preserving low complication rates.
- Corticosteroids and immunosuppression remain significant determinants of morbidity in patients undergoing intestinal colorectal surgery.
- Prehabilitation of the frail and elderly patient is critical in optimizing patients for surgery while attempting to mitigate perioperative morbidity and mortality.

Evaluation of the Routine Colorectal Patients

In Office by Surgeon

A detailed history and physical examination are paramount to the evaluation and optimal management of a preoperative patient. A thorough review of the patient's chief complaint as well as associated signs and symptoms and confounding issues or factors is necessary to synthesize an appropriate diagnosis and perioperative plan. Careful attention to the patient's medical comorbidities and past surgical history, as well as review and reconciliation of the patient's medications, is relevant to help coordinate perioperative management and operative planning. In patients who require multidisciplinary care such as inflammatory bowel disease and rectal cancer, it is imperative to ascertain the other specialists' contact information for optimal coordination of care. Similarly, specialist communication should be coordinated for patients who have significant cardiopulmonary disease or other major medical comorbidities. Personal review of source documentation for pertinent pathology, endoscopy, and radiological findings is critical in establishing a diagnosis and individualized plan of care. In many cases, the above may require coordination among more than one physician and more than one healthcare organization to achieve optimal perioperative care and outcomes, while minimizing morbidity.

Abdominal Surgery

In preparation for patients undergoing abdominal surgery, the history should include a reconciliation of active medications, including blood thinners and over-the-counter drugs or topical agents. The history should include complementary or alternative medicine practices and substances, including various legal or illegal drug use. Personal and/or family history of clotting or bleeding disorders (or bleeding complications from prior surgery) should be obtained. Additionally, the surgeon should ask about activity level in order to estimate exercise capacity. Frailty or poor baseline exercise capacity has been shown to adversely correlate with increased risk of perioperative cardiac complications. Can the patient walk up a flight of stairs, do heavy housework, or walk up a hill? A "Yes" to these questions indicates that the patient can perform at least four METs (metabolic equivalents), and if oth-

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erwise healthy, the patient does not need a preoperative cardiac workup [1]. Similarly, if patients are unable to get up from a chair and easily and briskly walk to the examination table, this is a surrogate marker for frailty and indicative of perioperative morbidity and need for preoperative optimization with prehabilitation (see "Frailty" below).

The history should also specifically investigate any prior operations that the patient may have had, including those requiring resection and particularly changes and/or alterations in mesenteric vascular anatomy. Knowing this a priori may help with decision-making including the need for preoperative imaging and staging as well as intraoperative assessment and surgical planning.

Anorectal Surgery

Due to the lower acuity and physiological demands placed on the patient during outpatient anorectal surgical procedures, most healthy patients generally do not require extensive preoperative workup. Patients with preexisting common comorbidities of hypertension, hyperlipidemia, or diabetes that are otherwise well controlled, as measured with normal physiological range of values, may not require an additional preoperative evaluation.

Preoperative Testing

Laboratory Studies

Multiple studies have demonstrated that routine preoperative labs have a low yield in identifying abnormalities that require a change in the management of otherwise healthy, asymptomatic patients. A selective approach to preoperative laboratory studies should be taken based on the evidence outlined in this section. A landmark retrospective study of 2000 patients undergoing elective surgery demonstrated that approximately 60% of all preoperative laboratory studies were not indicated and only 0.2% of these non-indicated tests (which occurred in ten patients) revealed abnormalities that could potentially result in a change in management [2]. Further analysis of these ten individual patient charts was performed and it was determined that no further actions were taken in any instance. When laboratory tests are indicated, results from the 3-month timeframe prior to surgery may be used, unless there has been a change in clinical status.

Hemoglobin is recommended for all patients of ages 65 or older who are undergoing abdominal surgery. Younger patients should be tested if there is potential for major blood loss, or if the history is suggestive of anemia. *White blood cell count* as a screening test is of limited utility but is certainly relevant in cases where recent infection has been treated or in the setting of immunosuppression. *Platelet counts* should be checked if the patient will undergo spinal or epidural anesthesia. *Coagulation studies and bleeding time* are not needed in patients with no personal or family history of bleeding disorders. Further, abnormal prothrombin time and bleeding time have not been shown in large studies to correlate with increased risk of intraoperative or postoperative bleeding complications [3, 4]. Pre-transfusion testing consisting of *ABO and Rh typing* ("type and screen") should be performed preoperatively in all patients undergoing major abdominal surgery, including bowel resection. This is particularly important for patients who have a significant transfusion history and who may have multiple alloantibodies.

Serum *creatinine* should be checked in patients 50 years or older, as elevated creatinine is an independent predictor of increased postoperative cardiac complications [5], as well as mortality [6] in elective noncardiac surgery. Further, some anesthetics require dose adjustments for patients with impaired renal function, so this information is vital to our anesthesia colleagues. Routine *electrolytes* are not required unless the patient has a history of prior electrolyte abnormalities, chronic kidney disease, or diuretic use. Routine blood **glucose** measurements are not indicated in nondiabetic patients, as the incidence of asymptomatic hyperglycemia is low [7]. The same logic also applies to *liver function tests*, which also should not be routinely ordered in a healthy, asymptomatic patient [4]. Routine *urinalysis* does not need to be performed in healthy, asymptomatic patients and should be only performed on a more selective basis in patients with history of frequent urinary tract infections or other relevant urinary symptoms. In most instances, asymptomatic patients with positive urinalyses may be treated empirically for urinary tract infection and may proceed with elective abdominal surgery as scheduled. Most studies of the utility of preoperative urinalysis are from the orthopedic surgery literature, and they do not demonstrate a correlation between preoperative positive urinalysis or bacteriuria and postoperative infectious complications [8]. *Pregnancy tests* should be performed on all women of childbearing age if the results would alter management [9]. While serum human chorionic gonadotropin (hCG) assays are the most sensitive in detecting very early pregnancy, most urine pregnancy tests are positive within a week of a missed period and can be processed quickly in the preoperative setting.

Electrocardiogram

Electrocardiograms (ECGs) are quick, noninvasive, and inexpensive; consequently, they are overutilized in the routine preoperative workup of most patients. In asymptomatic patients undergoing low-risk surgery, ECG is unlikely to identify abnormalities that result in a change in management. Further, the incidence of abnormal ECGs is very low in patients under 65 years old. According to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, preoperative ECG should be performed on patients with known heart disease, peripheral arterial dis-

ease, or cerebrovascular disease [10, 11]. Accordingly, implementation of these ACC/AHA guidelines in a preoperative clinic led to a reduction in exercise stress testing, lower hospital length of stay, increased beta-blocker therapy, and improved preoperative testing appropriateness while preserving a low cardiac complication rate [12].

Chest X-Ray

The American College of Physicians recommends obtaining chest X-ray (CXR) for patients with known cardiopulmonary disease, as well as all patients 50 years or older who require major abdominal surgery [13]. The American Heart Association also recommends CXR (posterior–anterior and lateral views) on obese patients with BMI ≥40 [14]. Despite these recommendations, CXR are low yield in identifying clinically significant abnormalities that necessitate or alter management [15].

Advanced Diagnostic Imaging

Depending on the underlying diagnosis, additional advanced diagnostic imaging may be either beneficial for operative planning or necessary for appropriate staging. In the setting of Crohn's disease, magnetic resonance enterography (MR enterography) is a valuable adjunct to evaluate the small and large intestine and determine if there is any other disease that may require attention intraoperatively. MR enterography has supplanted fluoroscopy or small bowel follow-through examinations. The benefit of MR enterography is its ability to provide objective functional assessment of motility as well as differentiation from active inflammatory disease vs. chronic fibrotic disease of the bowel wall, the former being more amenable to medical therapy and the latter often necessitating surgical intervention. Similarly, MRI of the pelvis is now the standard imaging modality for rectal cancer and is required for appropriate locoregional staging.

In the setting of colon or rectal cancer, CT of the chest, abdomen, and pelvis is recommended for appropriate distant metastatic disease evaluation. In addition, CT scan may benefit operative planning and determining if other organs are involved in the disease process and may require en-bloc resection (i.e., duodenum, pancreas, ureters) secondary to invasive T4 disease. Similarly, for diverticulitis, CT scanning may help with preoperative planning and adjacent structure inflammation. Furthermore, CT may be beneficial and is the preferred method in evaluation for abscess and fistula.

Cardiac Evaluation

Assessment of Cardiac Risk

Appropriate preoperative assessment is essential to identify patients who may be at increased risk. Further preoperative investigation and intervention will help minimize the potential for adverse perioperative cardiac events. In general, surgical risk groups are based on the type of surgery and defined as "low," "intermediate," and "high-risk," with 30-day cardiac event rates (MI and death) of <1%, 1–5%, and >5%, respectively [16]. The highest risk noncardiac procedures include vascular, thoracic, and transplant procedures [17]. All abdominal procedures involving the colon and rectum are included within the "intermediate" risk group (at a minimum) with perforated viscera classified as "high risk" (Table 6.1) [18]. Laparoscopic cases are treated similarly to open cases regarding cardiac risk. Patients presenting in the emergency setting should not be delayed for further cardiac workup such that the benefit of a detailed cardiac assessment is overshadowed by the risk of delaying care of an acute intra-abdominal pathology such as perforated viscus and sepsis.

Table 6.1 Surgical risk estimates according to the type of surgery or intervention [160]

Low risk: <1%	Intermediate risk: 1–5%	High risk: >5%
Superficial surgery	Intraperitoneal: splenectomy, hiatal hernia repair, cholecystectomy	Aortic and major vascular surgeries
Breast	Carotid symptomatic (CEA or CAS)	Open lower limb revascularization or amputation or thromboembolecomy
Dental	Peripheral arterial angioplasty	Duodeno-pancreatic surgery
Endocrine: thyroid	Endovascular aneurysm repair	Liver resection, bile duct injury
Eye	Head and neck injury	Esophagectomy
Reconstructive	Neurological or orthopedic: major (hip and spine injury)	Repair of perforated bowel
Carotid asymptomatic (CEA or CAS)	Urologic or gynecological: major	Adrenal resection
Gynecology: minor	Renal transplant	Total cystectomy
Orthopedic: minor (meniscectomy)	Intra-thoracic: non-major	Pneumonectomy
Urologic: minor (transurethral resection of the prostate)		Pulmonary or liver transplant

Initial Workup

The most common postoperative cardiac events include myocardial infarction, heart failure, arrhythmia, and cardiac arrest. The first step in determining whether a patient is at high risk is to obtain a detailed history and physical during the office consultation. Symptoms requiring further investi-

gation include but are not limited to palpitations, chest pain, syncope, dyspnea, and orthopnea. Not only is a history of cardiac disease important (including valvular or ischemic heart disease, cardiomyopathy, and arrhythmia), but also a history of diabetes, renal impairment, peripheral artery disease, and cerebrovascular disease can be extremely relevant in assessing risk due to their association with coronary artery disease [19]. Clinical cardiac risk factors include angina, prior MI, heart failure, stroke/transient ischemic attack (TIA), renal dysfunction, and Insulin-Dependent Diabetes Mellitus (IDDM). Additionally, exercise tolerance, ambulatory EKG changes, echocardiographic changes demonstrating prior MI, valvular disease or left ventricular diastolic dysfunction, and positive stress test have also been associated with increased risk of perioperative cardiac event [20].

Of specific importance is an assessment of a patient's functional capacity. It is estimated based on patient daily activity or measured with exercise testing. As a reference, 1 MET is an expended metabolic equivalent at rest, 4 METs are equivalent to climbing 2 flights of stairs, and 10 METs represent strenuous sports activities. Patients with greater than 4 METs do not require further cardiac workup, regardless of risk factors. Patients with less than 4 METs are considered to have poor functional capacity in which current guidelines recommend to undergo further cardiac evaluation and risk-benefit analysis (Table 6.2) [16, 21]. A recent study of 12,846 patients undergoing elective resection for colorectal malignancy demonstrated significantly lowered postoperative complications and mortality in patients who had preoperative leisure-time physical activity with MET ≥12 compared to those with an MET <12 (12.1% vs. 14.9%, $p = 0.006$ and 0.3% vs. 0.8%, $p = 0.009$, respectively). Indeed, this increased activity level also was significantly correlated with an increased disease-free and overall survival in these patients undergoing colorectal cancer surgery (62.8% vs. 55.7%, −< 0.0001 and 66.7% vs. 58.7%, $p < 0.0001$) [22]. There are several validated models that can be used by the clinician to predict the risk of peri-cardiac adverse events. The simplest of these models is the Revised Goldman Cardiac Risk Index (RCRI) (Table 6.3) [5]. Other user-friendly models including the American College of Surgeons National Surgical Quality Improvement Program (ACS–NSQIP) risk calculator require more input variables but will also provide procedure-specific quantification of other noncardiac risk factors [23].

Table 6.2 Cardiac risk metabolic equivalents are used to measure functional capacity and are often utilized for preoperative risk assessment in surgical candidates of all ages

Excellent (>7 METs)	Moderate (4–7 METs)	Poor (<4 METs)
Playing squash	Cycling	Vacuuming
Jogging – pace of 10 minutes/mile	Playing golf (no cart)	Activities of daily living
Scrubbing floors	Walking 4 mph	Walking 2 mph
Singles tennis match	Gardening	Writing

One MET = oxygen consumption of a 70 kg, 40-year-old at rest
Adapted from ACC/AHA guidelines

Table 6.3 Goldman Cardiac Risk Index is a tool used to estimate a patient's risk of perioperative cardiac complications [38]

	Points
History	
MI within 6 months	10
Age >70 years	5
Physical examination	
S3 or jugular vein depression	11
Significant aortic stenosis	3
Electrocardiogram	
Rhythm other than sinus or sinus rhythm with or without atrial premature complexes on last ECG	7
Five premature ventricular complexes/min any time before surgery	7
Other factors	
Poor general medical status	3
Intraperitoneal intrathoracic or aortic operation	3
Emergency operation	4
Total points	53

Probability of life-threatening complications based on risk index points

Class	**Points**	**None/minor complications (%)**	**Probability of life-threatening complications (%)**	**Cardiac death (%)**
I	0–5	99	0.7	0.2
II	6–12	93	5	2
III	13–25	86	11	2
IV	>26	22	22	56

Additional Testing

Further testing has been recommended for patients with a greater than 1% risk of perioperative death from cardiac disease as these patients are more likely to have a known history of recent myocardial infarction, unstable angina, heart failure, valvular disease, or arrhythmias [11]. These patients should be evaluated by their cardiologist. Additionally, anything less than 4 METs is considered poor functional capacity but is not strongly associated with worsened cardiac outcomes in abdominal surgery. Current guidelines recommend patients with poor functional capacity to undergo further cardiac evaluation and risk-benefit analysis [16, 21]. Figure 6.1 describes a generalized algorithm for determining the need for further workup in elective noncardiac colorectal surgery patients.

Further testing may include echocardiography, stress test (exercise or pharmacologic), 24-hour ambulatory monitoring, and cardiac catheterization. Patients undergoing medium risk surgery (i.e., abdominal surgery) without risk factors should be considered for an EKG evaluation per recent ACC/

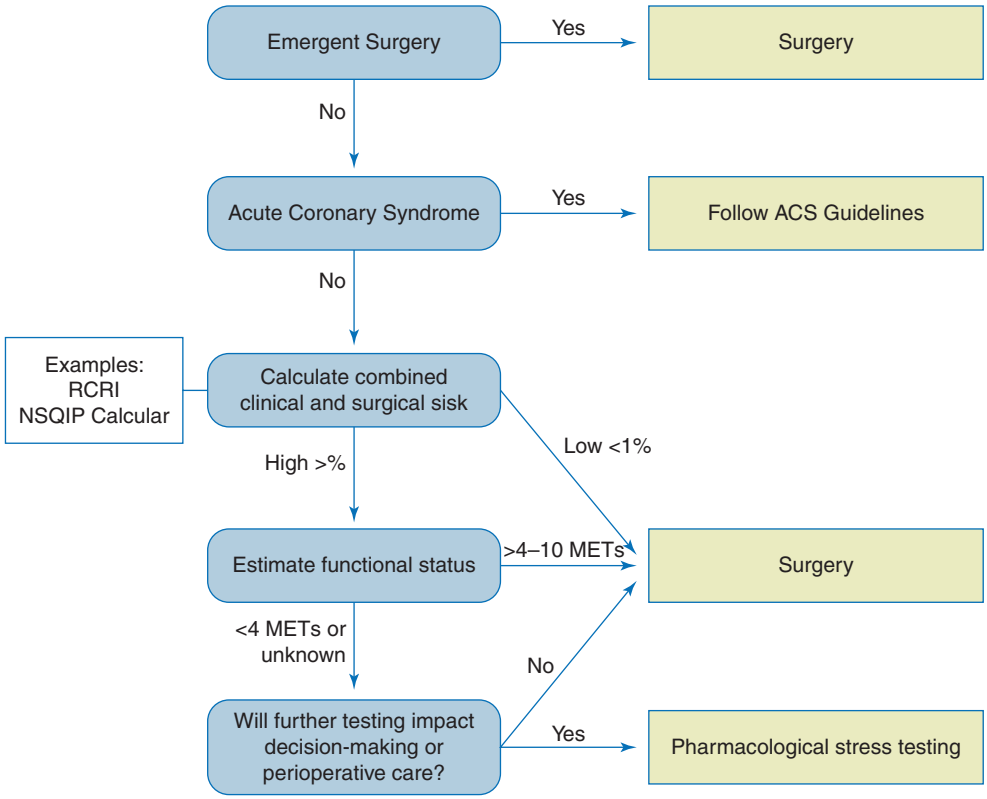

Fig. 6.1 Algorithm to determine the need for further cardiac workup in noncardiac patients undergoing colon and rectal surgeries

AHA guidelines. EKG is required for patients with presence of cardiac risk factors prior to any surgical intervention. Echocardiography is not required for patients free of cardiac symptoms but should be considered in patients undergoing high-risk surgery or who have cardiac risk factors [20, 21]. Image stress testing should be performed in patients with multiple risk factors undergoing medium-to-high risk surgery and poor or unknown functional capacity if it will change management.

Patients with unstable symptoms, a high-risk/abnormal stress test, concern for severe CAD (with or without left ventricle dysfunction), or those refractory to medical therapy, should undergo coronary angiography. Revascularization is indicated only when dictated by other guidelines; however, routine coronary revascularization should not be performed exclusively to reduce perioperative risks [11]. Interestingly, there is minimal evidence to suggest that preoperative revascularization reduces risk in non-cardiac surgery. Instead of cardiac catheterization, beta-blockade and statins pre- and perioperatively are strongly recommended [20].

Preoperative Optimization and Medical Therapy

The need for medical optimization prior to surgery is dictated by the findings of the cardiac evaluation. Patients on longstanding beta-blockers should be continued with their medical regimens. However, beta-blockers should not be initiated *de novo* in the preoperative setting. Multiple studies and meta-analyses have documented a significant increase in the risk of nonfatal stroke and myocardial ischemic events and hypertensive-related morbidity and mortality when beta-blockers are started within 24 hours prior to surgery [24, 25]. Antihypertension medications can be adjusted to avoid perioperative hypotension targeting a systolic blood pressure of 116–130 mmHg at a heart rate of 60–70 bpm. When diagnosed, new dysrhythmias can be controlled with antiarrhythmic agents. Decompensated heart failure increases perioperative risk and this risk may be mitigated by treatment with ACE inhibitors, aldosterone antagonist, and digoxin for at least 1 week preoperatively [26]. Patients may continue to take statins previously prescribed. Preoperative initiation of statins is reasonable in patients undergoing vascular surgery; however, there is no data to support starting statins preemptively in the setting of colorectal surgery [25].

Preoperative Anticoagulation

In recent years, several novel oral anticoagulants have become commercially available and are widely used in patients with atrial fibrillation or history of stroke in addition to placement of coronary or endovascular stents. Table 6.4 summarizes the more commonly seen anticoagulants and recommendations for perioperative management. For all patients taking anticoagulant therapy who are scheduled for a procedure, it is important to carefully review the medical history, medication list, and laboratory test results to identify

Table 6.4 Description and perioperative recommendations for common oral anticoagulant agents

Agent	Pathophysiology	When to interrupt	Temporary interruption recommendations (when to stop/restart)	Management of life-threatening bleed
Warfarin (Coumadin)	Vitamin K antagonist Inhibits the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X as well as the anticoagulant proteins C and S Half-life of approximately 36–42 hours	*Do not interrupt therapy with VKA in patients undergoing procedures with:* No clinically important or low bleed risk; *AND* Absence of patient-related factor(s) that increase the risk of bleeding *Interrupt therapy with a VKA in:* Patients undergoing procedures with intermediate or high bleed risk, *OR* Patients undergoing procedures with uncertain bleed risk and the presence of patient-related factor(s) that increase the risk of bleeding *Consider interrupting a VKA on the basis of both clinical judgment and consultation with the proceduralist and the patient's physician*	When interrupting VKA therapy, the VKA should be stopped: 3–4 days prior to procedure (for INR 1.5–1.9) 5 days prior to procedure (for INR 2.0–3.0) At least 5 days prior to procedure (for INR >3.0) The INR should be re-checked within 24 hours before the procedure Most abdominal procedures are safe to operate with INR <1.4 Provided adequate hemostasis during surgery, warfarin can be restarted as early as 12–24 hours after surgery, although timing will depend on the indication for anticoagulation	For urgent surgery, warfarin can be reversed with vitamin K (2.5–5 mg oral or intravenous) For emergency surgery, warfarin can be rapidly reversed with fresh frozen plasma (FFP)
DOCA 1. Apixaban 2. Dabigatran 3. Edoxaban 4. Rivaroxaban	Factor Xa inhibitor anticoagulant agents Rapid onset of action (1–3 hours) Dose must be decreased for Cr ≥5, age >80 and body weight ≤50 kg Do not require bridging with parenteral anticoagulants No need for routine monitoring of anticoagulation (will prolong PT/PTT/INR)	Interrupt therapy for intermediate, high, or uncertain bleed-risk procedures in: Patients treated with any of the approved DOACs for a duration based on the estimated CrCI	*Duration for withholding is based upon the estimated DOAC half-life* Uncertain, intermediate, or high procedural bleeding risk: 4–5 during half-lives *High-risk procedures:* Typically STOP 3 days prior (Cr CI >50); RESUME 2–3 days postop (provided adequate hemostasis during surgery) *Low-risk procedures:* Typically STOP 2 days prior; RESUME 1 day postop (provided adequate hemostasis during procedure)	*Management of life-threatening bleed:* *Dabigatran* – idarucizumab 2 doses of 2.5 g IV no more than 15 minutes apart; activated charcoal, supportive care; consider 4-component PCC *Apixaban, Edoxaban, Rivaroxaban* – Andexanet alfa (AndexXa), activated charcoal, supportive care, consider 4-component PCC
Clopidrogel	Platelet receptor PY12 blocker Typical maintenance dose 75 mg or orally per day Typically used in patients with history of MI or stroke or coronary stent placement		If discontinued prior to surgery: 5–7 days prior to the procedure Start as soon as possible postoperatively	Platelet transfusion
Heparin (unfractionated)	Binds to and inactivates antithrombin III Half-life of 45 minutes Easier to use, faster to reverse Preferable in patients with renal insufficiency		In preparation for surgery Hold 6 hours prior to surgery	Protamine sulfate

Table 6.4 (continued)

Agent	Pathophysiology	When to interrupt	Temporary interruption recommendations (when to stop/restart)	Management of life-threatening bleed
Heparin (low molecular weight heparin)	Half-life of 3–5 hours Comparable efficacy to unfractionated heparin Administered via subcutaneous injection Does not require monitoring		In preparation for surgery Twice daily dosing – the evening dose should be held on the night prior to surgery Once daily dosing – half dose should be given on the morning of the surgery	Protamine sulfate

factors that may increase the risk for bleeding. Temporary interruption or the omission of more than one dose of an oral anticoagulant in preparation for a procedure is frequently necessary to mitigate the increased bleeding risk with surgical procedures. Based on the clinical history and the type of procedure to be performed, the risks and benefits of temporary interruption should be discussed with the patient and a collaborative discussion should occur between the patient's anticoagulation management team and the surgeon [11].

Two main categories of anticoagulation are utilized for nonvalvular atrial fibrillation. Coumadin remains the most widely used vitamin K antagonist (VKA). More recently, direct oral anticoagulants (DOAC) are being frequently utilized with certain advantages over VKA including rapid onset of action (1–3 hours) and unrequired routine monitoring of anticoagulation, and most of the time bridging is not required. Since the DOACs became clinically available, there has been concern regarding their use due to the lack of a specific reversal agent in case of major bleeding complications. Recently, significant progress has been made in this area, with the approval of the monoclonal antibody fragment idarucizumab for the reversal of dabigatran [27, 28] and the approval of andexanet Alfa for the reversal of apixaban, edoxaban, and rivaroxaban [29]. Table 6.4 summarizes the most recent recommendation from the American College of Cardiology (ACC) for management of anticoagulation in the nonvalvular heart disease patient [11, 28]. When considering these recommendations, the importance of collaborating with the patient's primary care physician or cardiologist cannot be understated, given the complexity of the decision-making. It is worth noting that there remains a boxed warning regarding the association of DOACs and the increased risk of spinal or epidural hematomas with neuroaxial anesthesia. Therefore, DOACs should not be routinely utilized for perioperative anticoagulation if an epidural or spinal anesthesia is planned [28].

Coronary Stent Management

The current recommendation for management of coronary stents in patients with either bare-metal stent or drug-eluting stent is to continue dual antiplatelet therapy (DAPT – aspirin plus an oral antiplatelet agent such as clopidrogel, prasurgel, and ticagrelor) for at least 12 months. The risk of stent thrombosis in the perioperative period for both BMS and DES is highest in the first 4–6 weeks after stent implantation. Discontinuation of DAPT, particularly in this early period, is a strong risk factor for stent thrombosis [30]. Should urgent or emergency noncardiac surgery be required, a decision to continue aspirin or DAPT should be individualized, with the risk weighed against the benefits of continuing therapy. For patients who need to undergo nonemergent noncardiac surgery, the recommendation is to wait at least 30 days for patients with bare-metal stents before discontinuing the anticoagulation therapy. For those patients with drug-eluting stents, it is recommended to continue anticoagulation for more than 6 months after placement of the stent; however, based on an individual case review, 3–6 months of therapy can be considered. During the time of discontinuing the antiplatelet therapy, it is recommended to continue low-dose aspirin and resume the P2Y12 inhibitors as soon as possible. These recommendations are based on data that quantifies the risk of postoperative coronary and cerebrovascular thrombotic events in this patient population (Table 6.4) [28].

In situations where patients with a drug-eluting stent require emergent abdominal surgery within 3 months of stent placement, alternative anticoagulant therapy should be considered. These patients can be safely bridged with IV infusions of short-acting antiplatelet agents such as tirofiban. Tirofiban can be started within 24 hours of the operation, discontinued 4 hours preoperatively, and restarted 2 hours postoperatively until clopidrogel is resumed. It should be emphasized that in these special situations, coordination of the bridging between clopidrogel and short-acting agents requires close coordination between the surgeon, cardiologist, and anesthesiologist. [28]

Bridging

Assessment of a patient's thrombotic and bleeding risk is essential to determine the need for bridging therapy while anticoagulation is being held. For the most part, bridging is used for VKA, given DOACs typically do not require bridging. Several risk scores have been proposed to broadly evalu-

Table 6.5 General recommendation on when to bridge and restart anticoagulation therapy after surgical procedures [28]

When to Bridge
Use of bridging parenteral heparin should only be considered in the following two scenarios:
VKA-treated patients at high risk of stroke or systemic embolism (>10% per year), including those with a CHA_2DS_2-VASc score of 7–9 or a recent (within 3 months) ischemic stroke
Determine the patient's bleed risk to determine the appropriateness of bridging therapy
If increased risk of bleeding, interruption of the VKA without bridging is recommended
If NO significant bleed risk:
(a) In patients with prior stroke, TIA, or SE, consider use of a parenteral anticoagulant for periprocedural bridging (use clinical judgment, likely bridge);
(b) In patients with no prior stroke, TIA, or SE, the use of a parenteral anticoagulant for periprocedural bridging is not advised (use clinical judgment, likely do not bridge)
Low Thrombotic Risk
(<5%/year), with a CHA_2DS_2-VASc score of <4 or/and
No prior history of ischemic stroke, TIA, or SE
Discontinue the VKA prior to the procedure and resume *without* bridging
Moderate Thrombotic Risk
(5–10%/year) with a CHA_2DS_2-VASc score of 5–6 or
History of prior ischemic stroke, TIA, or
Peripheral arterial embolism (3 months previously)
Parenteral bridging anticoagulation should be considered
High Thrombotic Risk
High risk of stroke or systemic embolism (>10% per year) with a CHA_2DS_2-VASc score of 7–9 or
Recent (within 3 months) ischemic stroke, TIA, or SE
Parenteral bridging anticoagulation should be considered
When to Restart
Restarting VAC therapy post-procedure
Before restarting oral anticoagulation therapy, ensure complete hemostasis
VKA therapy can usually be restarted within 24 hours and parenteral heparin bridging (if indicated) within 24–72 hours depending on post-procedure bleeding risk
Restarting DOAC therapy post-procedure
Establish that hemostasis has been achieved
Following procedures with low postprocedural bleed risk, it is reasonable to resume DOAC therapy at full dose on the day following the procedure
Following high postprocedural bleed risk procedures, it is reasonable to wait at least 48–72 hours before resuming DOAC therapy at full dose
DOAC dosing should reflect postprocedural renal function
Bridging therapeutic anticoagulation with a parenteral agent is generally not required

ate bleeding risk in patients with atrial fibrillation, the most widely used of which is the HAS-BLED score (Tables 6.5 and 6.6) [31]. It incorporates hypertension; renal or hepatic impairment; prior stroke, TIA, or systemic embolization (SE); history of a major bleed; a labile INR; and age >65 years. The tool is used to assess 1-year risk of major bleeding in patients taking anticoagulants with a score of ≥3 indicating "high risk." The CHA_2DS_2-VASc score can be used to assess an individual patient's overall thrombotic risk.

Table 6.6 The HAS-BLED score: Used to assess a patient's thrombotic and bleed risk which is essential to determine the need for bridging therapy

HAS-BLED parameters
Hypertension
Abnormal renal function
Abnormal liver function
Prior stroke
History of or predisposition to (anemia) major bleeding
Labile INR (VKA)
Elderly (>65 years)
Concomitant use of an antiplatelet agent or nonsteroidal anti-inflammatory drug
Alcohol or drug usage history (≥ drinks/week)
Additional items included in the periprocedural management algorithm
Prior bleed event within 3 months (including intracranial hemorrhage)
Quantitative or qualitative platelet abnormality
INR above the therapeutic range at the time of the procedure (VKA)
Bleed history from previous bridging
Bleed history with similar procedure

The score incorporates multiple factors including hypertension; renal or hepatic impairment; prior stroke, TIA, or systemic embolization (SE); history of a major bleed; a labile INR; and age >65 years [31]

Table 6.7 CHA_2DS_2-VASc score can be used to assess an individual patient's overall thrombotic risk

Risk factors			Stroke risk per year	
			Score	% Rate per year
C	Congestive heart failure	+1 Point	0	0
H	Hypertension	+1 Point	1	1.3
A_2	Age ≥75	+2 Point	2	2.2
D	Diabetes	+1 Point	3	3.2
S_2	Stroke/TIA history	+2 Point	4	4.0
V	Vascular disease	+1 Point	5	6.7
A	Age 65–74	+1 Point	6	9.8
S	Sex (female)	+1 Point	7	9.6
			8	6.7
			9	15.2

It incorporates the known thrombotic risk factors into a scoring system. As the thrombotic risk increases, the need for bridging becomes more apparent [32]

It incorporates heart failure, hypertension, age, diabetes, stroke, or transient ischemic attack (TIA), vascular disease, and female sex into a scoring system (Table 6.7). The need for bridging correlates directly with thrombotic risk but must be evaluated against the risk of bleeding complications [32, 33]. General recommendations and guidelines for bridging and restarting anticoagulation can be found in Table 6.4 and are in accordance to the America College of Cardiology consensus statement for perioperative management of anticoagulation [28].

Patients who have undergone cardiac valve replacement may have received mechanical or bioprosthetic valves. Mechanical valves require lifelong anticoagulation but are durable and the need for a second surgery is significantly less

than with bioprosthetic valves. Anticoagulation with mechanical valves is achieved using warfarin. Bioprosthetic valves do not require lifelong anticoagulation and thus are associated with fewer bleeding complications but they are less durable and associated with higher morbidity and mortality rates. Bioprostheses require anticoagulation for 3 months unless a transcatheter aortic valve replacement (TAVR) was performed in which aspirin and clopidrogel may be considered an alternative. After 3 months, patients with minimal thrombotic risk may be managed on aspirin alone with additional anticoagulation for higher risk patients. Concomitant low-dose aspirin is recommended for patients with mechanical valves and as sole thromboembolism prophylaxis for patients receiving aortic or mitral bioprosthetic valves [28].

Like coronary stents, the risk of thromboembolism in the first few months after mechanical valve or bioprosthetic valve repair is increased. Therefore, elective noncardiac surgery should be avoided if possible. Evidence-based guidelines exist; however, these decisions should be made in collaboration with the patient's cardiologist and or hematologist. In general, for minor procedures with the ability to easily control bleeding, interruption of warfarin may not be required. If a patient taking warfarin is to undergo a surgical procedure that requires interruption of anticoagulation, bridging therapy with heparin is indicated if the patient has a mechanical aortic valve and any risk of thromboembolism. The warfarin should be held for 5 days. Bridging of anticoagulation with low molecular weight heparin (LMWH) should begin 3–4 days preoperatively or when the INR is <2.0. The last dose should be given 24 hours prior to the operation and an INR should be obtained the day of surgery. Most abdominal surgeries can safely proceed with INR ≤1.4. LMWH or an unfractionated heparin drip should be held during the first 48 hours postoperatively or until hemostasis is assured, while continuing standard DVT prophylaxis. The warfarin should be restarted at the preoperative dose as soon as possible after the procedure when deemed safe by the surgical team. If possible, continue aspirin through the perioperative stay [34].

AICD/Management

Patients with automatic implantable cardioverter defibrillators (AICD) often have underlying ischemic heart disease which should not be overlooked during the preoperative assessment. It is critical for both the surgeon and the anesthesiologist to communicate with the patient's cardiologist and for the anesthesiologist to find out whether the patient is pacemaker-dependent versus independent. Some patients may have pacemaker-dependent atrial, ventricular, or both chambers paced 100% of the time. For these patients, the device may need to be reprogrammed intraoperatively. For those patients who are not pacemaker dependent, the anesthesiologist should place a magnet over the device which will prevent inappropriate delivery of shocks and trigger of arrhythmic events. All AICD patients should have an external defibrillator and transcutaneous pacer immediately available and the electroconductive pad affixed to the patient at the start of the case. In the emergent settings, in which a formal cardiology consult is not feasible, a 12-lead EKG can be used to determine pacemaker dependence. Of note, the AICD activity can be affected by monopolar cautery causing electromagnetic interference. This can result in delivery of a shock to the patient or inadequate or inappropriate pacing. Minimal use of monopolar cautery and preferential use of alternative devices such as bipolar or ultrasonic energy can help decrease the risk of electromagnetic interference [28, 35].

Pulmonary Assessment

Postoperative pulmonary complications contribute significantly to overall morbidity and mortality. Complications may include atelectasis, infection, including bronchitis and pneumonia, hypoxemia, exacerbation of underlying chronic obstructive pulmonary disease (COPD), asthma, or respiratory failure (mechanical ventilation for >48 hours after surgery or unplanned reintubation). The reported frequency of postoperative pulmonary complications in the literature varies from 2% to 70% with one study utilizing the NSQIP database demonstrating a 6% rate of pulmonary complications in 165,196 patients who underwent major abdominal surgery [36]. A more recent multicenter prospective observational study by Fernandez-Bustamante et al. evaluated postoperative pulmonary complications (PPC) in 7 US academic institutions. The study demonstrated that at least one PPC occurred in 401 patients (33.4%), the majority of which included patients requiring prolonged oxygen therapy by nasal cannula (n = 235; 19.6%) and atelectasis (n = 206; 17.1%). Patients with one or more PPCs had significantly increased early postoperative mortality, intensive care unit (ICU) admission, and ICU/hospital length of stay [37].

Preoperative optimization is the best way to minimize risk. Routine pulmonary function tests are NOT indicated for healthy patients prior to surgery. Clinical findings are more predictive of the risk of postoperative pulmonary complications than are spirometric results. These findings include decreased breath sounds, prolonged expiratory phase, rales, rhonchi, or wheezes. Tests generally should be reserved for patients who have dyspnea that remains unexplained after careful clinical evaluation or other high-risk factors. Risk factors for pulmonary complications can be grouped into patient-related and procedure-related risks. Chronic obstructive pulmonary disease (COPD) has been demonstrated to be the single most important risk factor for development of postoperative pulmonary failure. Up to 25% of elderly

patients with COPD have an operative pulmonary complication, with mortality approaching 7% [21]. Other patient-related risk factors include advanced age, American Society of Anesthesiologists class 2 or higher, functional dependence, elevated Goldman Cardiac Risk Index [38], and congestive heart failure. Interestingly, obesity is not a pertinent risk factor [21]. Procedure-related risk factors include aortic aneurysm repair, non-resective thoracic surgery, abdominal surgery, neurosurgery, emergency surgery, general anesthesia, head and neck surgery, vascular surgery, and prolonged surgery [13].

Patients with increased risk factors should be evaluated by their primary care physicians and/or pulmonologists if they see a specialist. Bronchodilators should be continued perioperatively. Glucocorticoid use must be balanced against potential increased risk for complications such as anastomotic leak. In patients with history of tobacco abuse, smoking cessation for more than 6–8 weeks is recommended [20]. If patients pursue smoking cessation, duration needs to be greater than 2 months; otherwise, risk of pulmonary complications is significantly increased. This includes patients who cut down before surgery, with relative risk of 6.7 for individuals undergoing major non-cardiac surgery [39].

Obstructive sleep apnea is one of the most common sleep disorders and is characterized by upper airway obstruction causing apneic episodes. It is important to recognize obstructive sleep apnea preoperatively as it is a risk factor for perioperative cardiopulmonary complications and can be associated with unplanned ICU admissions [40]. Patients undergoing major abdominal surgery should be screened and managed for obstructive sleep apnea, similar to those patients with high BMI and multiple comorbidities. Common symptoms of sleep apnea include loud snoring, daytime sleepiness, and witnessed apnea by a sleep partner; however, other symptoms may include morning headaches, poor concentration, altered mood, vivid or disturbing dreams, restless sleep, GERD, and nocturia. Screening tools are available such as the STOP-Bang questionnaire, in which patients with high scores may be referred to a pulmonologist for formal workup [41].

Perioperative Steroid Management

Colorectal surgeons will often encounter patients on chronic steroid therapy as it is a primary treatment for many conditions such as inflammatory bowel disease, rheumatologic disease, reactive airway disease, and immunosuppression for transplant recipients. Due to the increased physiological stress, patients on chronic steroid therapy are at risk for developing secondary adrenal insufficiency that may manifest as an adrenal crisis in the perioperative period. Signs and symptoms of adrenal crisis may include altered mental status/psychosis, abdominal pain, nausea/vomiting, weakness, and hypotension. In addition to suppression of the hypothalamic-pituitary-adrenal (HPA) axis, the potential adverse effects of perioperative glucocorticoids are numerous. Adverse effects can include impaired wound healing; increased atrophy and tearing of skin, superficial blood vessels, and other tissues; increased risk of fractures, gastrointestinal hemorrhage, ulcer; and increased postoperative infections such as anastomotic leak. The surgeon, in collaboration with anesthesiology, will need to consider whether the benefit of administering perioperative stress dose steroids to mitigate the risk for an adrenal crisis outweighs its potential risks [42].

The decision to administer supplemental exogenous stress glucocorticoids is not always straightforward and there is a lack of data regarding standard protocols. This is in part related to the lack of data demonstrating the dose or duration of exogenous steroids required to cause a dysfunction in the HPA access. Prednisone, 20 mg/day, or its equivalent for more than 3 weeks, has been cited as the most common dose causing suppression. The exact time course of recovery from HPA axis suppression may differ between individuals; however, most agree that suppression does not continue beyond 1 year after cessation of exogenous steroid therapy, except for patients receiving intraarticular glucocorticoid injections [42].

Several approaches to glucocorticoid dosing have been proposed. These protocols categorize patients into high-, intermediate-, and low- risk groups for HPA-axis suppression or stratify based on the anticipated surgical stress associated with a minor, moderate, or major surgery (Table 6.8). Of note, patients who have diagnosed secondary adrenal insufficiency, as demonstrated by the short-acting ACTH test, will require perioperative stress-dose steroids with dosing based on surgical stress risk. Hydrocortisone is the drug of choice for acute stress and rescue-dose steroid coverage [42].

Recent data suggest that stress-dose steroids may not be necessary [43]. Instead, these patients may be maintained on their usual preoperative dose and treated with rescue dose steroids only if refractory hypotension presents in the perioperative period. In 2012, a retrospective cohort study of patients with inflammatory bowel disease undergoing surgery demonstrated that patients who received only low-dose perioperative steroids (the equivalent of their preoperative dose given intravenously) did not require vasopressors for hemodynamic instability or additional steroids for adrenal insufficiency [44]. Similarly, in a randomized trial of patients undergoing major colorectal surgery, no differences in postural hypotension or adrenal insufficiency were seen between those receiving high-dose glucocorticoids (hydrocortisone 100 mg intravenously three times daily) or low-dose glucocorticoids (the equivalent of their preoperative dose given intravenously) [45]. Although this data is promising, perioperative stress-dose steroid administration appears to carry minimal risk compared to the risk of adrenal crisis. Hence, patients who are at risk for HPA-axis suppression should be considered for steroid replacement therapy in the perioperative setting [42].

Diabetes

Diabetic patients represent a complex subset of surgical patients, who often have long-term complications of their

Table 6.8 Several approaches to glucocorticoid dosing have been proposed which categorize patients into high-, intermediate-, and low- risk groups for HPA-axis suppression or the anticipated surgical stress associated with a minor, moderate, or major surgery [42]

Surgery type	Examples	Recommendations
Superficial	Dental surgery Biopsy	Usual daily dose
Minor	Inguinal hernia repair Colonoscopy Anorectal surgery Uterine curettage Hand surgery	Daily dose plus hydrocortisone (25 mg IV)
Moderate	Lower extremity revascularization Total joint replacement Cholecystectomy Colon resection Abdominal hysterectomy	Daily dose plus hydrocortisone (50–75 mg IV; taper 1–2 days)
Major	Esophagectomy Total proctocolectomy Major cardiac/vascular procedures Hepaticojejunostomy Trauma	Daily dose plus hydrocortisone (100–150 mg IV; taper 1–2 days)
Risk for HPAA Suppression		**Recommendations**
Low	Treated with any dose of glucocorticoid for less than 3 weeks Morning doses of prednisone 5 mg/day or less Prednisone 10 mg/day every other day	Perioperative stress-dose steroids are not required unless they exhibit signs of HPAA suppression
High	Patients who have been treated with a glucocorticoid in doses equivalent to at least 20 mg/day of prednisone for more than 3 weeks or who have clinical features of Cushing syndrome	Patients would benefit from perioperative stress-dose steroids with dosing based on surgical stress

disease (neuropathy, visual impairment, peripheral, and mesenteric vascular disease), as well as other related comorbidities, such as chronic renal insufficiency and cardiovascular disease [5, 46] that can significantly impair perioperative outcomes. The initial office consultation with the surgeon should include a detailed history, focusing on the type and duration of diabetes, symptoms, how glucose is monitored at home, baseline glucose range, glycated hemoglobin (Hgb A1c) levels, related symptoms, as well as the contact information of their primary care physician and/or endocrinologist. Diabetic patients undergoing major abdominal surgery should have the following as part of their preoperative workup: ECG, CXR, serum creatinine, serum glucose, and an A1c level (within 4–6 weeks preoperatively). In particular, elevated A1c levels have been shown in cardiac surgery to be associated with increased risk of surgical complications, including infections, myocardial infarction, and death [47]. Close perioperative involvement of the anesthesiologist is also critical, as some patients undergoing major operations will require preoperative intravenous insulin infusion to attain euglycemia prior to initiation of surgery [48]. Additionally, these same patients may require insulin administration intraoperatively. The surgeon should be cognizant that most operations cause a catabolic state with elevated blood sugars. These elevated glycemic levels may be significantly more pronounced in a preexisting diabetic patient and necessitate attention postoperatively. All diabetic patients should be maintained on a postoperative insulin sliding scale regimen, in addition to their home medications. Perioperative elevated blood sugars are concerning as they may lead to perioperative wound infections and anastomotic dehiscence. Due to the cardiac complication rates, as well as increased incidence of septic sequelae, many centers will postpone operations in patients with elevated Hgb A1c levels >6.5 until improved blood sugar control can be achieved [49, 50].

Obesity

More than one-thirds of adults in the USA are obese, which is defined as having body-mass index (BMI) of 30 kg/m^2 or more. One in 20 adults is considered super-obese (BMI of 40 kg/m^2 or more) [51]. BMI is considered a screening tool to identify obesity and is calculated as the patient's weight (in kilograms) divided by square of the height (in meters). The obese patient creates substantial technical challenges for the surgeon. In terms of postoperative morbidity, obese patients undergoing nonbariatric abdominal surgery have been shown to have increased risk of perioperative venous thromboembolism and superficial site infection. A prospective study of over 6000 patients found that the risk of superficial site infection after open abdominal surgery was 4% for obese versus 3% for nonobese patients, $P = 0.03$ [52]. Other studies based on ACS-NSQIP data demonstrated incremental odds of surgical site infection with progressive classes of obesity, as well as increased wound disruption, sepsis, respiratory or renal complication, and urinary tract infection [53]. Studies have demonstrated increased thromboembolism, superficial site infection rates, and inability to create pouches or anastomoses to the lower rectum or anus in obese population [53–56]. Obesity also significantly increases operative time in colorectal procedures [55, 56]. Most importantly, obesity has been demonstrated to increase anastomotic (pouch-anal) leak rate [56].

Obese patients pose significant intraoperative challenges, some of which can be mitigated with appropriate preoperative planning. Much of the difficulty in operating on patients with obesity is due to the visceral adiposity and bulky mesentery, leading to difficult intraabdominal and pelvic exposure as well as manipulation and reach of the visceral contents [56]. For example, if a stoma may be needed, a visit

from the enterostomal therapist is extremely important, as marking on the slightly thinner upper abdomen will be helpful. It is especially important to ensure that these patients can reach their stoma, so they can care for it independently. Both laparoscopic and open surgeries are technically demanding in obese patients; however, if feasible, performance of laparoscopic surgery has the advantage of smaller incisions, less pain, and improved visualization for the surgeon. Avoiding lower midline and Pfannenstiel incisions is helpful in minimizing superficial site infections and other wound-related complications in obese patients with a large pannus. Clear communication with the operating room staff prior to the case is essential to ensure availability of long instruments, deep retractors, appropriate beds, and equipment such as blood pressure cuffs and large pneumatic compression boots. Due to the increased risk associated with operative outcomes in patients with obesity, many have advocated for weight loss preoperatively, and in some cases recommended bariatric surgery, to promote optimal outcomes [57, 58].

As will be discussed later, obesity itself does not predispose a patient from being malnourished. Indeed, the opposite can be quite true, and many patients with obesity demonstrate protein calorie malnutrition and sarcopenia, as demonstrated by low albumin and prealbumin levels as well as muscle wasting on cross-sectional imaging [59, 60]. Methods to reduce visceral and systemic adiposity while improving protein stores preoperatively are imperative to improve operative and postoperative outcomes [61]. Options include very low calorie diets, pharmacotherapy, or metabolic surgery. These allow for reduction in adiposity of the mesentery, shrinkage of the liver, and downsizing of the fat pads in the lower pelvis – all thereby permitting better exposure and visualization of the intraabdominal and pelvic spaces, safer identification of critical structures, and improved mobilization of the colon and/or small bowel for improved reach when required for more distal anastomoses [62].

It should be noted that in the setting of malignancy, increasing length of time to surgery while optimizing the patient status has no effect on disease-specific survival. Indeed, this preoperative management and prehabilitation intervention improve the patient's overall physiological status and subsequently reduce postoperative complications and mortality, while lowering the length of stay [58].

Malnutrition

Colorectal surgeons are commonly faced with challenging patients who are malnourished due to advanced malignancies or inflammatory bowel disease that results in intestinal blockages, intestinal fistulas, poor absorptive capacity, and large volume losses from the GI tract. Nutritional risk tends to be a reflection of the patient's overall health and in oncology has correlated with the Eastern Cooperative Oncology Group score and the presence of anorexia or fatigue [63].

Such nutritional risk is associated with increased postoperative complications, longer length of stay, and higher mortality following elective surgery [64, 65] and is particularly pronounced in patients with colorectal cancer [66]. Incidence remains under-recognized and malnutrition continues to negatively impact postoperative recovery and patient outcomes, as well as mortality [67]. Although logistically challenging, nutritional support can be delivered in the preoperative or postoperative setting and can be administered via the enteral and parenteral routes. Most studies are limited by heterogeneous patient populations, variable study designs, different feeding protocols that often result in parenteral overfeeding, and outdated methodologies. When delivered appropriately, malnourished colorectal patients realize several benefits from perioperative nutritional support including fewer postoperative complications, shorter hospital length of stay, and lower mortality [68].

The evaluation of potentially malnourished patients begins with the history and physical examination. Most patients will complain of some degree of intolerance of oral intake as a result of poor appetite, nausea, abdominal bloating, abdominal pain, and weakness. Patients will relate a recent weight loss, typically over a 1–3 month time period. On physical examination, the patient appears thin, pale, and weak with muscle wasting and loose skin. These variables can be objectified using grading systems such as the relatively intuitive Subjective Global Assessment (SGA) to classify patients as well nourished, moderately malnourished, or severely malnourished [69]. The SGA utilizes five features of the history (weight loss over 6 months, dietary intake change, gastrointestinal symptoms, functional capacity, and the impact of disease on nutritional requirements) and four features of the clinical exam (loss of subcutaneous fat, muscle wasting, ankle edema, sacral edema, ascites) to elicit an SGA rank based on subjective weighting. Serum albumin level has been considered the "classic" test reflecting overall nutritional status, with serum concentration <4.0 g/dL defining the "malnourished state."

Recent groups have recommended that hypoalbuminemia, with levels below 4/dL, serves as a negative prognostic marker for adverse postoperative outcomes including mortality and serious morbidity. These authors have recommended adding hypoalbuminemia as a risk factor when utilizing the ACS-NSQIP Surgical Risk Calculator to improve estimation of surgical risks to patients and surgeons [70]. However, in real practice, its utility and reliability are limited as levels fluctuate for many reasons, including production alterations in the catabolic or anabolic states, external losses, or redistribution between the various fluid compartments of the body [71]. Other short turnover proteins such as prealbumin, transferrin, and retinol-binding protein have similar limitations as nutritional markers as a result of variable half-lives and response to dietary intake and renal/

liver dysfunction, although all these proteins can be useful when followed as trends over time.

Similarly, sarcopenia has been investigated as a factor in preoperatively assessing risk for postoperative morbidity and mortality. This variable is generally measured using psoas muscle cross-sectional area on CT or MRI, generally at the lumbar vertebra (L3) and normalizing for patient height. A recent study evaluated 350 patients undergoing colorectal surgery for malignancy at a tertiary care center. Of these, nearly a third were found to be sarcopenic. Sarcopenia was associated with a significantly increased length of stay (13 days vs. 7 days; $p < 0.01$) and 1-year mortality (13.9% vs. 0.9%, $p < 0.01$). Sarcopenia was also associated with a significant increased risk of any complication (85.2% vs. 34.5%, $p < 0.01$) and of major complications (30.4% vs. 8.9%, $p < 0.01$) [72]. Preoperative identification of these sarcopenic malnourished patients affords the surgical team an opportunity to prehabilitate the patient with improved nutritional support and exercise regimen leading to an improved anabolic state. This is aimed with a goal of improved perioperative physiological status and risk mitigation.

Inflammatory bowel disease, intestinal obstruction, large tumors, fistulizing diseases, and patients with diarrhea are often unable to sustain themselves orally due to a poor appetite or resultant abdominal bloating and pain. This limits the ability to intervene preoperatively, particularly when considering utilizing the enteral route. Options include oral nutritional supplements (standard or immunonutrition) or feeding via nasoenteric feeding tubes. Total parenteral nutrition (TPN) can be used if central intravenous access is obtained, an appropriate formula is prescribed (1.5 g protein per kilogram and 25 kcal per kilogram), and tight glycemic control is maintained (serum blood sugars <150 g/dL).

Unfortunately, the use of preoperative nutrition has not been well studied in the malnourished GI surgery patient populations. A recent Cochrane review [73] highlights this paucity of evidence and the reality that many of the studies are outdated, with only two trials evaluating the administration of enteral nutrition (years 1992 and 2009) including only 120 participants and a high risk of bias. Neither study showed any difference in primary outcomes. The three studies that evaluated preoperative parenteral nutrition (years 1982, 1988, and 1992) showed a significant reduction in postoperative complications, predominantly in malnourished patients.

Solid Organ Transplant Recipients

The introduction of novel, more effective immunosuppression regimens has resulted in improved long-term survival after solid organ transplant. Over 150,000 patients in the USA are living with functional kidney transplants, and this number is on the rise. It is increasingly common for surgeons to encounter transplant patients in their practice, in both the elective and emergency settings. The vast majority of these patients are maintained on chronic immunosuppressive regimens. These agents are generally continued throughout the perioperative and early postoperative period in order to minimize the risk of rejection. Many patients are now on life-long chronic immunosuppressive agents. It is therefore essential that surgeons familiarize themselves with the more commonly used immunosuppressive agents and their effect on wound and anastomotic healing and subsequent impact on perioperative outcomes. Coordination of care with the transplant team is necessary prior to elective surgery.

The newer immunosuppressive agents, sirolimus and everolimus, which belong to the drug class known as inhibitors of the mammalian target of rapamycin (mTOR), have been shown to negatively impact healing of surgical wounds. mTOR is a cytoplasmic kinase that is essential for cell growth and proliferation [74]. Inhibition of lymphocyte proliferation despite stimulation results in immunosuppression. This same mechanism is also responsible for inhibition of the wound healing process. In a prospective trial of 123 patients randomized to receive either sirolimus or tacrolimus on postoperative day 4 after kidney transplant, Dean et al. found a significantly higher rate of wound-related complications (including superficial site infection and incisional hernias) in the sirolimus cohort compared to those receiving tacrolimus (47% vs. 8%, $P < 0.0001$) [75]. This data has prompted clinicians to replace mTOR inhibitors with tacrolimus for 6 weeks prior to elective surgery. Whenever possible, non-operative management may be prudent in patients on chronic immunosuppression. Patients who are on therapy status post-transplant are more likely to require emergency operation and more likely to have a stoma created, whether or not restoration of intestinal continuity is achieved at the index operation. These patients similarly have an increased mortality rate when compared to patients who have not undergone solid organ transplants and are on immunosuppression [76]. Traditionally, patients who were immunocompromised had been recommended to undergo early elective resection for diverticulitis. However, this is no longer the case and should be addressed on an individual basis.

Substance Abuse

All surgical patients should be asked about their use of tobacco, alcohol, and street drugs. A large database study from 2002 determined that 7.6% of Americans had a substance abuse disorder within the prior year (95% CI 6.6–8.6%) [77]. The surgeon must also recognize narcotic dependency and use of prescription opioids that are not medically indicated. It is important for surgeons to make patients feel comfortable in answering these questions honestly and accurately. It is never safe to simply assume that a particular patient does not fit the expected profile of an "alcoholic" or "drug addict." Substance abuse has been shown to affect the elderly [78], as well as

highly functional individuals with families and careers [79]. It is therefore critical to screen *all* patients preoperatively in order to minimize perioperative risk.

Alcohol

Alcoholism has been shown to be associated with a number of different perioperative complications in a dose-dependent manner. Large studies have demonstrated that alcoholism is associated with surgical site and other infections, cardiopulmonary complications, and also correlates with longer hospital stay, increased rates of ICU stay, and increased rates of reoperation [80, 81]. The AUDIT-C questionnaire is a validated screening tool that can be used by the clinician to identify patients at high risk for perioperative complications [82]. A randomized controlled trial of 41 patients with alcoholism (defined as consumption >60 g ethanol per day) undergoing elective colorectal surgery demonstrated that abstinence 1 month preoperatively was associated with fewer cardiac complications, including myocardial ischemia (23% vs. 85%, $P < 0.05$) and arrhythmias (33% vs. 86%, $P < 0.05$), as well as overall decreased complication rate (31% vs. 74%, $P = 0.02$) [83]. It is unknown what the optimal alcohol-free interval is prior to elective surgery, in terms of maximizing risk reduction, although the trial investigators recommend 3–8 weeks, highlighting the importance of intensive counseling and monitoring of these patients during this interval [83].

Tobacco

Smoking has been shown in multiple studies to increase perioperative pulmonary risk, as well as risk of wound infections, neurologic complications, and ICU admission [84]. The best way to minimize this risk is to encourage patients to quit smoking prior to elective surgery. Previously it was felt that smoking cessation less than 8 weeks preoperatively was associated with a paradoxical increase in pulmonary complications, possibly due to a compensatory increase in secretions. This has now been disproven in multiple large studies. A large trial of 522 smokers undergoing gastric cancer surgery compared risk of postoperative pulmonary complications between three groups: (1) active smokers or those who quit less than 2 weeks prior to surgery, (2) those who quit 4–8 weeks prior, and (3) those who quit 8 or more weeks prior to surgery. The odds ratios for postoperative pulmonary complications were 2.92 for group 1 (95% CI 1.45–5.90), 0.98 for group 2 (0.28–3.45), and 1.42 for group 3 (0.66–3.05) [85]. Therefore, the recommendation is to encourage smoking cessation, regardless of the timing of surgery, although ideally surgery can be planned for at least 4 weeks from the "quit date."

Opioids

There are many different types of patients with chronic opioid dependence, including abusers of street drugs such as heroin; abusers of prescription-only opioids; patients with prior history of opioid abuse, maintained on long-acting agents such as methadone; and patients on long-term narcotics prescribed for a chronic medical condition. Overall, prescription opioid use is on the rise in the USA and therefore this is being encountered by the surgeon with increasing frequency [86]. For all patients on narcotics, the surgeon should always ask preoperatively what the indication is, how long they have been taking it, side effects (such as constipation), whether there is a plan to wean off the drug, and who has been prescribing it. The patient's responses should be corroborated with the prescribing physician and/or medical record. Regardless of whether it is warranted for an underlying condition, opioid dependency will result in increased narcotic requirements perioperatively. Whenever possible, it is helpful to involve the acute pain management service preoperatively in order to provide the best perioperative pain management. Non-narcotic adjunct therapies can be considered, including thoracic epidural catheters, transversus abdominus plane (TAP) blocks, and drugs such as ketorolac (Toradol), acetaminophen, and gabapentin (Neurontin). Preoperatively, a clear plan should be made with the patient and the clinician who has been prescribing chronic opioids regarding postoperative pain management following hospital discharge, particularly who will be prescribing and for how long. This is instrumental in avoiding concerns in the outpatient setting with overprescribing and relapse.

Other Illicit Drugs

All patients undergoing elective surgery should be screened for the use of illicit drugs – not just "street drugs" but also other prescription-only drugs, such as benzodiazepines, that are not medically indicated. For patients requiring elective surgery, intensive efforts should be made to encourage cessation prior to planned surgery. This requires clear communication with the patient's primary care physician and/or psychiatrist. Discussion of individual drugs is beyond the scope of this chapter; however, additional information is well summarized in this 2014 reference from the anesthesia literature [87].

Consideration of Specific Perioperative Medication Management

Immunosuppressive Agents

When reviewing the literature on patients with diverticulitis on immunosuppression, there was an increased rate of emergent operation (40%) with index presentation compared to the general population (10–25%). On Biondo's review, the only variable associated with higher risk of surgery was chronic corticosteroid therapy, and this was likely attributed

to the masking of clinical symptoms of sepsis and delay in presentation and diagnosis. Consequently, morbidity was higher in the immunosuppressed patients (30.7%), despite a very high success rate with non-operative management (60.7%) of all patients presenting with acute diverticulitis. Mortality was 6.9% and this was in patients with severe comorbidities that precluded surgical management. Overall, there was a low recurrence rate, and similar to patients not on immunosuppression. Recurrent episodes were primarily related to the initial severity index. Recurrence was significantly higher (5×) and predominantly noted in patients with chronic renal failure or collagen vascular disease (~36%), and for this reason, careful consideration for elective sigmoid resection may be justified in this select cohort [88].

Corticosteroids have been shown to impair wound healing in both animal models and clinical studies. In animal models, corticosteroids have been shown to alter multiple independent signaling pathways, impairing all three phases of wound healing: inflammatory, proliferative, and remodeling. Clinical studies have also demonstrated a higher rate of anastomotic complications in patients on chronic steroids [89]. A prospective study performed in the 1980s specifically evaluated the risk of steroids in Crohn's patients and demonstrated in multivariate analysis that corticosteroids were associated with an increased overall postoperative complication rate in Crohn's patients undergoing surgery involving bowel anastomosis (15.4% vs. 6.7%; $p = 0.03$) [90]. One of the largest studies looking at anastomotic leak (AL) in colorectal patients included 250 left-sided resections with anastomosis. The overall anastomotic leak rate was 7.5%. When patients were administered corticosteroids, either perioperatively or on long term, the multivariate model concluded that corticosteroid use increased the risk for AL by more than seven times (OR, 7.52; standard error, 4.47; $P = 0.001$; 95% CI, 2.35–24.08) [91]. A meta-analysis evaluating the risk of corticosteroids on colorectal anastomotic integrity that included 9564 patients from 12 studies demonstrated an overall leak rate of 6.77% (95% CI 5.48–9.06) compared to 3.26% (95% CI 2.94–3.58) in the non-corticosteroid group [92]. In ulcerative colitis, doses greater than 4 mg/day led to a statistically significant increase in complication. Similarly, in the Crohn's Therapy, Resource, Evaluation and Assessment Tool (TREAT), corticosteroids were shown to slightly increase the infectious complications (OR 2.21) [92].

In addition, corticosteroids impact wound healing and are a risk factor for the development of superficial and deep surgical site infections and have even been shown to impact postoperative mortality [74]. Another more recent meta-analysis on the effect of corticosteriods in the setting of ulcerative colitis and ileal pouch anastomotic complications demonstrated equivocal results [93]. Ultimately, this understanding allows the surgeon to better counsel the patient regarding possible postoperative complications, wean steroids during the preoperative period when possible, and make decisions in the operating room (such as the decision to create diverting stoma and wound closure) to optimize patient outcomes. Current recommendations state that patients who are on greater than 20 mg of prednisone daily, on steroids for greater than 2 months duration, and/or combined immunosuppression with biologics within 12 weeks are at highest risk for septic complications. In these patients, recommendations are to delay pouch creation or other anastomosis (consider modified 2- vs. 3-stage procedures), divert in the setting of, or delay, anastomosis, and wean steroids to less than or equal to 20 mg of prednisone daily for 2 weeks.

Immunomodulators, including azathioprine and 6-mercaptopurine, are used in both Crohn's disease and ulcerative colitis to maintain steroid-induced remission. These drugs often take 3–4 months until clinical benefit is apparent and have infrequent but serious side effects such as leucopenia, liver function abnormalities, pancreatitis, and lymphoma. A retrospective study of 417 operations involving bowel anastomoses for Crohn's disease demonstrated no difference in the rate of anastomotic complications for patients on immunomodulators (10% vs. 14%; $p = 0.263$) [75, 94]. Similar to the studies above, they also found that in multivariate analysis, corticosteroids (preoperative prednisolone 20 mg or more) was a predictor of anastomotic complication (OR 0.355, 95% CI 0.167–0.756; $p = 0.007$). Accordingly, these medications may be continued until surgery in some cases.

Biologic agents, including infliximab (Remicade), adalimumab (Humira), and cetolizumab (Cimzia), are chimeric monoclonal antibodies that target tumor necrosis factor, a proinflammatory cytokine that has been shown to be elevated in inflamed tissue of IBD patients. Biological and immunological agents, including infliximab, have been demonstrated to induce remission and control symptoms in patients with moderate-to-severe Crohn's and Ulcerative Colitis. Other biologic agents are more targeted in their behavior and mechanism of action: ustekinumab – anti-IL12/IL23; natalizumab – selective GI-specific anti-adhesion molecules(MadCAM-1); tofacitinib – JAK (Janus kinase) inhibitors - prevent STAT translocation, gene transcription, and lower cytokine production; vedolizumab – humanized monoclonal antibody to α4β7 integrin specific to GI endothelial cells blocking T-cell migration to inflamed GI tissue, also critical for anastomotic healing. With more widespread use of biologic agents in other inflammatory conditions such as rheumatoid arthritis and psoriasis, surgeons are seeing a larger percentage of patients on these agents perioperatively. Critically, though many of these newer agents are more selective in their mechanism and site of action, they also have the paradoxical effect on inhibiting the pathways necessary for appropriate anastomotic wound healing. Krane et al. performed a retrospective analysis

of 518 patients with IBD undergoing elective laparoscopic bowel resection, of which 142 patients were on preoperative infliximab [95]. There was no difference in the rate of anastomotic leak, which was overall low in both groups (2.1% with infliximab versus 1.3% without; $p = 0.81$). A significantly higher percentage of the patients on infliximab were also on steroids, 73.9% vs. 58.8%, $p = 0.006$, and still this did not impact anastomotic leak rate. A recent meta-analysis by Wong evaluated anti-TNF agents and postoperative outcomes in Crohn's disease. Though there was significant conflicting and controversial results secondary to heterogeneity in the trials, there was a consistent increase in infection complications by approximately 20% (OR 1.5) [96].

Similarly, when evaluating postoperative outcomes with ileal pouch anal anastomoses and the effects that anti-TNF biologic agents have, there was a split on the effect of these agents and adverse pouch-related and infectious complications [93]. Other studies at institutions with high volumes of inflammatory bowel disease and patients on biologics similarly supported an increase in infectious complications, OR 3.5 (anastomotic leaks $p = 0.02$, pouch specific complications $p = 0.01$, other infectious complications $p < 0.01$, and postoperative sepsis, OR 13.8) [97].

A more recent study reviewed 3860 patients undergoing colectomy for Crohn's disease from the NSQIP database. When investigating steroids and/or biologics within 30 days of elective colectomy, multivariate analysis concluded that immunosuppression led to statistically significant increases in infectious complications (OR 1.25; 95% CI 1.03–1.52), overall SSI (OR 1.40; 95% CI 1.13–1.74), organ space SSI (OR 1.47; 95% CI 1.09–1.98), and anastomotic leak (OR 1.41; 95% CI 1.02–2.25) [98].

Vedolizumab is a humanized monoclonal antibody to α4β7 integrin specific to GI endothelial cells. This agent results in blocking of T-cell migration to inflamed GI tissue. This same pathway and migration, however, are also critical for anastomotic healing. When investigating vedolizumab and SSI rate in surgical IBD patients, vedolizumab was demonstrated to increase all postoperative complications more so than when compared to anti-TNF agents or no treatment at all. Vedolizumab use within 12 weeks independently predicted 30-day postoperative SSI [99].

Most recently, the PUCCINI trial investigating risk factors for postoperative infection in patients with IBD was completed and recently published. This group concluded that preoperative use of anti-TNF drugs, as determined by history or by drug levels, was not an independent factor for postoperative infections. When evaluating surgical site infection, there was no statistically significant increase with preoperative TNF use within 12 weeks of surgery ($P = 0.92$) or if there was any detectable TNF level ($p = 0.513$). The results were similar when investigating any infectious complication ($p = 0.80$ and 0.985, respectively). Interestingly, no differences were seen with steroid use or preoperative use of other immunosuppressive agents [100, 101].[1] One of the biggest arguments against the findings in this study was that the group looked at any use within 12 weeks preoperatively. This window was significantly outside the 3× multiple of the biological agents half-life, with only 1.5% of the concentration bioavailable. This concentration would have no effect on any tissue and could not be expected to cause any effect on outcomes. Similarly, the study contradicts many other findings of the deleterious effect of corticosteroids on postoperative complications.

Overall, the current literature is quite conflicting and controversial in their findings. Biologics have significantly improved medical management of IBD, though without a significant reduction in role of surgery. While delaying necessity for surgery (particularly in UC), this comes at a cost of increased malnourishment and chronic illness of patients. Biologics have been shown to adversely impact wound healing and increase the risk of postop infectious and surgical complications. Though newer GI-specific therapies may resolve many of these issues, most surgeons and high-volume IBD centers prefer to hold these agents for the equivalent of 3.5 half-lives (6–8 weeks for most anti-TNFa agents, 12 weeks for vedolizumab) prior to major abdominal surgery [95]. Additionally, steroids should be weaned to 20 mg of prednisone daily and sustained for a minimum of 2 weeks preoperatively. Temporarily diverting stoma should be considered when unable to optimize these medical therapies preoperatively.

Chemotherapy Through a myriad of mechanisms, the final common pathway of cytotoxic chemotherapy is induction of cell death during the otherwise rapid proliferation and growth phase of neoplastic cells. Ideally this effect is minimized in nontumor cells, including healing anastomoses. Large studies have attempted to evaluate the overall effect of neoadjuvant and adjuvant chemotherapy on the rate of anastomotic leak, and there have been conflicting results. In a recent single-center study of 797 patients with a single anastomosis, Lucan et al. determined in multivariate analysis that preoperative chemotherapy was one of the strongest independent risk factors for anastomotic leak, with an odds ratio of 2.85 (95% CI 1.21–6.73, $P = 0.017$) [101]. Morse et al. performed a similar study of 682 patients with intestinal anastomoses over a 5-year period and determined in bivariate analysis that chemotherapy (administered within 6 weeks of the operation) was not a risk factor for anastomotic leak.

Nash published a series of 131 patients with diverticulitis in the setting of chemotherapy. Severity of symptoms was not associated with recent chemotherapy administration.

[1] Cohen et al. [100].

However, chemotherapy patients were more likely to recur with more severe disease, more likely to undergo emergent surgery (75.0% vs. 23.5%, $p = 0.03$), more likely to be diverted (100.0% vs. 25.0%, $p = 0.03$), more likely to incur a postoperative complication (100% vs. 9.1%, $p < 0.01$) following interval resection. These patients also were found to have a significantly increased overall mortality, with a lower median survival (3.4 years) (median survival not reached in non-chemotherapy patients). In summary, the group found that nonoperative management of diverticulitis was very successful in patients receiving chemotherapy and should be pursued. Though recurrent diverticulitis was not more common in cancer patients on chemotherapy, it was more likely to be complicated and led to surgery in the select cohort. The group also concluded that the interval of colon resection after a single episode of diverticulitis was not routinely indicated and that, indeed, chemotherapy can safely be resumed in most patients after acute diverticulitis episodes had resolved with medical management [102].

Biondo also published their review on the effects of immunosuppression in the setting of diverticulitis. Chronic corticosteroid therapy was associated with higher rates of emergency surgery. Recurrence was highest during the first year after the index episode, suggesting the need for appropriate surveillance. The need for emergency surgery for recurrence is comparable to that in the general population, and elective surgery in immunosuppressed patients should be individually indicated according to persistence of symptoms or early recurrences. Contrary to prior guidelines, and appropriately redirecting future practice parameters, Biondo concluded that prophylactic colectomy in immunosuppressed patients with diverticulosis cannot be recommended [88].

Bevacizumab (Avastin) is a humanized monoclonal antibody, which targets vascular endothelial growth factor A (VEGF-A) and is thought to work in solid tumors by restricting neoangiogenesis, which is necessary for tumor growth. It is the first of the antiangiogenic drugs to be approved for first-line treatment of metastatic colorectal cancer and is also used for other solid tumors including breast, kidney, ovarian, and lung cancers. Bevacizumab is associated with increased incidence of postoperative complications, including impaired wound healing and anastomotic leak.

Consequently, phase II and III studies of bevacizumab for colorectal cancer excluded patients who underwent major surgery within the previous 28 days [103–105]. Yoshioka et al. retrospectively evaluated 78 patients with resectable advanced or metastatic colorectal cancer who received neoadjuvant bevacizumab prior to surgical resection (this included 46 rectal resections and 4 colectomies) [106]. Overall median interval from last bevacizumab dose to surgery was 9 weeks; anastomotic leaks occurred in six patients, four of which required re-laparotomy. The mean interval from surgery to diagnosis of anastomotic leak was 15.8 days (range 4–34 days). Although the authors did not document mean in-hospital length of stay, presumably most of the leaks occurred after discharge. In multivariate analysis, primary colorectal anastomosis was the only independent predictive risk factor for major postoperative complications (OR 8.285; $P = 0.013$). Interestingly, the interval from last bevacizumab dose to surgery was not an independent risk factor for postoperative complications. Bevacizumab has also been associated with late anastomotic complications [106]. Unsurprisingly, other newer antiangiogenic drugs have also been implicated in the development of anastomotic leak, including pazopanib and aflibercept in small series and case reports [107]. As with most chemotherapy agents, current recommendations are to hold these antiangiogenic agents for at least 6 weeks before major surgery. Intestinal anastomosis and/or proximal diversion should be carefully considered due to the significant complication and leak rate.

Newer checkpoint inhibitors (anti-PD/PD-L1 immunotherapy) such as prembolizumab, nivolumab, or ipilimumab have been increasingly used in the armamentarium for colorectal and other diseases. In rare instances, urgent intestinal operation may be required. Though no specific intestinal surgical studies have been performed, other studies investigating bladder resections and conduit reconstruction in patients on pembrolizumab found that the morbidity rate was acceptable (69% >= Clavien-Dindo grade 2 complication) with no mortality appreciated [108]. Similarly, when evaluating safety and feasibility of lung surgery following immunotherapy, though the operations were technically challenging, significant morbidity appeared to be rare (32%), with encouraging postoperative disease-free survival [109].

Preoperative Assessment in the Elderly

Historically, advancing age has been utilized as a risk factor in predicting adverse perioperative outcomes in patients like other factors such as emergency surgery, ASA, and preoperative comorbidities, for instance, COPD or morbid obesity. As such, prior risk stratification models such as Colorectal Physiologic and Operative Severity Score for enumeration or Mortality and Morbidity (CR-POSSUM) [110, 111] and National Surgery Quality Improvement Program (NSQIP) Morbidity and Mortality Risk Calculator [112] utilize chronological age as a variant predictor of adverse perioperative outcomes. However, chronologic age has been shown to be a poor reflection of the functional, physical, and cognitive decline a patient may experience in their elder years. This poses a difficult challenge for today's surgeons as most surgeries in the United States are performed on patients older than the age of 65. Thus, most persons facing surgery are elderly, underlying the importance of appropriate preoperative evaluation of this patient population.

Defining the Elderly

The older population is a heterogeneous group with varying levels of health status. Commonly used predictors of postoperative complications are not tailored to the geriatric population. For example, the American Society of Anesthesiology classification is determined by a subjective estimate of organ system disease and likelihood of survival, while the Lee and Eagle Criteria account for cardiac function only. Growing evidence demonstrates that these models are limited in predicting perioperative risk since they do not account for the diverse levels of physiologic reserves in the older surgical patients.

The term "frailty" has been increasingly recognized as a surrogate for decreased physiologic reserve in the elder population. There is a lack of consensus on a standard definition of frailty in the literature, although it continues to evolve. It has been described as several phenotypes associated with the dysregulation of multiple physiologic systems. The two most utilized phenotypes include phenotypic frailty which includes assessment of physical activity, muscle strength, and energy level [113], while deficit-driven phenotype includes assessment of nutrition, cognition, medical condition, and functional decline [114].

Assessing Frailty

A multidimensional comprehensive geriatric assessment (CGA) is considered the gold standard for assessing frailty by geriatricians. The CGA generally includes a compilation of validated tools to assess comorbidity, functional status (including ability to live at home), physical performance, cognitive impairment, psychological status, nutritional status, medication review, and social support (Table 6.9)

Table 6.9 A comprehensive geriatric assessment (CGA) should be a key part of the treatment approach for all older cancer patients [115, 116]

Domain	Measures
Functional status	(1) Activities of Daily Living (Subscale of MOS Physical Health) [161] (2) Instrumental Activities of Daily Living (Subscale of the OARS) [162] (3) Karnofsky Performance [163] (4) Timed Up and Go [164] (5) Number of Falls in Last 6 Months [165]
Comorbidity	Physical Health Section (OARS Subscale) [162]
Cognition	Blessed Orientation-Memory-Concentration Test [166]
Psychological	Hospital Anxiety and Depression Scale [167–169]
Social Functioning	MOS Social Activity Limitations Measure [161]
Social Support	MOS Social Support Survey: Emotional/ Information & Tangible Subscales [161, 170]
Nutrition	(1) Body Mass Index [170] (2) % Unintentional Weight Loss in Last 6 Months [171, 172]

[115, 116]. On the whole, the benefits of a CGA include prolongation of life and prevention of hospitalizations and admissions to adult living facilities [117–120], prevention of geriatric syndromes such as delirium and falls [121, 122], prevention of cognitive decline [123], and detection of unsuspected conditions that may affect cancer treatment in more than 50% of patients aged 70 or over [124].

Complete Geriatric Assessment

Several studies have demonstrated the ability of CGA to predict surgical outcomes in the elder population [125, 126]. Early studies include a Norwegian study by Kristjansson et al. [127] in which the CGA was predictive of surgical morbidity in 178 elderly colorectal cancer patients with a median age of 80. This study is consistent with previous work identifying frailty as a predictor of surgical outcomes. Robinson and colleagues used seven frailty characteristics (Time Up and Go, Katz score, Mini-Cog, Charleston Index, anemia, poor nutrition, and geriatric syndrome of falls) to define frail, pre-frail, and non-frail individuals. Of the 201 patients who underwent major cardiac or colorectal procedures, frailty was independently associated with increased postoperative complications, prolonged hospital stay, and higher 30-day readmission rates [125]. More recently, a 2015 systemic review evaluated six studies on CGA and surgical outcomes in the geriatric oncology population. All studies included were prospective, cohort design and utilized validated questionnaires with data collected prior to surgery. Primary outcomes included 30-day postoperative complications (POC), mortality, and discharged to a non-home institution. Deficiencies in instrumental activities of daily living (iADL), activities of daily living (ADL), fatigue, cognition, frailty, and cognitive impairment were associated with increased postoperative complications. Although there were no CGA predictors for postoperative mortality, frailty, deficiencies in iADL, and depression were found to be predictive of discharge to a non-home institution. Major complications happen more frequently in patients with cognitive impairment, iADL, and activities of daily living (ADL). Interestingly, age was not associated with complication rates [128]. Similarly, a study by Shahrokin et al. evaluating 980 oncogeriatric patients aged 75 years or older demonstrated association between CGA deficits and 6-month mortality after stratification for multiple variables. Of note, ASA classification was not associated with 6-month mortality while each additional impairment identified on the CGA was associated with a 40% increase in the risk of a 6-month postoperative mortality [129].

Frailty Scores

Although comprehensive geriatric assessment is the most consistent in predicting outcomes in the geriatric population, a full CGA can take several hours to complete and may not be feasible in a busy surgical practice. Shorter more efficient

Table 6.10 Frailty score has been described as an age-associated decline in five domains: shrinking, weakness, exhaustion, low physical activity, and slow walking speed [113]

Domain	Definition
Shrinking	Unintentional weight loss ≥10pounds in the last year
Decreased grip strength	Patient squeezed a hand-held dynamometer (strength measurement was adjusted for BMI and gender)
Exhaustion	Response to questions about effort and motivation
Low physical activity	Survey about leisure time activities
Slowed walking speed	Speed at which patient could walk 15 feet

Adapted from Makary 2010 [126]

geriatric assessments have been developed to address the time constraints during acute evaluations, while demonstrating their ability to be as effective as the CGA in predicting postoperative complications [130–132]. In 2001, Fried et al. characterized frailty as an age-associated decline in five domains (Table 6.10): shrinking, weakness, exhaustion, low physical activity, and slow walking speed. The definition was instrumental in providing the framework to help define this challenging population [113]. In 2010, Makary and colleagues used the Fried criteria to establish the Hopkins' Frailty Score, which demonstrated that the frailty was a potentially useful tool in predicting poor outcomes in the elderly surgical population. Frailty was prospectively measured in 594 patents (aged 65 years or older who presented for elective major and minor surgeries). Patients scoring 4–5 were classified as frail, 2–3 were intermediately frail, and 0–1 were non-frail. Utilizing multiple logistic regression, frailty was shown to be independently associated with the development of postoperative complications (OR 2.54; 95% CI 1.12–5.77), length of stay (OR 1.69; 95% CI 1.28–2.23) and discharge to a skilled or assisted living facility after previously living at home (20.48; 95% CI5.54–75.68). In addition, when combined with other current risk assessment models such as ASA and Lee and Eagle scores, assessing frailty improved their predictive power [126].

In 2012, the American College of Surgeons recognized the importance of a CGA in the preoperative evaluation of elder patients. The American College of Surgeons NSQIP and American Geriatric Society collaborated to create best practices guidelines for the perioperative care of geriatric surgical patients. In addition to conducting a complete history and physical, the authors recommended evaluations of preoperative domains which included problems specific to elderly individuals. These domains are very similar if not the same domains included in the CGA discussed above and include cognitive impairment, frailty, poly-pharmacy, risk of malnutrition, and lack of family or social support. A proposed checklist was drafted for surgeons across all specialties to utilize in the evaluation of a surgical geriatric patient; however, translating the information into predicting clinical outcomes remained challenging (Table 6.11) [133].

Table 6.11 Preoperative workup for geriatric patients undergoing colorectal surgery

Cardiac assessment
I. Patients with active cardiac conditions require cardiology assessment and workup
II. Patients with over two clinical risk factors require heart rate management, but do not need cardiac testing unless results will change operative management
III. Patients undergoing low risk surgery, more than 3 METs, or fewer than 3 clinical risk factors may proceed with surgery
Pulmonary assessment
IV. Encourage smoking patients to quit more than 8 weeks postop, although 4 weeks may be long enough in some studies
V. Aggressive management of COPD and asthma
VI. Routine CXR and PFTs not indicated
Diabetes and glucose assessment
VII. Obtain baseline glucose level
VIII. Obtain baseline BUN and creatinine
Nutritional assessment
IX. Patients with BMI <18 or unintentional weight loss over 10% in 6 months require evaluation by a registered dietician
X. Preoperative nutritional
Anemia and hematologic assessment
XI. Obtain baseline hemoglobin and hematocrit
Cognitive assessment
All patients require adequate history from patient and family member
All patients require cognitive assessment (Mini-Cog)
All patients require anxiety/depression assessment
All patients require assessment of alcohol use, identification of possible abuse
All patients require evaluation of decision-making capacity to ensure informed consent
Any new findings, or worsening of existing findings, require further evaluation by appropriate geriatrician or mental health care provider
Laboratory and noninvasive testing
Unless previously indicated above, routine CBC, BMP, PT/PTT, EKG, CXR are not required

Composite indexes obtained from retrospective analysis of large national data spaces are more frequently being utilized to adequately assess the elder population in the preoperative setting, given they are considered quick and simple tools. One example is the modified frailty index (mFI) which was developed utilizing the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database [134]. This screening tool is favored among multiple surgical disciplines because it is based on easily identifiable relevant patient characteristics which can be extracted using a straightforward history and physical examination. It consists of 11 variables each of which corresponds to one point. The mFI has been shown to predict the 30-day readmission, major complications, wound complications, failure to adhere to enhance recovery protocols, discharge to non-home facilities, and mortality for surgical patients [135–137]. The risk analy-

sis index (RAI) is another composite index frequently used to predict outcomes and surgical patients. It consists of a 14-question survey which evaluates domains such as ADLs and cognitive decline along with more standard factors such as age, sex, and medical comorbidities. Initial studies by Hall et al. demonstrated the RAI to predict prolonged length of stay, out of ICU admission, discharged to nursing home, and mortality [138, 139].

Improving the preoperative evaluation of the elderly surgical patient to assess frailty is the first step in improving surgical outcomes in this heterogeneous, complex population. Preoperative assessments should not only be designed for early detection and treatment of surgical medical complications but should also be aimed at identifying at-risk individuals with modifiable risk factors in which targeted therapy may improve their outcomes. This sets the stage for the increasing interest in evaluating the impact of prehabilitation on the elderly population undergoing surgical intervention.

Table 6.12 Pre- and perioperative risk factors associated with increased risk of postoperative occurrence of delirium

Preoperative
Dementia
Age [20]
Malnutrition [145]
Cognitive impairment [155]
Visual impairment [155]
Dehydration [20]
Immobilization [20]
Polypharmacy [20]
Severe illness [155]
Perioperative
Poor fluid status [145]
Poor glycemic control >150 mg/dL
Metabolic derangements [20, 145]
Uncontrolled pain (PCA necessary to improve delirium in elderly patients) [155]
Addition of more than 4 new medications [145]
Bladder catheters [145]
Serum urea nitrogen to creatinine ratio >17 [155]
Prolonged bed rest
Physical restraints [145]

Cognitive Dysfunction and Delirium

Cognitive dysfunction is common in elderly patients, with rates between 5% and 15% in the general population but as high as 60% in high-risk groups [140]. The degree of dysfunction can vary between severe, otherwise known as dementia, and mild cognitive impairment (MCI). With MCI, the level of impairment is not severe enough to interfere with independent function [141, 142]. Both forms of cognitive dysfunction have been shown to be associated with worse surgical outcomes. Multiple studies have implicated both MCI and dementia as high-risk factors for postoperative delirium.

The American College of Surgeons and American Society of Geriatrics have advocated for the use of the MiniCog preoperatively to detect MCI [143]. The MiniCog screening test is a 3-minute instrument that can increase the detection of cognitive impairment in older adults. It consists of two components: a 3-item recall test for memory and a simply scored clock drawing test. Other tests include the Self-Administered Gerocognitive Examination (SAGE) which was developed by Scharre et al. [144]. It is a 12-item examination that is self-administered to detect MCI and early dementia in geriatric patients.

Delirium is the one of the most common postoperative complications in the elderly. It has been defined as a documented change in mental status characterized by reduced environmental awareness and attention disturbance. In a prospective analysis of patients aged over 70, undergoing abdominal surgery, the overall incidence of delirium was 60% with a 30-day mortality of 20% in those patients. In fact, 40% of patients had three or four risk factors for delirium [145]. In the Hospital Elder Life Program, focus and management of six factors reduced delirium: visual impairment, hearing impairment, cognitive impairment, sleep deprivation, immobility, and dehydration (Table 6.12). Treatment should not utilize medications as first-line therapy. Instead, avoidance of triggers, reorientation, massage, relaxing music, and one-on-one care with family are recommended. If medication is required, Haldol should be initially be considered and the clinician should refrain from restraints except in the most severe cases [146].

Prehabilitation

Increasing utilization of preoperative screening tools, such as mFI, in the geriatric population has resulted in further awareness of elders at risk for functional decline not only from a physical aspect but also from a nutritional and psychological status. These factors may be considered modifiable in which improvement may shift outcomes in a positive direction for this high-risk population. For this reason, there has been a concurrent in interest in developing preventive strategies to restore the functional capacity after surgery, reducing the clinical impact of reduced functional capacity. Prehabilitation is a multidisciplinary intervention focused on utilizing the perioperative period to optimize the patient to prevent or diminish the surgery-related stress leading to functional decline and its consequences. The multimodal approach includes exercise training, nutritional therapy, and anxiety reduction strategies [147].

Although the body of evidence is growing regarding prehabilitation, standardized consensus definition of rehabilitation remains lacking. And as such, there is signifi-

cant variation in the reported types of interventions and the recommended types of interventions, frequency, and duration [148–152]. Duration of intervention may vary between 5 days and 6 weeks and may occur at the patient's home, rehabilitation center, and outpatient or inpatient physiotherapy units. It is no surprise that all trials included exercises and elements of rehabilitation to improve the functional capacity and physiologic reserve.

Exercise

The goal of a prehabilitation program is to identify those with modifiable risk by assessing with screening tools for specific conditions and intervening prior to surgery. Based on the growing body of literature, exercise has been shown to be the main component. Programs focus on the ability of exercise to deliver a physiologic stress that causes an adaptive response in all organs and tissues and as such improve the ability of the body to withstand incoming stress for surgery. Training programs often utilize the three main categories of exercise (aerobic, resistance, and flexibility training) to complement each other and lead to a comprehensive functional outcome improvement [153]. Majority of programs demonstrated improvement in physical performance after undergoing a rehabilitation program. Screening tools that identify patients with decreased performance status include the ACS NSQIP surgical risk calculator along with a revised cardiac risk index. Performance status and functional capacity are often expressed and metabolic equivalents (METs) as described earlier in this chapter [16, 21].

Nutrition

Malnourishment affects between 2% and 32% of elderly, and that's among the "healthy" geriatric population. In hospitalized elderly patients, prevalence of malnourishment is between 1% and 83% [154, 155]. There is a sixfold increased risk of complications in malnourished elderly patients [21], which may be further amplified in the setting of gastrointestinal cancer. Further, poor preoperative nutritional status was independently associated with postoperative delirium and mortality in elderly patients. Therefore, optimization of nutritional status and enhancement of protein metabolism are paramount [145]. Nutritional screening tools can be used to properly identify the presence of undernutrition or the risk of developing undernutrition to select patients for nutritional therapy. Screening tools may include tools such as Subjective Global Assessment (SGA) Nutritional Risk Screening 2002 or Mini Nutritional Assessment (MNA) [154]. The nutritional intervention should be multimodal but individualized to the patient focusing on ensuring the patient (1) meets the energy requirements of daily expenditure, maintains energy stores, and promotes physiologic metabolic processes; (2) maintains a high protein diet; and (3) receives a balanced meal with adequate intake and proportion of all macronutrients.

Psychosocial Therapy

Physiologic stress of surgery is not only entirely related to the trauma of the surgery itself but can also be related to the psychological distress caused to the patient. Preoperative anxiety and depression have been shown to have a negative impact not only in quality life but also in wound healing, infection rates, length of stays, and adherence to medical treatments [153]. The psychological component of a multimodal rehabilitation program is aimed at reducing anxiety symptoms and distress with cognitive behavioral therapy. Interventions may include educational sessions to improve knowledge about surgery, relaxation, and imagery techniques such as passive breathing exercises, meditation skills, and guided imagery [156].

Outcomes

In theory, prehabilitation programs should mitigate surgical complications in high-risk individuals such as elders; however, currently there is little evidence to support this. Several studies have investigated the effect of prehabilitation on postoperative complications with only one study by Waite et al. demonstrating a significant impact on complications with a decrease in overall complications by 30% and severe complications by 20% in those patients awaiting cardiac surgery [157]. Reports vary on the effective prehabilitation with regard to mortality and length of stay. Most of the literature demonstrate no difference in mortality between those who undergo prehab and those who do not, except for the study by Waite et al. who demonstrated significant decrease in both 30-day mortality and 3-month mortality. Majority of the literature also demonstrate no difference between the length of stay and discharged institutionalization with no difference between the two groups. One study by Mazzola et al. demonstrated a trend toward reduced length of stay, while Waite et al. demonstrated a significant decrease in the length of stay for those undergoing prehab [150, 157].

Carli et al. performed a randomized trial evaluating the effectiveness of prehabilitation (versus rehabilitation) specifically on frail patients undergoing colorectal surgery for cancer [158]. In a cohort with a mean age of 78 years and with almost 80% of patients undergoing minimally invasive surgery, there was no difference in the primary outcome measure, 30-day Comprehensive Complications Index, or secondary outcome measures (30-day overall and severe complications, primary and total length of hospital stay, 30-day emergency department visits and hospital readmissions, recovery of walking capacity, and patient-reported outcome measures).

A recent systematic review of 5921 patients undergoing prehabilitation was recently published. Thirty-five studies (n = 3402) on patients undergoing major abdominal surgery were included. Only 45 studies compared the impact of prehabilitation versus no prehabilitation on postoperative outcomes (abdominal, n = 26; cardiothoracic, n = 19), but in those studies, patient's receiving prehabilitation for major abdominal surgery had significantly lower rates of overall complications (n = 10, odds ratio: 0.61, confidence interval 95%: 0.43–0.86, P = 0.005), pulmonary (n = 15, odds ratio: 0.41, confidence interval 95%: 0.25–0.67, P < 0.001), and cardiac complications (n = 4, odds ratio: 0.46, confidence interval 95%: 0.22–0.96, P = 0.044) [159].

Conclusion

Preoperative assessment of the colon and rectal surgical patient remains the first critical step in appropriate decision-making and improving outcomes. A keen understanding of various medical therapies being utilized and their effects on wound and anastomotic healing and resultant septic complications is critical in the timing of and preparation for procedures. Attention to patient's other physiological organ systems (cardiac, pulmonary, renal, endocrine, nutrition and metabolism, and immunologic) and alterations in normal function is necessary for perioperative optimization to enhance the ability of the patients to tolerate the operation and also recover with minimal morbidity and improved long-term function. In some cases, timing of interventions may necessitate judicious delay to optimize the surgical and medical milieu of the patient. Special consideration is necessitated in the elderly, given the multiple domains involved in defining this complex population, particularly as prehabilitation for frailty has demonstrated significant benefits in improving surgical outcomes. Preoperative assessments, with multidisciplinary input, should be designed at early detection, stratification, and optimization to mitigate medical morbidity and minimize or eliminate surgical complications. These should be a component of a robust enhanced recovery protocol that incorporates early mobilization, narcotic-sparing multimodal pain management, and discharge planning.

References

1. Practice Advisory for the Perioperative Management of Patients with Cardiac Implantable Electronic Devices: Pacemakers and Implantable Cardioverter-Defibrillators 2020: An Updated Report by the American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Cardiac Implantable Electronic Devices: Erratum. Anesthesiology. 2020;132(4):938.
2. Kaplan EB, et al. The usefulness of preoperative laboratory screening. JAMA. 1985;253(24):3576–81.
3. Peterson P, et al. The preoperative bleeding time test lacks clinical benefit: College of American Pathologists' and American Society of Clinical Pathologists' position article. Arch Surg. 1998;133(2):134–9.
4. Smetana GW, Macpherson DS. The case against routine preoperative laboratory testing. Med Clin North Am. 2003;87(1):7–40.
5. Lee TH, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999;100(10):1043–9.
6. Mathew A, et al. Chronic kidney disease and postoperative mortality: a systematic review and meta-analysis. Kidney Int. 2008;73(9):1069–81.
7. Grek S, et al. A cost-effective screening method for preoperative hyperglycemia. Anesth Analg. 2009;109(5):1622–4.
8. Bouvet C, et al. Is there any benefit in pre-operative urinary analysis before elective total joint replacement? Bone Joint J. 2014;96-B(3):390–4.
9. Committee on Standards and Practice Parameters, et al. Practice advisory for preanesthesia evaluation: an updated report by the American Society of Anesthesiologists Task Force on Preanesthesia Evaluation. Anesthesiology. 2012;116(3):522–38.
10. Dakik HA, Kobrossi S, Tamim H. The yield of routine preoperative cardiovascular evaluation in stable patients scheduled for elective non-cardiac surgery. Int J Cardiol. 2015;186:325–7.
11. Fleisher LA, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. Developed in collaboration with the American College of Surgeons, American Society of Anesthesiologists, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Vascular Medicine Endorsed by the Society of Hospital Medicine. J Nucl Cardiol. 2015;22(1):162–215.
12. Devereaux PJ, et al. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. Ann Intern Med. 2011;154(8):523–8.
13. Smetana GW, et al. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. Ann Intern Med. 2006;144(8):581–95.
14. Poirier P, et al. Cardiovascular evaluation and management of severely obese patients undergoing surgery: a science advisory from the American Heart Association. Circulation. 2009;120(1):86–95.
15. Archer C, Levy AR, McGregor M. Value of routine preoperative chest x-rays: a meta-analysis. Can J Anaesth. 1993;40(11):1022–7.
16. Poldermans D, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). Eur J Anaesthesiol. 2010;27(2):92–137.
17. Smilowitz NR, et al. Perioperative major adverse cardiovascular and cerebrovascular events associated with noncardiac surgery. JAMA Cardiol. 2017;2(2):181–7.
18. Tashiro T, et al. Perioperative risk of major non-cardiac surgery in patients with severe aortic stenosis: a reappraisal in contemporary practice. Eur Heart J. 2014;35(35):2372–81.
19. Eagle KA, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative

Cardiovascular Evaluation for Noncardiac Surgery). Circulation. 2002;105(10):1257–67.
20. Tan KY, et al. Optimizing the management of elderly colorectal surgery patients. Surg Today. 2010;40(11):999–1010.
21. Audisio RA, et al. Preoperative assessment of surgical risk in oncogeriatric patients. Oncologist. 2005;10(4):262–8.
22. You JF, Hsu YJ, Chern YJ, et al. Association of a preoperative leisure-time physical activity with short- and long-term outcomes of patients undergoing curative resection for stage I to III colorectal cancer: a propensity score matching analysis. Dis Colon Rectum. 2020;63(6):796–806. https://doi.org/10.1097/DCR.0000000000001651.
23. Bilimoria KY, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. J Am Coll Surg. 2013;217(5):833–42.e1–3.
24. POISE Study Group, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet. 2008;371(9627):1839–47.
25. Wijeysundera DN, et al. Perioperative beta blockade in noncardiac surgery: a systematic review for the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130(24):2246–64.
26. Kumar R, et al. Adverse cardiac events after surgery: assessing risk in a veteran population. J Gen Intern Med. 2001;16(8):507–18.
27. Pollack CV Jr, et al. Idarucizumab for dabigatran reversal – full cohort analysis. N Engl J Med. 2017;377(5):431–41.
28. Tomaselli GF, et al. 2017 ACC expert consensus decision pathway on management of bleeding in patients on Oral anticoagulants: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017;70(24):3042–67.
29. Connolly SJ, et al. Andexanet Alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med. 2016;375(12):1131–41.
30. van Werkum JW, et al. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. J Am Coll Cardiol. 2009;53(16):1399–409.
31. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel- user friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138(5):1093–100.
32. Bergqvist D, Agnelli G, Cohen AT, et al; ENOXACAN II Investigators. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med. 2002;346:975–80.
33. Fleming F, Gaertner W, Ternent CA, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guideline for the Prevention of Venous Thromboembolic Disease in Colorectal Surgery. Dis Colon Rectum. 2018;61:14–20.
34. Nishimura RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(22):e57–185.
35. Practice Advisory for the Perioperative Management of Patients with Cardiac Implantable Electronic Devices: Pacemakers and Implantable Cardioverter–Defibrillators 2020: An Updated Report by the American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Cardiac Implantable Electronic Devices. Anesthesiology. 2020;132(2):225–2.
36. Yang CK, et al. Pulmonary complications after major abdominal surgery: National Surgical Quality Improvement Program analysis. J Surg Res. 2015;198(2):441–9.
37. Fernandez-Bustamante A, et al. Postoperative pulmonary complications, early mortality, and hospital stay following noncardiothoracic surgery: a multicenter study by the perioperative research network investigators. JAMA Surg. 2017;152(2):157–66.
38. Goldman L, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med. 1977;297(16):845–50.
39. Smetana GW. Preoperative pulmonary assessment of the older adult. Clin Geriatr Med. 2003;19(1):35–55.
40. Kaw R, et al. Meta-analysis of the association between obstructive sleep apnoea and postoperative outcome. Br J Anaesth. 2012;109(6):897–906.
41. Chung F, Abdullah HR, Liao P. STOP-bang questionnaire: a practical approach to screen for obstructive sleep apnea. Chest. 2016;149(3):631–8.
42. Liu MM, et al. Perioperative steroid management: approaches based on current evidence. Anesthesiology. 2017;127(1):166–72.
43. Glowniak JV, Loriaux DL. A double-blind study of perioperative steroid requirements in secondary adrenal insufficiency. Surgery. 1997;121(2):123–9.
44. Zaghiyan K, et al. Safety and feasibility of using low-dose perioperative intravenous steroids in inflammatory bowel disease patients undergoing major colorectal surgery: a pilot study. Surgery. 2012;152(2):158–63.
45. Zaghiyan K, et al. A prospective, randomized, noninferiority trial of steroid dosing after major colorectal surgery. Ann Surg. 2014;259(1):32–7.
46. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. Circulation. 1979;59(1):8–13.
47. Halkos ME, et al. Elevated preoperative hemoglobin A1c level is predictive of adverse events after coronary artery bypass surgery. J Thorac Cardiovasc Surg. 2008;136(3):631–40.
48. Pezzarossa A, et al. Perioperative management of diabetic subjects. Subcutaneous versus intravenous insulin administration during glucose-potassium infusion. Diabetes Care. 1988;11(1):52–8.
49. Cima RR, et al. Outcomes are local: patient, disease, and procedure-specific risk factors for colorectal surgical site infections from a single institution. J Gastrointest Surg. 2017;21(7):1142–52.
50. Palermo NE, Garg R. Perioperative management of diabetes mellitus: novel approaches. Curr Diab Rep. 2019;19(4):14.
51. Flegal KM, et al. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA. 2012;307(5):491–7.
52. Dindo D, et al. Obesity in general elective surgery. Lancet. 2003;361(9374):2032–5.
53. Wahl TS, et al. The obese colorectal surgery patient: surgical site infection and outcomes. Dis Colon Rectum. 2018;61(8):938–45.
54. Efron JE, et al. Restorative proctocolectomy with ileal pouch anal anastomosis in obese patients. Obes Surg. 2001;11(3):246–51.
55. Canedo JA, et al. Restorative proctectomy with ileal pouch-anal anastomosis in obese patients. Dis Colon Rectum. 2010;53(7):1030–4.
56. Klos CL, et al. Obesity increases risk for pouch-related complications following restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA). J Gastrointest Surg. 2014;18(3):573–9.
57. Boodaie BD, et al. A perioperative care map improves outcomes in patients with morbid obesity undergoing major surgery. Surgery. 2018;163(2):450–6.
58. Hangaard Hansen C, et al. The effect of time from diagnosis to surgery on oncological outcomes in patients undergoing surgery for colon cancer: a systematic review. Eur J Surg Oncol. 2018;44(10):1479–85.
59. Malietzis G, et al. The role of body composition evaluation by computerized tomography in determining colorectal cancer treatment outcomes: a systematic review. Eur J Surg Oncol. 2015;41(2):186–96.

60. Weimann A. Influence of nutritional status on postoperative outcome in patients with colorectal cancer – the emerging role of the microbiome. Innov Surg Sci. 2018;3(1):55–64.
61. Alyaqout K, et al. Minimally invasive colorectal cancer procedures in patients with obesity: an interdisciplinary approach. Tech Coloproctol. 2019;23(6):583–7.
62. Holderbaum M, et al. Effects of very low calorie diets on liver size and weight loss in the preoperative period of bariatric surgery: a systematic review. Surg Obes Relat Dis. 2018;14(2):237–44.
63. Mariani L, et al. Weight loss in cancer patients: a plea for a better awareness of the issue. Support Care Cancer. 2012;20(2):301–9.
64. Mullen JL, et al. Implications of malnutrition in the surgical patient. Arch Surg. 1979;114(2):121–5.
65. Sorensen J, et al. EuroOOPS: an international, multicentre study to implement nutritional risk screening and evaluate clinical outcome. Clin Nutr. 2008;27(3):340–9.
66. Schwegler I, et al. Nutritional risk is a clinical predictor of postoperative mortality and morbidity in surgery for colorectal cancer. Br J Surg. 2010;97(1):92–7.
67. Panis Y, et al. Mortality after colorectal cancer surgery: a French survey of more than 84,000 patients. Ann Surg. 2011;254(5):738–43; discussion 743–4.
68. Wu GH, et al. Perioperative artificial nutrition in malnourished gastrointestinal cancer patients. World J Gastroenterol. 2006;12(15):2441–4.
69. Baker JP, et al. Nutritional assessment: a comparison of clinical judgement and objective measurements. N Engl J Med. 1982;306(16):969–72.
70. Hu WH, et al. Assessment of the addition of hypoalbuminemia to ACS-NSQIP surgical risk calculator in colorectal cancer. Medicine (Baltimore). 2016;95(10):e2999.
71. Doweiko JP, Nompleggi DJ. The role of albumin in human physiology and pathophysiology, Part III: albumin and disease states. JPEN J Parenter Enteral Nutr. 1991;15(4):476–83.
72. Richards SJG, Senadeera S, Frizelle FA. Sarcopenia, as Assessed by Psoas Cross-Sectional Area, Is Predictive of Adverse Postoperative Outcomes in Patients Undergoing Colorectal Cancer Surgery. Dis Colon Rectum. 2020;63(6):807–15.
73. Burden S, et al. Pre-operative nutrition support in patients undergoing gastrointestinal surgery. Cochrane Database Syst Rev. 2012;11:CD008879.
74. Bootun R. Effects of immunosuppressive therapy on wound healing. Int Wound J. 2013;10(1):98–104.
75. Dean PG, et al. Wound-healing complications after kidney transplantation: a prospective, randomized comparison of sirolimus and tacrolimus. Transplantation. 2004;77(10):1555–61.
76. Sartelli M, et al. WSES Guidelines for the management of acute left sided colonic diverticulitis in the emergency setting. World J Emerg Surg. 2016;11:37.
77. Narrow WE, et al. Revised prevalence estimates of mental disorders in the United States: using a clinical significance criterion to reconcile 2 surveys' estimates. Arch Gen Psychiatry. 2002;59(2):115–23.
78. Kraemer KL, Conigliaro J, Saitz R. Managing alcohol withdrawal in the elderly. Drugs Aging. 1999;14(6):409–25.
79. Pihkala H, Sandlund M. Parenthood and opioid dependence. Subst Abus Rehabil. 2015;6:33–40.
80. Bradley KA, et al. Alcohol screening and risk of postoperative complications in male VA patients undergoing major non-cardiac surgery. J Gen Intern Med. 2011;26(2):162–9.
81. Rubinsky AD, et al. AUDIT-C alcohol screening results and postoperative inpatient health care use. J Am Coll Surg. 2012;214(3):296–305.e1.
82. Bush K, et al. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. Arch Intern Med. 1998;158(16):1789–95.
83. Tonnesen H, et al. Effect of preoperative abstinence on poor postoperative outcome in alcohol misusers: randomised controlled trial. BMJ. 1999;318(7194):1311–6.
84. Grønkjær M, et al. Preoperative smoking status and postoperative complications: a systematic review and meta-analysis. Ann Surg. 2014;259(1):52–71.
85. Jung KH, et al. Preoperative smoking cessation can reduce postoperative complications in gastric cancer surgery. Gastric Cancer. 2015;18(4):683–90.
86. Frenk SM, Lukacs SL, Gu Q. Factors associated with prescription opioid analgesic use in the US population, 2011–2014. Pain Med. 2019;20(7):1338–46.
87. Vadivelu N, et al. Perioperative analgesia and challenges in the drug-addicted and drug-dependent patient. Best Pract Res Clin Anaesthesiol. 2014;28(1):91–101.
88. Biondo S, et al. Outcomes of colonic diverticulitis according to the reason of immunosuppression. Am J Surg. 2016;212(3):384–90.
89. Wang AS, Armstrong EJ, Armstrong AW. Corticosteroids and wound healing: clinical considerations in the perioperative period. Am J Surg. 2013;206(3):410–7.
90. Post S, et al. Risks of intestinal anastomoses in Crohn's disease. Ann Surg. 1991;213(1):37–42.
91. Slieker JC, et al. Long-term and perioperative corticosteroids in anastomotic leakage: a prospective study of 259 left-sided colorectal anastomoses. Arch Surg. 2012;147(5):447–52.
92. Eriksen TF, Lassen CB, Gogenur I. Treatment with corticosteroids and the risk of anastomotic leakage following lower gastrointestinal surgery: a literature survey. Color Dis. 2014;16(5):O154–60.
93. Lightner AL, et al. Results at up to 30 years after ileal pouch-anal anastomosis for chronic ulcerative colitis. Inflamm Bowel Dis. 2017;23(5):781–90.
94. El-Hussuna A, et al. Biologic treatment or immunomodulation is not associated with postoperative anastomotic complications in abdominal surgery for Crohn's disease. Scand J Gastroenterol. 2012;47(6):662–8.
95. Ali T, Yun L, Rubin DT. Risk of post-operative complications associated with anti-TNF therapy in inflammatory bowel disease. World J Gastroenterol. 2012;18(3):197–204.
96. Wong SG, et al. Evaluation of a physiatrist-directed prehabilitation intervention in frail patients with colorectal cancer: a randomised pilot study protocol. BMJ Open. 2017;7:e015565.
97. Selvasekar CR, et al. Effect of infliximab on short-term complications in patients undergoing operation for chronic ulcerative colitis. J Am Coll Surg. 2007;204(5):956–62. discussion 962-3
98. Aimaq R, Akopian G, Kaufman HS. Surgical site infection rates in laparoscopic versus open colorectal surgery. Am Surg. 2011;77(10):1290–4.
99. Lightner AL, et al. Postoperative outcomes in vedolizumab-treated patients undergoing abdominal operations for inflammatory bowel disease. J Crohns Colitis. 2017;11(2):185–90.
100. Cohen B, Fleshner P, Kane S, et al. 415a – Anti-tumor necrosis factor therapy is not associated with post-operative infection: results from Prospective Cohort of Ulcerative Colitis and Crohn's Disease Patients Undergoing Surgery to Identify Risk Factors for Postoperative Infection I (Puccini). Gastroenterology. 2019;156:S-80.
101. Luján JJ, et al. Factors influencing the outcome of intestinal anastomosis. Am Surg. 2011;77(9):1169–75.
102. Samdani T, et al. Colonic diverticulitis in chemotherapy patients: should operative indications change? A retrospective cohort study. Int J Surg. 2014;12(12):1489–94.
103. Hurwitz H, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335–42.

104. Kabbinavar F, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol. 2003;21(1):60–5.
105. Kabbinavar FF, et al. Addition of bevacizumab to fluorouracil-based first-line treatment of metastatic colorectal cancer: pooled analysis of cohorts of older patients from two randomized clinical trials. J Clin Oncol. 2009;27(2):199–205.
106. Yoshioka Y, et al. Postoperative complications following neoadjuvant bevacizumab treatment for advanced colorectal cancer. Surg Today. 2014;44(7):1300–6.
107. Eveno C, et al. Late anastomotic colonic dehiscence due to anti-angiogenic treatment, a specific drug-class complication requiring specific treatment: an example of pazopanib complication. Clin Res Hepatol Gastroenterol. 2011;35(2):135–9.
108. Briganti A, et al. Surgical safety of radical cystectomy and pelvic lymph node dissection following neoadjuvant pembrolizumab in patients with bladder cancer: prospective assessment of perioperative outcomes from the PURE-01 trial. Eur Urol. 2020;77(5):576–80.
109. Bott MJ, et al. Safety and feasibility of lung resection after immunotherapy for metastatic or unresectable tumors. Ann Thorac Surg. 2018;106(1):178–83.
110. Bromage SJ, Cunliffe WJ. Validation of the CR-POSSUM risk-adjusted scoring system for major colorectal cancer surgery in a single center. Dis Colon Rectum. 2007;50(2):192–6.
111. Tekkis PP, et al. Development of a dedicated risk-adjustment scoring system for colorectal surgery (colorectal POSSUM). Br J Surg. 2004;91(9):1174–82.
112. Cohen ME, et al. Development of an American College of Surgeons National Surgery Quality Improvement Program: morbidity and mortality risk calculator for colorectal surgery. J Am Coll Surg. 2009;208(6):1009–16.
113. Fried LP, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146–56.
114. Robinson TN, et al. Frailty for surgeons: review of a National Institute on Aging Conference on Frailty for Specialists. J Am Coll Surg. 2015;221(6):1083–92.
115. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol. 2007;25(14):1824–31.
116. Extermann M, et al. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Crit Rev Oncol Hematol. 2005;55(3):241–52.
117. Alessi CA, et al. The process of care in preventive in-home comprehensive geriatric assessment. J Am Geriatr Soc. 1997;45(9):1044–50.
118. Inouye SK, et al. Importance of functional measures in predicting mortality among older hospitalized patients. JAMA. 1998;279(15):1187–93.
119. Reuben DB, et al. Value of functional status as a predictor of mortality: results of a prospective study. Am J Med. 1992;93(6):663–9.
120. Siu AL, Morishita L, Blaustein J. Comprehensive geriatric assessment in a day hospital. J Am Geriatr Soc. 1994;42(10):1094–9.
121. Tinetti ME, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. N Engl J Med. 1994;331(13):821–7.
122. Inouye SK, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med. 1999;340(9):669–76.
123. Stuck AE, et al. Comprehensive geriatric assessment: a meta-analysis of controlled trials. Lancet. 1993;342(8878):1032–6.
124. Extermann M, et al. Comorbidity and functional status are independent in older cancer patients. J Clin Oncol. 1998;16(4):1582–7.
125. Robinson TN, et al. Redefining geriatric preoperative assessment using frailty, disability and co-morbidity. Ann Surg. 2009;250(3):449–55.
126. Makary MA, et al. Frailty as a predictor of surgical outcomes in older patients. J Am Coll Surg. 210(6):901–8.
127. Kristjansson SR, et al. Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: a prospective observational cohort study. Crit Rev Oncol Hematol. 2010;76(3):208–17.
128. Feng MA, et al. Geriatric assessment in surgical oncology: a systematic review. J Surg Res. 2015;193(1):265–72.
129. Shahrokni A, et al. Geriatric assessment, not ASA physical status, is associated with 6-month postoperative survival in patients with cancer aged >/=75 years. J Natl Compr Cancer Netw. 2019;17(6):687–94.
130. Kothari A, et al. Components of geriatric assessments predict thoracic surgery outcomes. J Surg Res. 2011;166(1):5–13.
131. Huisman MG, et al. Screening for predictors of adverse outcome in onco-geriatric surgical patients: a multicenter prospective cohort study. Eur J Surg Oncol. 2015;41(7):844–51.
132. PACE Participants, et al. Shall we operate? Preoperative assessment in elderly cancer patients (PACE) can help. A SIOG surgical task force prospective study. Crit Rev Oncol Hematol. 2008;65(2):156–63.
133. Chow WB, et al. Optimal preoperative assessment of the geriatric surgical patient: a best practices guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. J Am Coll Surg. 2012;215(4):453–66.
134. Obeid NM, et al. Predictors of critical care-related complications in colectomy patients using the National Surgical Quality Improvement Program: exploring frailty and aggressive laparoscopic approaches. J Trauma Acute Care Surg. 2012;72(4):878–83.
135. Keller DS, et al. Using frailty to predict who will fail early discharge after laparoscopic colorectal surgery with an established recovery pathway. Dis Colon Rectum. 2014;57:337–42.
136. Panayi AC, et al. Impact of frailty on outcomes in surgical patients: a systematic review and meta-analysis. Am J Surg. 2019;218(2):393–400.
137. Wahl TS, et al. Association of the modified frailty index with 30-day surgical readmission. JAMA Surg. 2017;152(8):749–57.
138. Hall DE, et al. Development and initial validation of the risk analysis index for measuring frailty in surgical populations. JAMA Surg. 2017;152:175–82.
139. Hall DE, et al. Association of a frailty screening initiative with postoperative survival at 30, 180, and 365 days. JAMA Surg. 2017;152:233–40.
140. Plassman BL, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. 2007;29(1–2):125–32.
141. Plassman BL, et al. Prevalence of cognitive impairment without dementia in the United States. Ann Intern Med. 2008;148(6):427–34.
142. Watt J, et al. Identifying older adults at risk of delirium following elective surgery: a systematic review and meta-analysis. J Gen Intern Med. 2018;33(4):500–9.
143. Borson S, et al. The Mini-Cog as a screen for dementia: validation in a population-based sample. J Am Geriatr Soc. 2003;51(10):1451–4.
144. Scharre DW, et al. Self-administered Gerocognitive Examination (SAGE): a brief cognitive assessment Instrument for mild cognitive impairment (MCI) and early dementia. Alzheimer Dis Assoc Disord. 2010;24(1):64–71.
145. Ganai S, et al. Adverse outcomes of geriatric patients undergoing abdominal surgery who are at high risk for delirium. Arch Surg. 2007;142(11):1072–8.
146. Monk TG, et al. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology. 2008;108(1):18–30.
147. Silver JK, Baima J. Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment

options, and improve physical and psychological health outcomes. Am J Phys Med Rehabil. 2013;92(8):715–27.
148. Waite I, et al. Home-based preoperative rehabilitation (prehab) to improve physical function and reduce hospital length of stay for frail patients undergoing coronary artery bypass graft and valve surgery. J Cardiothorac Surg. 2017;12(1):91.
149. Chia CLK, Mantoo SK, Tan KY. 'Start to finish trans-institutional transdisciplinary care': A novel approach improves colorectal surgical results in frail elderly patients. Color Dis. 2016;18(1):O43–50.
150. Mazzola M, et al. Frailty in major oncologic surgery of upper gastrointestinal tract: how to improve postoperative outcomes. Eur J Surg Oncol. 2017;43(8):1566–71.
151. Hoogeboom TJ, et al. Preoperative therapeutic exercise in frail elderly scheduled for total hip replacement: a randomized pilot trial. Clin Rehabil. 2010;24(10):901–10.
152. Oosting E, et al. Preoperative home-based physical therapy versus usual care to improve functional health of frail older adults scheduled for elective total hip arthroplasty: a pilot randomized controlled trial. Arch Phys Med Rehabil. 2012;93(4):610–6.
153. Minnella EM, Carli F. Prehabilitation and functional recovery for colorectal cancer patients. Eur J Surg Oncol. 2018;44(7):919–26.
154. Pirlich M, Lochs H. Nutrition in the elderly. Best Pract Res Clin Gastroenterol. 2001;15(6):869–84.
155. Jin F, Chung F. Minimizing perioperative adverse events in the elderly. Br J Anaesth. 2001;87(4):608–24.
156. Parker PA, et al. The effects of a presurgical stress management intervention for men with prostate cancer undergoing radical prostatectomy. J Clin Oncol. 2009;27(19):3169–76.
157. Waite I, et al. Home-based preoperative rehabilitation (prehab) to improve physical function and reduce hospital length of stay for frail patients undergoing coronary artery bypass graft and valve surgery. J Cardiothorac Surg. 2017;12:1–7.
158. Carli, F., et al., Effect of multimodal prehabilitation vs postoperative rehabilitation on 30-day postoperative complications for frail patients undergoing resection of colorectal cancer: a randomized clinical trial. JAMA Surg, 2020.
159. Kamarajah SK, et al. Critical appraisal on the impact of preoperative rehabilitation and outcomes after major abdominal and cardiothoracic surgery: a systematic review and meta-analysis. Surgery. 2020;167(3):540–9.
160. Kristensen SD, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J. 2014;35(35):2383–431.
161. Stewart AL, et al. Functional status and well-being of patients with chronic conditions. Results from the Medical Outcomes Study. JAMA. 1989;262(7):907–13.
162. Fillenbaum GG, Smyer MA. The development, validity, and reliability of the OARS multidimensional functional assessment questionnaire. J Gerontol. 1981;36(4):428–34.
163. Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer. 1980;45(8):2220–4.
164. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39(2):142–8.
165. Naeim A, Reuben D. Geriatric syndromes and assessment in older cancer patients. Oncology (Williston Park). 2001;15(12):1567–77, 1580; discussion 1581, 1586, 1591.
166. Kawas C, et al. Reliability of the blessed telephone information-memory-concentration test. J Geriatr Psychiatry Neurol. 1995;8(4):238–42.
167. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361–70.
168. Carroll BT, et al. Screening for depression and anxiety in cancer patients using the Hospital Anxiety and Depression Scale. Gen Hosp Psychiatry. 1993;15(2):69–74.
169. Hopwood P, Howell A, Maguire P. Screening for psychiatric morbidity in patients with advanced breast cancer: validation of two self-report questionnaires. Br J Cancer. 1991;64(2):353–6.
170. Landi F, et al. Body mass index and mortality among older people living in the community. J Am Geriatr Soc. 1999;47(9):1072–6.
171. Dewys WD, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med. 1980;69(4):491–7.
172. Newman AB, et al. Weight change in old age and its association with mortality. J Am Geriatr Soc. 2001;49(10):1309–18.

Optimizing Outcomes with Enhanced Recovery

7

Julie Thacker and Nancy Morin

Key Concepts

- Enhanced recovery is the process of defining modifiable sources of perioperative stress to the surgical patient and applying standardized evidence-based interventions through all phases of care to avoid complications, facilitate faster recovery and discharge (without increasing readmission rates), and reduce hospital costs.
- Champions from surgery, anesthesia, and nursing are essential to the ERAS team, while other members for protocol creation include pharmacy, IT, nutrition, and administration.
- Key elements of patient care delivery can be broken down into five phases, each assigned to and delivered by a different team while certain elements present across phases: preoperative, perioperative, intraoperative, postoperative, and post-discharge.
- Implementation of the Enhanced Recovery Program, ERP, requires order sets, team education, and administrative help as well as databases to facilitate data collection and ensure optimal compliance and quality control.
- ERAS principles are widely applicable and have been proven safe and beneficial in emergency and IBD patients, those with diverting ostomies, and elderly patients, realizing that readiness for discharge rather than length of stay is a more accurate outcome measure.
- Moving forward, technology will assist in gathering patient recovery-centric outcome measures in addition to the traditional audit measures to further quality improvement efforts.

Intrinsic to the personality of a surgeon is the drive toward perfect outcomes. Benchmarking, quality improvement comparisons, and inherent competitiveness all allow surgeons the means to evaluate their performance. Enhanced recovery principles, by contrast, focus on intervention elements. Specifically, enhanced recovery focuses on the surgical stress imposed on unique patient populations. This chapter focuses on enhanced recovery efforts, details, challenges, and future directions in the elective colorectal surgery patient.

Enhanced Recovery, Origins, and Overview

Besides a buzz word on hospital webpages for administrators to publicize adoption of popular care maps for surgical services lines, enhanced recovery has a multi-faceted history and widely diverse definitions. To some, enhanced recovery refers to the patient-focused decrease of surgical stress described in the late 1990s and early 2000s in Scandinavia as "ERAS, enhanced recovery after surgery." To others, "ERAS" is simply an order set or protocolized perioperative care. Enhanced recovery; enhanced recovery programs, "ERP"; and enhanced recovery after surgery, "ERAS" will be used interchangeably in this chapter.

Most clearly, enhanced recovery is the application of evidence-based, perioperative medicine to the care of the surgical patient with a goal of best surgical outcomes. In this chapter we review the thoughtful development of this aspect of perioperative medicine, and, specifically, we discuss the aspects of perioperative medicine that have been defined as enhanced recovery for the colorectal surgery patient.

Building on the understanding of nutrition and stress science from the preceding decades, surgeon scientists began specifically addressing the impact of depleted or supported nutritional reserves at the time of surgical stress on surgical outcomes. After decades of individual work relating operative outcomes to perioperative metabolism, stress, and nutrition, Douglas Wilmore of Boston and Henrik Kehlet of Copenhagen reported the importance of considering the

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patient's physiologic reactions, helpful and hurtful, to surgical stress [1–3].

Their work proposed that, with a better understanding of the physiologic stress impact of operations, surgical teams could mitigate this stress. From a background of perioperative nutrition science, these early enhanced recovery efforts began to define modifiable sources of perioperative stress. Wilmore and Kehlet identified several sources of perioperative stress that were worse with traditional perioperative care, and they hypothesized that different care plans might help patients avoid complications [4]. The complexity of physiologic interactions is shown diagrammatically in Fig. 7.1 with representative enhanced recovery interventions to combat these stresses shown in Fig. 7.2.

From modifying perioperative stress to fast-track surgery to enhanced recovery, perioperative care was being revolutionized in Europe in the early 2000s. Simultaneously, in the USA, a trend toward minimally invasive approaches to abdominopelvic operations was taking off. Observed shifts in patient care paradigms followed patient recovery curves

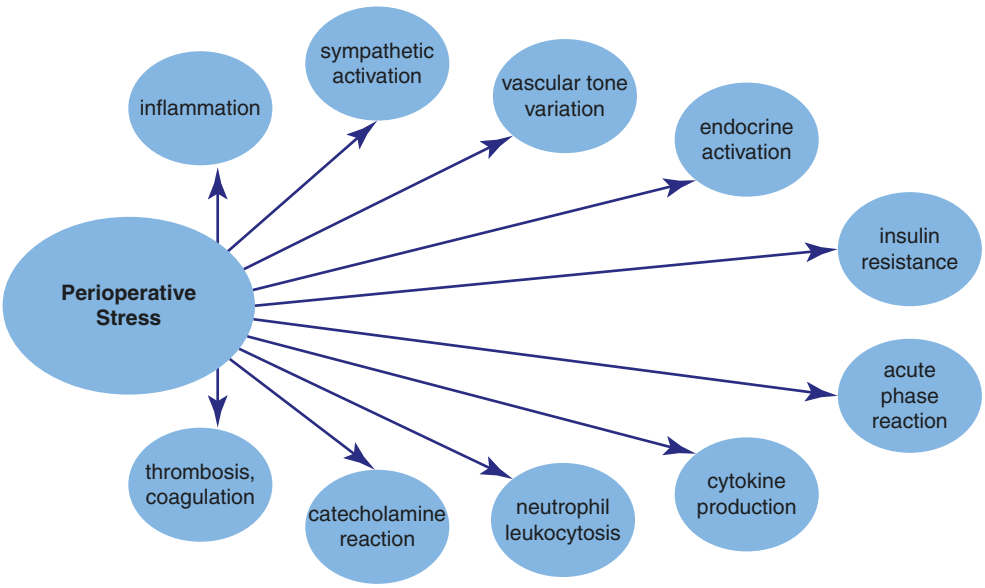

Fig. 7.1 Perioperative stress and reactions

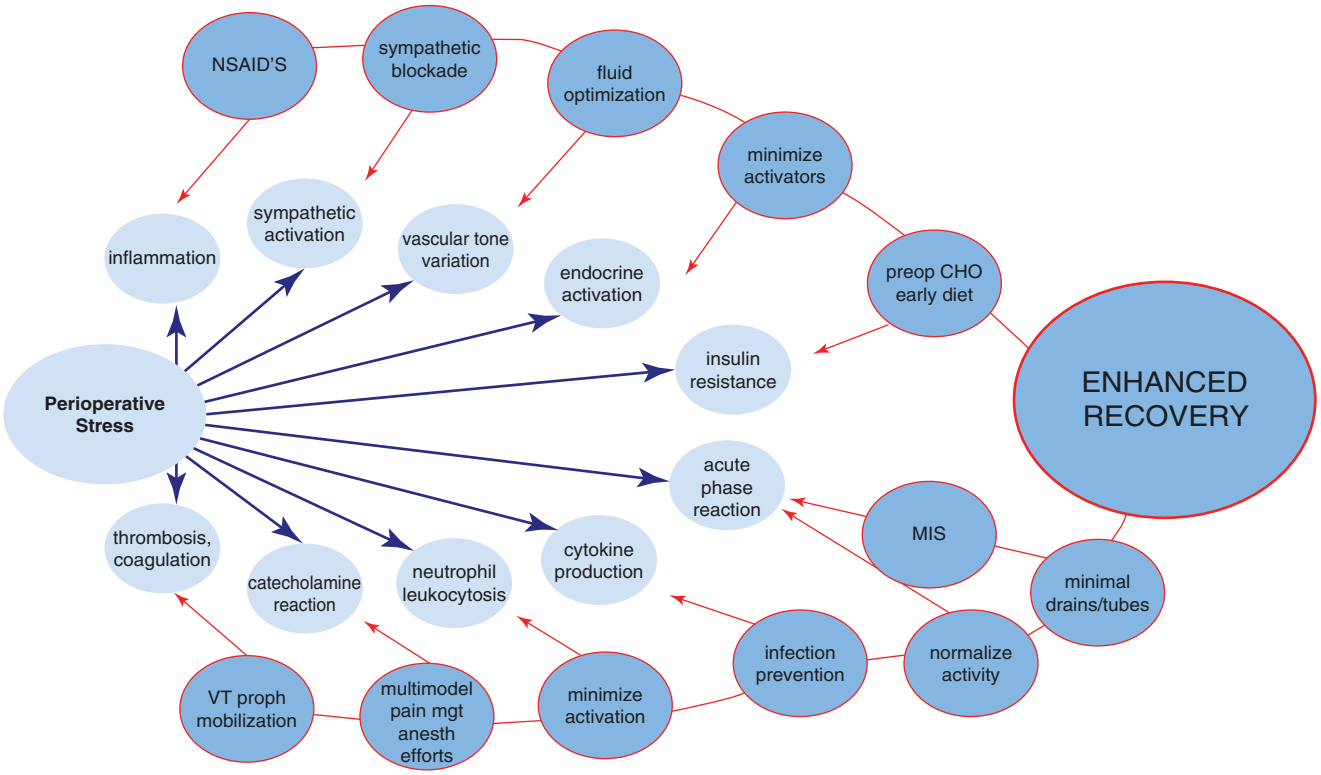

Fig. 7.2 Common ERAS elements to combat perioperative stress

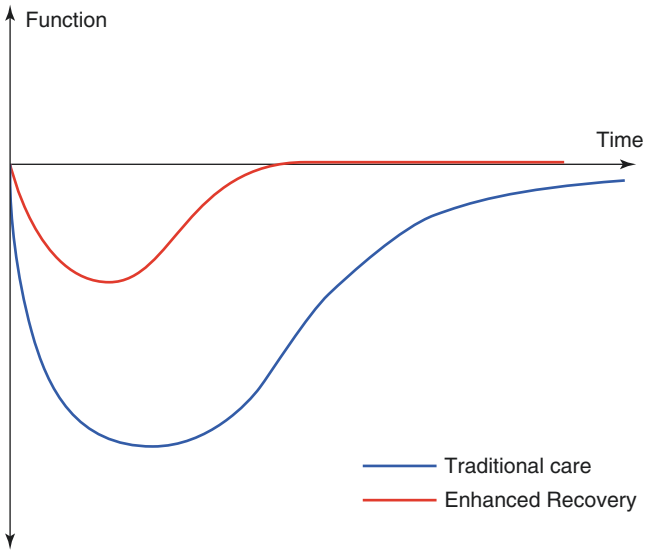

Fig. 7.3 Kehlet and Wilmore's representation of lessened perioperative stress resulting in improved recovery curve

and included earlier postoperative oral intake, earlier mobility, and earlier readiness for discharge from the hospital. Laparoscopic surgeons were responding to patients' decreased surgical stress and facilitating faster recoveries. Through critical review of laparoscopic studies and perioperative care standardization, it became obvious that allowing patients to recover more quickly worked [5]. More directly, Dr. Kehlet's parallel efforts began actively addressing perioperative care elements relative to surgical stress. He reported that an immediate diet and immediate activity, in combination with multimodal analgesia, led to quicker discharge readiness after open operations [6, 7]. He explained that the traditional care paradigms worsened surgical stress and prolonged the amount of recovery below the patient's baseline at time of operation. As demonstrated in Fig. 7.3, and as he simply described, patients did not experience the dip relative to baseline health when they had surgery on his protocol.

Specific to colorectal surgery, the two paradigm shifts collided in the early 2000s. Open operations under this new care paradigm and laparoscopic operations with inherently faster recovery were resulting in decreased narcotic need, earlier diet tolerance, and shortened hospital stays. Surgeons performing predominantly open colorectal operations in Scandinavia adopted Professor Kehlet's perioperative principles, and with the explosion of MIS equipment availability in the USA, more and more surgeons were approaching the colon laparoscopically. In 2004, the American College of Surgeons' Commission on Cancer released the non-inferiority COST trial [8], showing that laparoscopic oncologic resection for colon cancer did not have worse outcomes compared to the open approach. This led to increasing numbers of MIS colon resections in North America, particularly at academic and training centers, where academicians had been reluctant to adopt the technology without reassurance of safety in cancer. In 2005, the first publication of the "ERAS group" shared their attempt to push surgeon-driven adoption of Kehlet's protocols for open colorectal resection patients on their colorectal surgery wards. Admitting that their results were not as amazing as the very confined implementation of Kehlet's single-center and small-sample population, the ERAS group set out to apply implementation science techniques to the idea of changing the perioperative management of colorectal surgery at their centers. Subsequent development and spread of these focused change management strategies has been widely successful [9].

By 2008, worldwide improvement of colorectal surgery outcomes, predominantly in length of stay and decreased wound complications, had been reported by many high-volume laparoscopic centers. Perioperative optimization strategies such as intentional fluid management and opioid stewardship began timely growth from the anesthesia literature. Parallel to the incremental changes happening around the growth of laparoscopic colorectal surgery was the successful effort of the ERAS Society, so named in 2007 [10]. With westerly drift of ideas, US and Canadian centers became aware of the principles of enhanced recovery. This spread was facilitated by the uptake of enhanced recovery in the UK. The 2008 economic recession drove the National Health Service to implement many care changes to improve service and to decrease cost. The implementation of enhanced recovery for surgery patients was mandated across the country, beginning with colorectal surgery. This effort was to save money from decreasing length of stay and complications, and the NICE program was hugely successful at its mission [11]. Enhanced Recovery Partnership Programme in the National Health Service, NHS, of the UK was the first mandated and the first truly multidisciplinary approach to the improving perioperative outcomes reported. Since 2010, the published work of major centers, predominantly shared anesthesia and surgery efforts, has skyrocketed [12–15]. North American efforts have been stimulated by the 2014 creation of American Society for Enhanced Recovery (ASER at www.enhancedrecovery.org) and the American chapter of the ERAS Society, in 2017 (Fig. 7.4).

In short and most holistically, enhanced recovery is the process of considering and implementing the best evidence for each system-patient touch from diagnosis of surgical disease to complete recovery from operative management of that disease. Currently, the best outcomes attributed to enhanced recovery work tend to start with intentional preop-

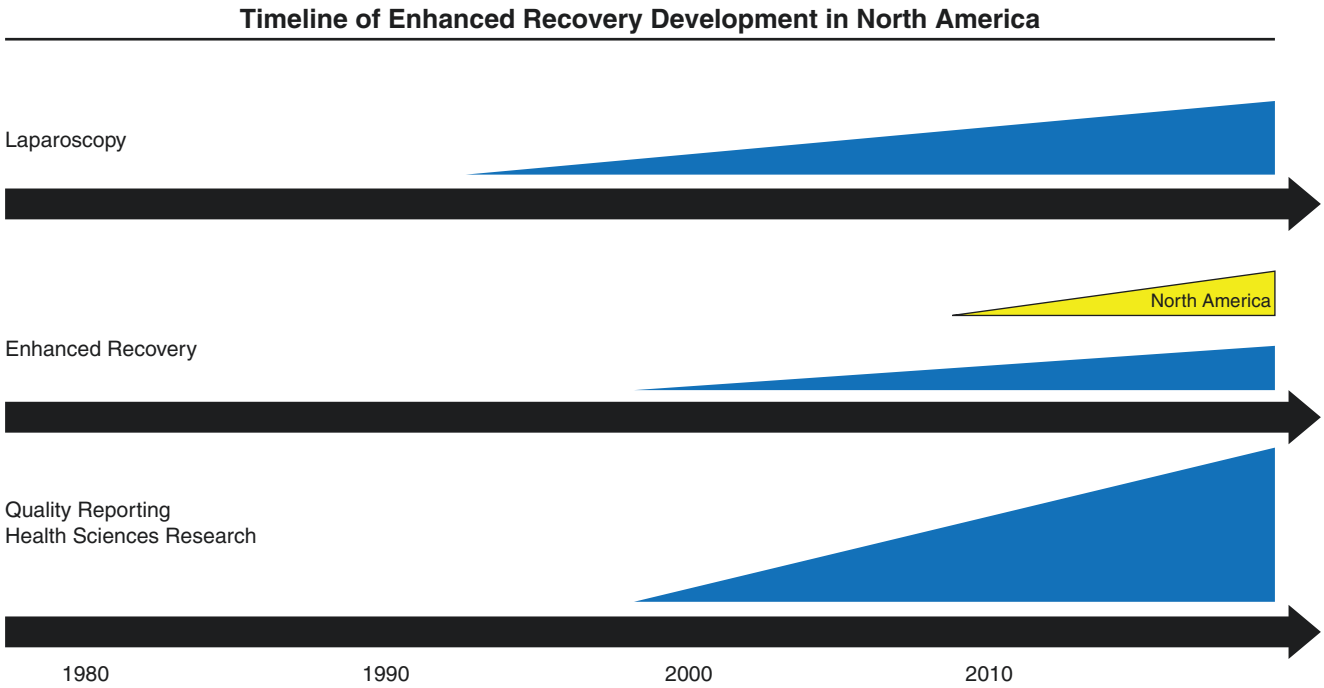

Fig. 7.4 Alignment of improvement strategies in colorectal surgery including laparoscopy, ERAS, and quality improvement research

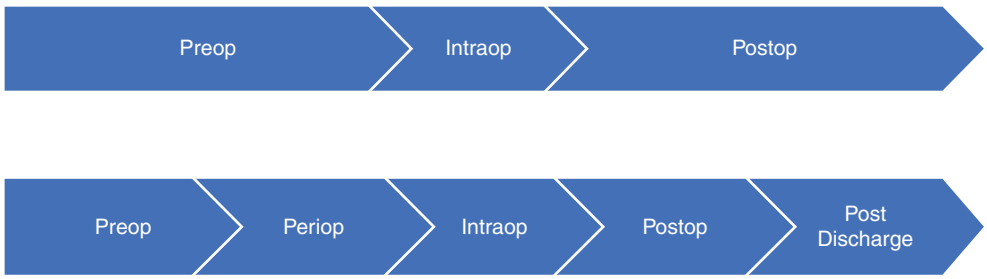

Fig. 7.5 Models of care for change management planning; three phases and five phases

erative education regarding surgical planning, followed by evidence-based management steps via preoperative anesthesia assessment, intraoperative best practices, and intentional postoperative management schemes to minimize perioperative stress and optimize outcomes. Herein, we will discuss the evidence of common care variables of enhanced recovery for colorectal operations, reported implementation schemes, and examples of improved outcomes. In addition to order sets and patient-focused care elements, enhanced recovery efforts frequently lead to continuous improvement platforms. Such platforms, via change management efforts, are tough to create and even harder to maintain. Identification of these barriers and how to break these barriers down is offered. Enhanced recovery has been attractive to administrators and payers because of economic impacts which are discussed toward the end of the chapter. Lastly, next steps and the future of enhanced recovery for colorectal patients are covered.

Enhanced Recovery Models

There are two ways to consider the care elements of most enhanced recovery models. One is to define action in a particular phase of care. Another considers the impact on physiologic stress, allowing for potentially multiple interventions along the surgical continuum.

Dividing the operative experience into phases is somewhat artificial, but it works well when creating an implementation strategy. Care delivery can be divided by time and shown as preoperative → intraoperative → postoperative. Care delivery can also be divided by location, which further defines the team members present in each phase. This five-phase care perioperative scheme is consistent with the Quality Red Book published by the American College of Surgeons (Fig. 7.5) [16].

Preoperatively, the patient is prepared for surgery with information and testing. Intraoperatively, engagement of the

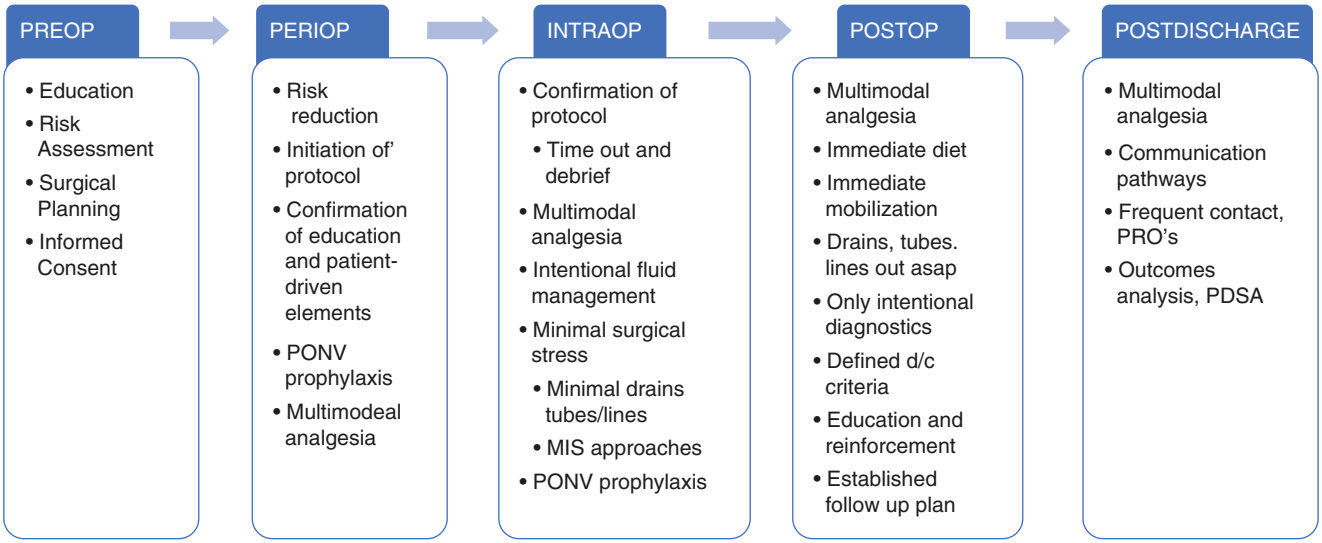

Fig. 7.6 Common enhanced recovery elements; five phases of care model

anesthesia team is key. Important elements in the operating room include intentional fluid management and minimally stressful surgical techniques. Postoperatively, the patient is guided back to baseline health, acutely in the hospital and over the weeks following an operation. Each of these phases is delivered by a different team. The patient and the surgeon are the only two players in each phase. A surgeon's understanding of who does what and when is a key first step to enhanced recovery care. Then key elements in each phase are defined from the evidence. An example of how some elements fall into phases of care is shown (Fig. 7.6).

As is obvious by the repetition of items across the phases, some interventions need to be carried out at multiple time points. Therefore, when creating a protocol, it is important to consider the principles of care and the evidence of interventions.

First Steps to Creating an Enhanced Recovery Program

To start, the ERAS team needs to define what outcomes need to be improved. Seemingly obvious, this initial step is often skipped with teams jumping into building order sets. The second step is to create an evidence library. Once outcomes of interest are defined, and the evidence is collected, the team assigns the elements of impact to phases of care and team members. The lift of implementation often includes an order set, team education, and administrative help. Pearsall et al. detail the team and facilitators nicely in a chapter on implementation in *Surgical Clinics of North America* [17]. Champions from surgery, anesthesia, and nursing are essential. Other team members for protocol creation will be from the pharmacy, IT, administration, and nutrition.

Enhanced Recovery Elements in Colorectal Surgery

This section covers elements common to most protocols for enhanced recovery of the elective colorectal surgery patient. General groupings into phases of care are used to organize the information as one would to create a protocol (Table 7.1).

Preoperative Elements of ERAS in Elective Colorectal Surgery

Education

Patient education is a key element of enhanced recovery. Setting expectations for patients at every phase of care helps to manage stress and encourage participation. Common language and instructions throughout the surgical journey allow the patient to be more relaxed and receptive to the care plan.

Information needs to be at the simplest appropriate literacy level in written, spoken, and, if possible, video versions to reach all learners. Important to every phase of enhanced recovery, the greatest educational effort may be spent at its introduction in the surgery clinic. The anesthesia assessment team, the preoperative holding team, and even the recovery room team – all of these seemingly separate teams – become part of the patient-focused care in enhanced recovery. When this philosophy is adopted, variability decreases.

Preoperative Optimization

The explosion of evidence regarding preoperative optimization outreaches this chapter. There is abundant research ongoing to define readiness for operation. Subjecting patients to exercise-based challenges, evaluating interleukin levels, and reading nutritional parameters on CT scans are just a few of the areas being aggressively studied [18]. This section,

Table 7.1 Common enhanced recovery elements in elective CRS

Phase	Element	Outcomes of interest
Preoperative	Informed consent	Shared decision-making and appropriateness
	Education	Patient participation and decreased stress
	Optimization	Best management of modifiable risk factors
Perioperative	Bowel preparation	Decrease surgical site infection
	Limiting fasting	Encourage euvolemia for safe induction
	Carbohydrate load	Decrease insulin resistance and infection
	Identify/ document	Increase compliance to protocol and audit
	PONV prophylaxis	Optimize early PO tolerance and patient experience
	Multimodal analgesia	Decrease opioid-related complications
Intraoperative	VTE prophylaxis	Decrease thrombotic complications
	Antibiotic prophylaxis	Decrease infectious complications
	Multimodal analgesia	Minimize opioids during general anesthesia
	Goal-directed IVF	Optimize the right fluid relative to needs
	MIS	Decrease surgical stress and optimize recovery
	Minimize drains, tubes, and lines	Decrease foreign body reaction and complication risk without evidence of benefit
	PONV prophylaxis	Optimize early PO tolerance and patient experience
Postoperative	Multimodal activity	Minimize opioids during general anesthesia
	Immediate diet	Encourage return of bowel function, minimize catabolism
	Immediate activity	Minimize complications of inactivity
	VTE prophylaxis and teaching	Decrease thrombotic complications and begin discharge teaching
	Education	Reinforce discharge criteria and goals to minimize unnecessary length of stay and stress
Post-discharge	Multimodal analgesia	Minimize opioid complications and opioids in the community
	Continued activity	Encourage rehabilitation and muscle preservation
	VTE prophylaxis	Decrease thrombotic complications
	Close contact	Decrease stress and recognize problems early to prevent readmissions

PO Per os, *PONV* postoperative nausea and vomiting, *IVF* intravenous fluid, *VTE* venous thromboembolism, *MIS* minimally invasive surgery

though, is a brief review of well-established and feasible recommendations that should be routine in all preoperative preparation programs: smoking cessation, preoperative nutrition, and anemia and diabetes management recommendations. Since acquiring the "Strong for Surgery" program, the best guide for this preparation for surgery elements is the American College of Surgeons webpage, https://www.facs.org/quality-programs/strong-for-surgery, which includes resources for clinicians, preoperative programs, and patients.

Smoking Cessation

The association of smoking with worse operative outcomes is well established [19]. For colorectal surgeons, concerns include increased risk of anastomotic complications, impaired microcirculation, increased postoperative pulmonary complications, and special considerations in inflammatory bowel disease (IBD). Particular recommendations include taking advantage of the life-changing moment of a surgical diagnosis as motivation for patients to quit tobacco use and encouraging even 2–3 weeks of preoperative cessation as beneficial. For many patients, smoking is not their only modifiable risk factor; smoking cessation can be one goal added to increased physical activity, alcohol intake moderation, and improved blood sugar management during even a brief elective case delay. Resources available on Strong for Surgery are thorough. Having a local team with specific addiction focus and training does result in higher success of these efforts [20].

Preoperative Nutrition

The evidence that malnutrition is independently associated with worse colorectal surgery outcomes and increased costs is abundant. The problem is often underestimated, but it is substantial. Work by Wischmeyer et al. [21] produced this infographic defining the impact of inadequate preoperative nutritional status (Fig. 7.7).

However, surgeons' understanding of this has not easily translated to universally applicable recommendations for our patient population. Options to use a diseased gastrointestinal tract to improve nutrition are limited. Making nutritional preparation for CRS more challenging is the difficulty of clinically diagnosing malnutrition. A fast screening plan is proposed by the ASER and PeriOperative Quality Initiative (www.POQI.org) consensus statement by Wischmeyer et al. [21] (https://thepoqi.org/POQI-2-Manuscripts). Detailed discussion of preoperative supplements and the rare indication for parenteral preoperative repletion is available in the online resource linked above. Generally, the recommendations include protein calories, regular mineral and vitamin supplements, and evaluation for nutrient deficiencies and potential directed supplements. Practical implementation is

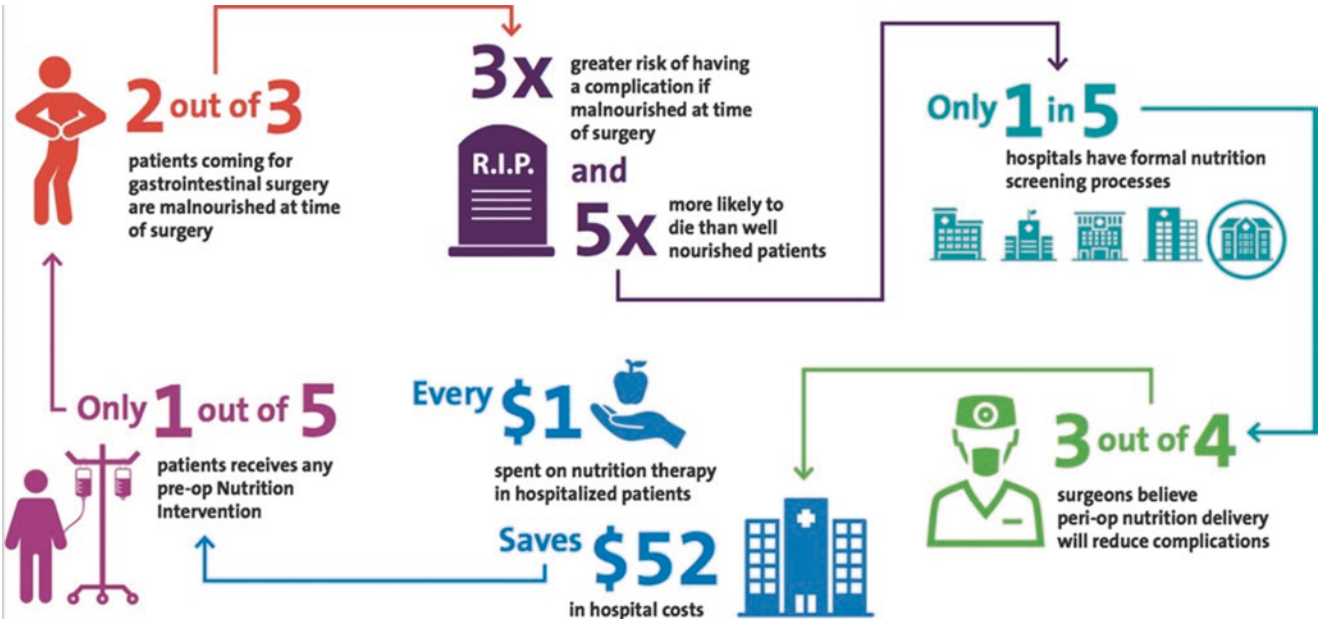

Fig. 7.7 Impact of perioperative malnutrition (Reused with permission from Ref. [21]. Copyright © Wolters Kluwer)

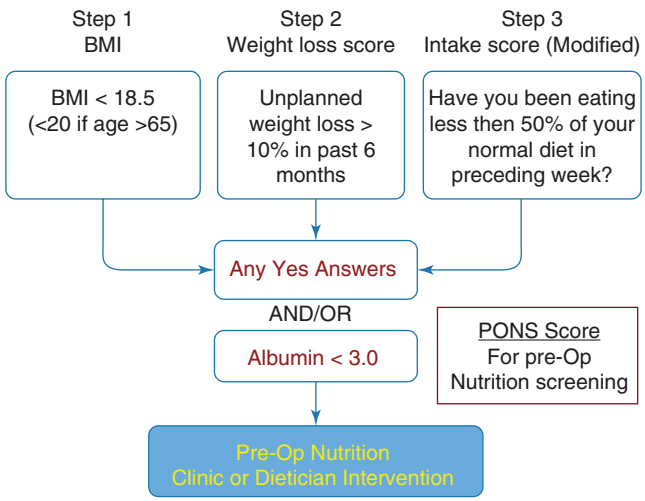

Fig. 7.8 PONS Score for preoperative nutritional assessment (Reused with permission from Ref. [21]. Copyright © Wolters Kluwer)

to wait for uptrending weight and prealbumin to ensure improvement. To minimize complications, prealbumin and other nutritional parameters should be normal before operation (Fig. 7.8).

Preoperative Anemia

Anemia is a significant and modifiable risk factor for worse outcomes from elective operations; however it is not uncommon for surgeons to feel helpless in correcting anemia in the GI surgery patient. Chronic GI losses are often the culprit of preoperative anemia in our patients, and until the operation, the source of bleeding exists. Here, we have created a practical management guide by summarizing recommendations for our patient population (Fig. 7.9) [22–24].

Perioperative Hyperglycemia

Perioperative hyperglycemia is strongly associated with increased infections, reoperations, and death; however, this increased risk is not seen in patients who are well-managed around the time of operation with insulin therapy. This is well described in a review of 11,633 patients in the Surgical Care and Outcomes Assessment Program in Washington State [25]. Good perioperative management of hyperglycemia must start with good preoperative management [26]. Kiren et al. added to our understanding that the degree of hyperglycemia is linearly associated with the severity of complication [27]. Elaborate management of diabetics and non-diabetics with elevated blood sugar in preparation and around the time of surgery has been created. However, most of the recommendations are part of algorithms for preoperative optimization before complete elective operations, such as knee replacements or ventral hernia repairs. Our population of colorectal surgery patients may be able to work on optimization for 2–4 weeks; however longer delays, referral to endocrinology, and documented improvement in HbA_{1C} are not reasonable. As per American Diabetes Association screening guidelines, the following patients meet criteria for HbA^{1C} screening: over 45 years of age; personal history of diabetes (DM1, DM2, or gestational); polycystic ovarian disease; or abnormally high fasting blood glucose. Additionally, a patient with BMI >/= 25 and anyone with inactive lifestyle; HTN; hyperlipidemia; or first-degree relative with diabetes should be tested [28]. The above evidence

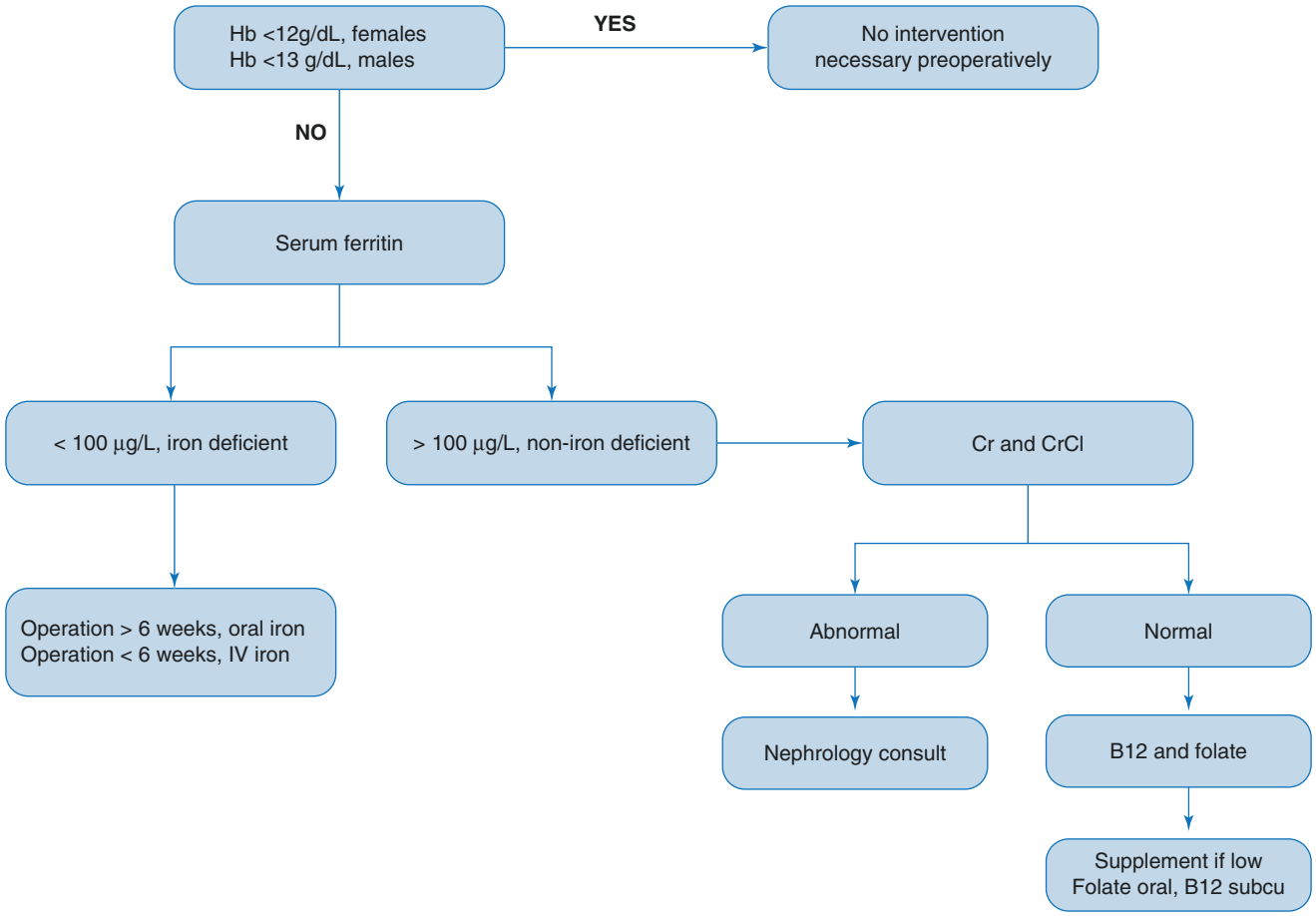

Fig. 7.9 Practical consideration of preoperative anemia in elective CRS

and recommended protocol elements are summarized in functional guide to blood sugar management in elective CRS (Fig. 7.10) [29–31].

Preoperative Fasting Period and Preoperative Carbohydrate Drink

The origins of ERAS Society guidelines date back to work on insulin resistance and the use of preoperative carbohydrate loading by Ljungqvist [32]. In animal trauma models and then in human surgical patients, his lab showed that pre-stress maltodextrin carbohydrate loading decreased postoperative insulin resistance and complications. Currently many products are available commercially and to health systems to fulfill this element. Notably, just carbohydrates, without the studied maltodextrin source, have not been shown to have the same effect. The mechanism of preoperative carbohydrate influence on postoperative insulin resistance has been described as being mediated by AMP-activated protein kinase activation [33]. With this understanding, perhaps more in-depth analysis of the best preop carb drink can be accomplished.

Preoperative carbohydrates and other liberal clear fluids should be encouraged as part of enhanced recovery perioperative preparation. The American Society of Anesthesia guidelines include preoperative clear fluid intake to continue up to 2 hours before induction of general anesthesia [34]. The challenge to institute this recommendation from over 40 years ago is a good reminder of the teamwork that must go into practice changes across phases of care.

Bowel Preparation

Bowel preparation, with antegrade laxative preparation and oral antibiotics, is recommended for operations with a planned lower bowel resection. The literature was recently reviewed, and guidelines were published by the ASCRS Practice Guidelines Committee [35]. Early ERAS Society guidelines did not endorse routine mechanical bowel preparation. However, the evidence of benefit since the earlier ERAS guidelines is robust and clear; most current enhanced recovery programs for CRS include bowel prep.

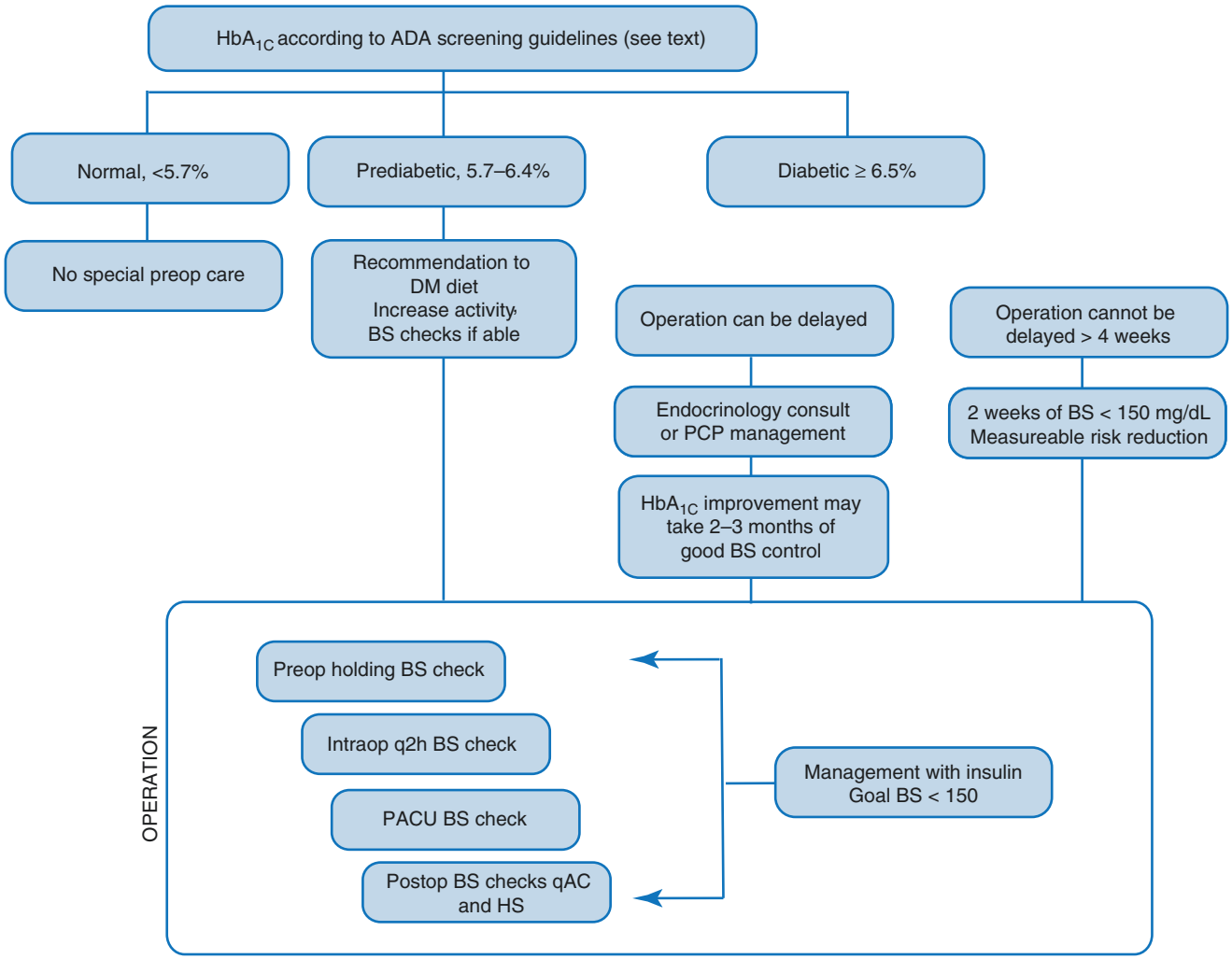

Fig. 7.10 Practical consideration of preoperative hyperglycemia in elective CRS

In-hospital Preoperative Enhanced Recovery Elements

Education and continued, constant messaging are essential for patient participation and stress reduction. At the time of admission, many elements that will continue throughout the hospitalization begin in the preoperative holding area.

Prevention of Postoperative Nausea and Vomiting (PONV)

Combatting the common complication of nausea after general anesthesia must begin in the preoperative space. The role of the surgeon is to identify patients at increased risk and to ensure pre-emptive management by anesthesia. Gan et al. updated the guidelines for the management of PONV; included is an easy cursory scale for PONV risk [36]. Each binary risk factor is 1 point if present: female, non-smoker, history of PONV, or postoperative opioids. These factors are additive, with baseline PONV risk of 10%, any one risk factor correlates to 20%, any two 40%, and any three 60%. If all four risk factors are present, there is an 80% chance of PONV. This prediction model should be applied in preoperative clinic to inform the patient and the anesthesia team before general anesthesia to consider prophylaxis in at-risk patients. Most enhanced recovery protocols include multimodal PONV prophylaxis as per anesthesia recommendations [37].

Multimodal Analgesia (MMA)

Pain receptors and the sensation of pain are mediated by several pathways. Opioids impact a patient's sensation of pain, but opioid-related complications can be minimized or completely avoided by strategies to impact different pain pathways simultaneously [38]. While it might be too stringent to aim for narcotic-free major CRS, the key to MMA is to recognize the cost of each narcotic dose. Even an exposure of as little as ten morphine equivalents has been associated with an increase incidence of postoperative ileus in CRS [39]. A scheme to summarize general MMA approaches is shown (Fig. 7.11).

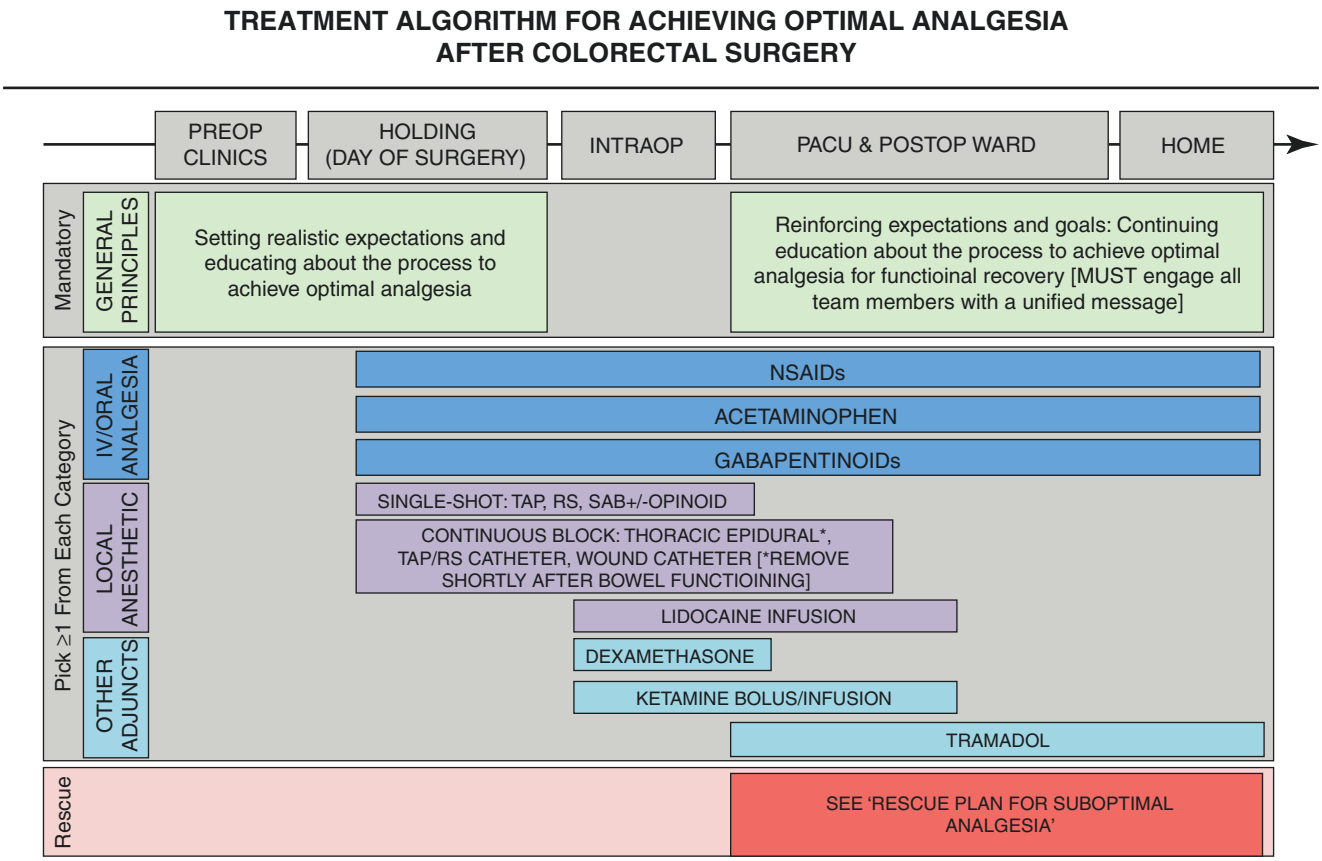

Fig. 7.11 PeriOperative Quality Initiative multimodal analgesia strategy [38]

Multimodal analgesia in enhanced recovery always raises discussion of epidural as a mandatory element. What is often missed in interpretation of earlier ERAS guidelines is the incidence of open operation. Current recommendations for open CRS still include epidural analgesia if the use is supported locally [40, 41]. If inadequate experience and oversight exists, epidurals can increase time to mobility, urinary catheter removal, and discharge. The authors offer experience of expeditiously placed, safely managed epidurals with extremely high success rates and decreased costs [12]. Many other non-catheter blocks are available and in combination with other components of MMA are more appropriate than epidural catheters for MIS cases. They may also be proven to be more appropriate for open cases.

Multimodal analgesia is aggressively studied and re-evaluated with each new pain medicine released. The plan shown above summarized an MMA model with recommendations current to its publication. Some evidence suggests that gabapentin may be related with drowsiness and respiratory depression, and the use oral acetaminophen before placement of gastric decompression may not be as effective as intravenous acetaminophen at fascial closure. Improvement in MMA can be made about every 6–9 months to keep pace with the literature. The pain management scheme for ERAS protocols should be addressed with every interval protocol review. The perception of providers must be that MMA is effective since the implementation of an enhanced recovery protocol was associated with increased use of perioperative MMA in non-ERP patients [42].

VTE Prophylaxis and Antibiotics

Evidence for best VTE strategies and antibiotic coverage for CRS is well established in the literature and elsewhere in this text (Chap. 6). The line item is included here to remind surgeons that not everyone along the continuum of the patient's surgical journey will know these details. The appropriate preoperative antibiotic and the VTE prophylaxis timing, inpatient plan, and plan at discharge with required teaching must be visible to the entire team.

Intraoperative Enhanced Recovery Elements

Surgical outcomes are impacted by every aspect of care while the patient is in the operating room – every dose of narcotic, every liter of fluid, every tube or drain, every incision. While it is impossible to study any one intraop care element independent of the rest of the operation, general principles have been investigated. Including the anesthesiology team throughout the creation of an enhanced recovery pathway is essential for success.

Multimodal Analgesia

MMA must continue during general anesthesia. The details of medication combinations, available blocks and neuraxial approaches, as well as intraop and postop infusional choices are all subject to local formularies and anesthesiologists' talents and preferences. The anesthesia team's knowledge of ERAS and their expertise relative to narcotic-sparing management has to be garnered during the creation of any enhanced recovery pathway. Infusional lidocaine has been shown to be effective in center reports, but Cochrane review failed to find convincing evidence for recommendation [43].

Intentional Fluid Management

The evidence supporting the safest fluid management for intraoperative enhanced recovery is still evolving. There was little discussion of fluid management in the first colorectal ERAS guidelines, as this was developing in the anesthesiology literature simultaneously. Studies and opinions about this are now abundant; most are anesthesiologist designed and directed.

Specifically, trial design often includes a statement such as "an enhanced recovery pathway was in place," and a diversity of patient populations are included to ensure power. In the larger trials, from which the anesthesiology community is defining their understanding of best fluid management, surgical outcomes, such as length of stay in the hospital, readmissions, surgical complications, and ileus, are recorded. However, the postoperative fluid management is not reviewed. As has been proven, excessive or inadequate fluid management postoperative also impacts these same outcomes. The data can be difficult to interpret.

Contradiction between "restrictive and liberal" protocols can be clarified by analysis of the details. Myles et al. claimed higher incidences of acute kidney injury (AKI), in enhanced recovery protocol patients who randomized to the restrictive fluid arm of a multinational study of over 3000 [44]. Given there was no analysis of the enhanced recovery elements or preoperative fluid allowance, this study also lacked direction for perioperative fluid management. The thoughtful comments of a surgeon in Denmark who has studied perioperative fluid management since the 1990s are helpful describing the benefits of intentional fluid management and limitations of the Myles study [45]. Evidence for best fluid management is still accruing; therefore watching for studies with a defined perioperative protocol and deeper evaluation than just high-level, reported surgical outcomes is prudent. Though the Myles study showed association with AKI, a careful observational study out of Mayo failed to show increased AKI in ERAS. Their chief finding, however, was potential increase of ileus in patients receiving greater volumes of fluid on their protocol [46].

As we await further science behind patient responses to fluid and associated surgical outcomes with well-defined care protocols [47], safest and cheapest management of fluid around the time of colorectal operations has three tenets [48, 50]:

1. Liberal fluid encouraged during bowel prep and until 2 hours before induction of general anesthesia.
2. Zero-balance intraoperative fluid management based on weight.
3. Normotension and urine output should be maintained with reactive intravenous fluid until oral intake is adequate.

Minimally Invasive Surgical Approaches

Discussed previously and covered thoroughly elsewhere in this text, minimally invasive approaches decrease surgical stress and improve outcomes. These benefits are additive when combined with enhanced recovery care plans [51].

Minimal Use for Drains, Tubes, and Lines

Early in literature for enhanced recovery, the promotion of minimizing the use of intra-abdominal drains, nasogastric tubes (NGT), and central venous access lines (CVL) was promoted. These recommendations persist with evidence of no benefit to abdominal drains; harm with NGT except in obstruction; and increased infection and complication with CVL [51, 52].

Postoperative Enhanced Recovery

Aarts et al. reported a review by the iERAS group in Canada that postoperative ERAS interventions have the greatest impact on optimal recovery [53]. Confounded by the fact that postoperative elements are more successful if earlier occurring elements show high compliance, the postoperative phase is, indeed, the longest of the in-patient phases and the most impactful on outcomes.

Early Diet, Early Mobilization, and Early Oral Medications

The success of postoperative elements of enhanced recovery often demonstrates the success of earlier elements. Education leads the patient toward a low stress discharge plan. A minimally stressful operation results in faster return to regular diet and oral management of fluid needs. Well-managed, opioid-sparing analgesia is less likely to result in ileus. The elements of immediate diet and mobilization are well supported as safe and beneficial. Low residue diet is better than clear liquid diet at promoting earlier return of bowel function and earlier discharge with fewer complications [54]. However, Clough et al. showed persistent reluctance to adopt early feeding in a comparative cohort study. Lack of adoption of these well-founded elements further represents the need for evidence-based care protocol implementation, such as enhanced recovery [55].

Multimodal Analgesia

Details of MMA are discussed above. Important aspects of MMA in the postop period include rescue therapy and education. Not all patients will be well-managed with the prescribed MMA. Anxiety and pre-existing pain conditions make postop analgesia challenging. ASER-POQI 2 addressed this with the rescue plan shown in Fig. 7.12 [38].

Postoperative reiteration of the goals of MMA, medication names, and an opioid-sparing plan is essential. This message needs to be consistent from the first dose of medication in the postoperative experience, through discharge instructions, and with the clinic contacts after discharge.

Standard Discharge Criteria

An international consensus to determine readiness for discharge criteria created a simple five-item list [56]. GI function and general recovery are well assessed by solid diet tolerance, adequate liquid intake, oral pain management, and activity. Objective readiness is confirmed with ward data, such as blood pressure, heart rate, urine output, temperature, and spontaneous voiding. A rigorous and well-known enhanced recovery program demonstrated that the delays typical of discharge after a patient meets discharge criteria are minimized with standard practice. In the review at McGill, readiness for discharge and actual discharge most often were at the expected 3 days after colorectal resection [57].

Considerations in Special ERAS Populations

Enhanced Recovery in Stoma Creation and Reversal

Diverting ileostomy is a frequent source of delayed discharge and readmission. High ileostomy output and dehydration readmission rates are reported in up to 15% of these patients. Index admission length of stay among diverted patients has been shown to be prolonged significantly, mitigating the effects of laparoscopy on LOS [58], even in the context of an ERP [59]. With the expected expedited recovery on an ERAS protocol, new ileostomy patients leave the hospital sooner, leaving little time for a patient with a newly formed stoma to learn the practical skills of caring for the stoma. In fact, many studies looking at the impact of ERAS exclude patients undergoing stoma creations. This section discusses the application of ERAS to even these patients and the special considerations necessary.

A controlled randomized study [60] out of Norway investigated whether an ERAS program with a dedicated ERAS and stoma nurse specialist could reduce the length of hospital stay, readmission, and stoma-related complications, compared to standard of care pathways in patients undergoing planned stoma. Preoperative and postoperative stoma education in the context of an ERAS program was associated with a significantly shorter hospital stay with no difference in

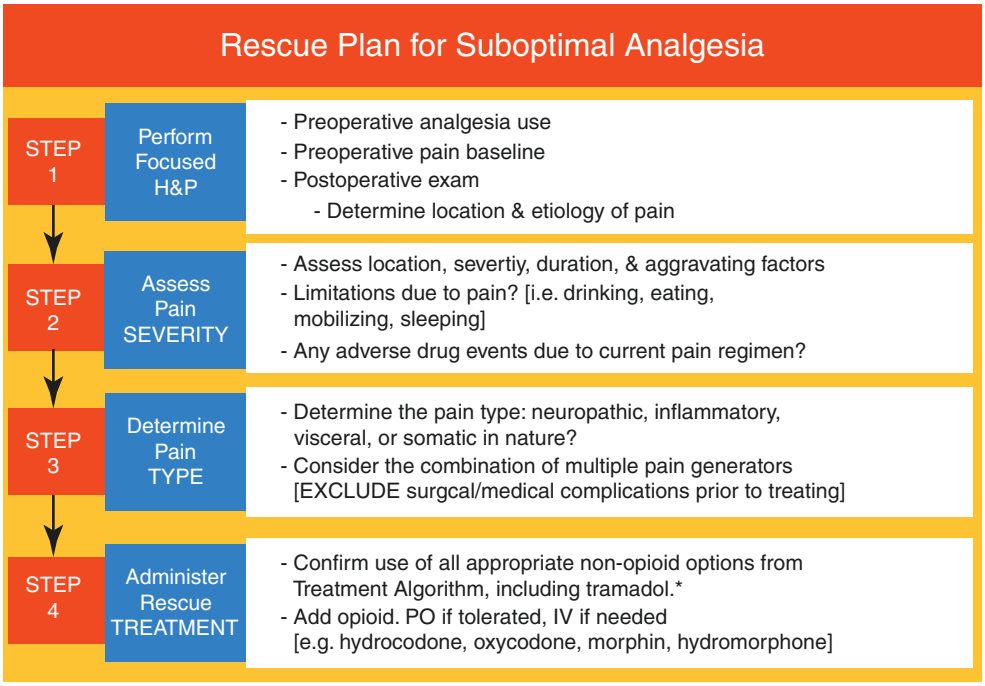

Fig. 7.12 Rescue plan in MMA breakthrough. *MMA* Multimodal analgesia [38]

readmission rate or early stoma-related complications. In a UK-based pre-/post-ERAS study of anterior resection patients with ileostomy, Younis et al. [61] showed significant reductions in average LOS (nearly half) with preoperative stoma management teaching as part of an ERP. The readmission rates in both groups were low (2.5% pre-ERP vs. 0% post-ERP), and none was due to stoma management issues. Patients were closely monitored in the community by stoma care specialist nurses and any stoma complications managed promptly in conjunction with GPs. This is in line with other studies that confirm that length of hospital stay need not to be prolonged among patients with a stoma if adequate patient education is provided [62], particularly in the context of ERAS [63, 64]. The Ontario Provincial ERAS Enterostomal Therapy Nurse Network recently published best practice guidelines for care of patients with fecal diversion [65], addressing coordinated preoperative, postoperative, as well as discharge phases of care in the community, in order to improve outcomes, decrease complications, and reduce hospital costs.

ERAS in Emergency Surgery and Trauma

ERAS is well established in elective colorectal surgery; however the feasibility and benefit of ERAS in emergency colorectal surgery has only been reviewed more recently. In 2019, Lohsiriwat et al. [66] reviewed six retrospective observational studies [67–72] on patients undergoing emergency operations managed by enhanced recovery principles. The authors concluded the following: (1) Compared to ERAS-CRS for elective cases, ERAS after emergency colorectal surgeries is associated with a longer length of stay and a higher rate of unplanned reoperation without a difference in rates of anastomotic leak or readmission. Overall compliance with ERAS protocol was lower, with comparable compliance to elective cases in the operating room. (2) Compared to emergency surgeries performed without ERAS programs, ERAS is safely applicable in emergency colorectal surgery and confers similar beneficial effects seen in the elective setting.

A recent meta-analysis of 6 ERAS protocols in 1334 total emergency abdominal surgery patients [73] confirms these findings. The authors conclude that ERAS protocols favorably resulted in reduced postoperative complications, accelerated recovery of bowel function, and shorter length of stay without increased readmission in emergency abdominal surgery patients. As in all patient populations, ERAS in emergency colorectal surgery should be guided by the concept of reducing stress responses to surgery [74].

Enhanced Recovery in the Elderly

ERAS pathways in the elderly are safe and effective. Bagnall et al. [75] performed a systematic review that included 16 studies involving 5965 patients who underwent colorectal surgery. Two randomized controlled trials demonstrated shorter hospital stay and fewer complications in elderly patients >65 and >70 years of age who were on an ERAS pathway compared with an age-matched group receiving standard perioperative care. There are no significant differences in morbidity and mortality between the elderly and younger patients on ERAS pathways, although older patients tended to have a longer length of stay compared to the younger patients. Only two studies in the systematic review above reported any data on adherence to the ERAS pathway: Rumstadt et al. [76] found lower compliance among patients >79 years of age (not the group of patients age 70–79 years). Feroci et al. [77] showed that patients age >75 years had poor adherence to many postoperative items. In this study, poor compliance in this age group was the greatest predictor of poor outcomes. However, two later studies [78, 79] did not show any effect of age on adherence to ERAS pathway, and they did not demonstrate a difference in morbidity or mortality. Interestingly, Baek et al. found that there was no difference among older versus younger patients in return of bowel function, diet advancement, urinary catheter removal, complications, or length of hospital stay, but there were increased rates of emergency room visits and readmission in older patients [80]. The most recent study by Owodunni et al. [81] evaluating compliance to ERAS pathway in patients age ≥ 65 years did not show any significant difference in overall compliance rates compared to younger patients. While ERAS intervention in the older patients resulted in significant decrease in length of hospital stay, a further reduction in length of stay occurred in ERAS patients undergoing laparoscopy. In all studies, the greatest benefit was seen in older patients achieving high compliance with the ERAS variables.

A recent Italian study confirmed the feasibility, safety, and benefit of a tailored ERAS program in octogenarian patients undergoing minimally invasive surgery for colorectal cancer [82]. The majority of patients met release criteria in a median of 5 days, which was significantly shorter than the actual days of dismissal (6+/−4.2). The authors commented that a consideration should be made for the very elderly for whom length of hospital stay could be a misleading outcome; readiness to discharge might be a more accurate measure. They speculate that several factors may explain the discordance between these variables including social and geographical isolation, unavailability of nursing assistance, and limitation of communication with caregivers.

Management on an ERAS pathway appears to be safe and beneficial in the elderly, though with slightly lower rates of adherence to certain aspects of the protocol and increased length of hospital stay and readmission compared to the younger patients. These differences in adherence and outcome in the elderly are likely due to their comorbidities and baseline functional status [74]. Caution must be taken to not overinterpret "lower compliance," when compliance is considered across a population. Enhanced recovery, at its best, is patient-focused. The geriatric patient on anticoagulation, who does not qualify for an epidural, is not non-compliant for that element. The patient is not eligible, and should not be considered non-compliant. However, that ineligibility may, indeed, portend a slower recovery.

Enhanced Recovery and Inflammatory Bowel Disease

Patients with inflammatory bowel disease (IBD) frequently present with malnutrition, immunosuppression, anemia, as well as intra-abdominal abscesses, fistulas, and bowel obstruction placing them at higher risk for significant postoperative morbidity. As such, patients undergoing surgery for IBD, as a group, have prolonged hospitalizations and increased readmissions and hospital costs. In addition, many IBD operations are less suitable for laparoscopy. This drives the question whether enhanced recovery would be able to achieve similar benefits in IBD patients as in patients with colorectal cancer or other benign conditions.

Ban et al. [83] investigating the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database for patients with enhanced recovery variable data undergoing elective colectomy have shown that a preoperative diagnosis of IBD is associated with prolonged length of stay and higher odds of readmissions and morbidity/mortality when compared with patients who had undergone colectomies for non-IBD diagnoses. In a single-institution ERAS retrospective analysis, Dai et al. [84] demonstrated that IBD patients had higher incidence of postoperative ileus compared to colorectal cancer patients (28.8% vs. 14.8% ($P < 0.001$), respectively). The results from these two studies do in fact question whether there is any benefit in ERAS protocols for IBD patients in the first place.

Enhanced recovery pathways do improve outcomes after bowel resection for IBD. D'Andrea et al. [85] analyzed pre-/post-ERP implementation IBD patients undergoing elective bowel resection. The ERAS group had significantly reduced rates of SSI, ileus, and anastomotic leak with a decreasing trend in the LOS, readmission, reoperation, sepsis, and wound disruption. Another pre-/post-ERAS study showed ERAS-managed IBD patients had reduced LOS and hospital costs without an associated increase in complications or readmissions. In addition, MIS was independently associated with reduced LOS, while ERP within the MIS group was associated with an even shorter LOS. Crohn's disease (CD) diagnosis was associated with a longer LOS. However, the post-ERP group still had a shorter LOS despite having a higher rate of CD. Patients with IBD undergoing major abdominal and pelvic surgery, despite being a complex patient population, benefit from the implementation of an ERP, at least with respect to LOS and in-hospital costs.

Clearly ERAS principles are widely applicable and beneficial to these unique patient populations. Increased physician and nursing training to promote widespread implementation and adherence to ERAS principles (as many as feasibly possible) can further improve the quality and cost of healthcare administered. Modified programs are appropriate for different patient populations, with the common goal of decreasing surgical stress and its effects and costs.

Economic Impact and Value of Enhanced Recovery to the Healthcare System

In the most recent systematic review and meta-analysis on cost analysis of ERPs in colorectal surgery, ERP induced mean saving costs of $3101 USD per patient [86]. It is generally accepted that ERPs reduce healthcare costs by virtue of shorter duration of hospital stay and decreased rate of complications without increasing readmission rates, as demonstrated in several systematic reviews [87–89]. These pathways achieve such cost savings by using defined evidence-based processes that are monitored to allow optimal resource management and minimal variability. Roulin et al. [90] found specific gains in medication, laboratory, and radiology costs. Standardization not only ensures that patients receive routine care items that might otherwise be forgotten, it also prevents unnecessary diagnostics without increasing the complication rate.

However, there are many limitations when examining the mechanisms of impact of ERPs on cost using these traditional audit measures [70, 91, 92]. The true costs and systemic values need to be considered. Future economic models of ERP costs need to incorporate societal costs and patient, as well as recovery-centric outcomes, in addition to the traditional audit measures. In fact, ERAS can and should fulfill what is now referred to as the "Quadruple Aim": achieving not only better patient outcomes, at a lower cost, and improved patient satisfaction but also medical, nursing, and provider satisfaction [93–96]. A recent review of the literature by Li et al. [97] confirms that the application of ERAS pathways following colorectal surgery does not lead to worse outcomes in patient satisfaction, quality of life, fatigue, and return to activities: however, no publications have assessed surgeon or care provider satisfaction with ERAS pathways.

Current Directions and the Future of ERAS

Societies and Governments Assist Implementation Across Canada and the USA

ERAS is quickly becoming the standard of care in colorectal surgery. In North America, adoption of enhanced recovery has been mostly driven by individual providers or healthcare systems, without government collaboration or incentive. At our training centers, adoption has been occurring insidiously via substantive, unfunded academic effort and inculcating trainees by incorporation of ERAS principles in training and on certification exams [98]. Nonetheless, barriers to implementation remain a challenge. Results from a Canadian qualitative study suggest that although clinicians see the value in implementing an ERAS program, lack of nursing staff, lack of financial resources, resistance to change, and poor communication and collaboration are perceived as barriers to its adoption [99]. There is no unified enhanced recovery assessment program or compensation program in the USA, but the American Society for Enhanced Recovery (ASER) promotes best practice via multidisciplinary collaboration between surgical, anesthesia, certified registered nurse anesthetists, and nursing societies. In addition, quality initiatives and protocols that arise from ASER are undertaken with an understanding of US healthcare strategies – cost structures, interactions of siloed stakeholders, and shared outcomes without shared inflow of resources [98]. In an exceptional effort to expand the implementation of ERAS pathways across the USA, a multimillion-dollar grant was awarded by the US Agency for Healthcare Research and Quality (2017–2020). The "Safety Program for Improving Surgical Care and Recovery" team plans to introduce enhanced recovery in approximately 750 US hospitals [98, 99]. Similarly, in Canada, the Canadian Patient Safety Institute's Integrated Patient Safety Action Plan for Surgical Care Safety, with support from numerous partner organizations from across the country, formed Enhanced Recovery Canada (ERC) in 2017.

Future Directions

Innovation of technology provides opportunities to overcome challenges with ERAS [100–102]. Databases facilitate core data collection, ensure optimal adherence to protocols, and reduce variability in clinical care. More robust data collection is particularly useful for ERAS clinical studies [103]. In the future, such dataset will also allow us to investigate the impact of the perioperative period on long-term patient outcomes such as cancer survival or disease recurrence in IBD [100]. Wearable sensors measure, store, and transmit large amounts of patient and environmental data and have been used to objectively and continuously monitor physical activity (an important indicator of functional recovery) within the hospital setting and at home following discharge [104–106]. To provide a complete recovery picture beyond activity tracking, smart devices will also be ready to collect patient-reported outcome data concerning other relevant aspects of postoperative recovery [107, 108]. In recent years, the role of telemedicine (TM) in postoperative care, implemented by way of smart devices with text messaging or mobile health applications, including pictures and videos, has grown. TM has demonstrated excellent clinical outcomes, a high degree of patient satisfaction, decreased driving distance and wait times, and cost savings to both the patient and healthcare systems, particularly for surveillance after ambulatory surgery [109, 110]. A prospective multicenter study in France confirmed the feasibility of home surveillance by TM after major surgery, in colorectal patients within an ERP. TM with automatic alerts led to early, timely detection of postoperative complication and less time spent answering phone calls by the surgical team and avoided ER visits. A more recent cohort study [111] looked at an active post-discharge surveillance (APDS) program as part of an ERAS protocol in colorectal patients in the USA. The program's interface is also centered on a text messaging paradigm with automatic alerts and is accessible via any smart device or desktop. It employs automated protocols (defined by the surgery team) to automatically communicate with patients not only after discharge but also before and after surgery to ensure compliance with protocol perioperatively. Patients, physicians, office staff, nurses, care coordinators, and extended care nurses are all able to communicate and coordinate care via the APDS. The study also concluded that APDS allows many postoperative issues to be resolved in an outpatient setting without ER visits or readmissions. The biggest limitation in this study was attrition bias as patients enrolled in the APDS and engaging with the program initially would stop responding. It is unclear if this was due to technical difficulties or that patients were simply overwhelmed by the frequent reminders and checks. Future studies should look further into the difficulties of TM technology. Integrating patient-centered recovery data in electronic health records [112] will provide an opportunity for recovery auditing and further database-driven research aimed at quality improvement [107].

Summary

The principles of enhanced recovery require thoughtful analysis of the perioperative literature and application of the evidence to everyday care. This process has fit the practice of colorectal surgery as we are always striving for better outcomes in our patients with known risks having operations

with known complication profiles. Our specialty encompasses a significant portion of elective operations, providing us with research opportunities and volume to merit quality improvement efforts. The change management of enhanced recovery requires the development of a team that is then in place for whatever the next, best thing is. This deliverable, from working through the implementation phase of enhanced recovery, sets up colorectal practices and their hospitals for continuous, efficient improvement. The enhanced recovery process brings as much to the surgeon and system, as it does to our patient population. The authors' hope is that we as individuals and as change management agents keep an open mind to all possible future care improvement strategies and that we encourage an open platform for continuous improvement.

References

1. Kehlet H, Nikki P, Jäättelä A, Takki S. Plasma catecholamine concentrations during surgery in unsupplemented glucocorticoid-treated patients. Br J Anaesth. 1974;46(1):73–7.
2. Wilmore DW. Alterations in protein, carbohydrate, and fat metabolism in injured and septic patients. J Am Coll Nutr. 1983;2(1):3–13.
3. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg. 2002;183(6):630–41.
4. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg. 2008;248(2):189–98.
5. Wexner SD. Standardized perioperative care protocols and reduced lengths of stay after colon surgery. J Am Coll Surg. 1998ay;186(5):589–93.
6. Kehlet H, Mogensen T. Hospital stay of 2 days after open sigmoidectomy with a multimodal rehabilitation programme. Br J Surg. 1999;86(2):227–30.
7. Basse L, Jakobsen D, Billesbølle P, Werner M, Kehlet H. A clinical pathway to accelerate recovery after colonic resection. Ann Surg. 2000;232(1):51–7.
8. Clinical Outcomes of Surgical Therapy Study Group, Nelson H, Sargent DJ, Wieand HS, Fleshman J, Anvari M, Stryker SJ, Beart RW Jr, Hellinger M, Flanagan R Jr, Peters W, Ota D. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med. 2004;350(20):2050–9.
9. Nygren J, Hausel J, Kehlet H, Revhaug A, Lassen K, Dejong C, Andersen J, von Meyenfeldt M, Ljungqvist O, Fearon KC. A comparison in five European Centres of case mix, clinical management and outcomes following either conventional or fast-track perioperative care in colorectal surgery. Clin Nutr. 2005;24(3):455–61.
10. Ljungqvist O, Young-Fadok T, Demartines N. The history of enhanced recovery after surgery and the ERAS society. J Laparoendosc Adv Surg Tech. 2017;27(9):860–2.
11. NHS Institute, Elective Care & Diagnostics Branch. Enhanced Recovery Partnership Programme Project Report. http://www.dh.gov.uk/publications. Mar 2011.
12. Miller TE, Thacker JK, White WD, Mantyh C, Migaly J, Jin J, Roche AM, Eisenstein EL, Edwards R, Anstrom KJ, Moon RE, Gan TJ, Enhanced Recovery Study Group. Reduced length of hospital stay in colorectal surgery after implementation of an enhanced recovery protocol. Anesth Analg. 2014;118(5):1052–61.
13. Neville A, Lee L, Antonescu I, Mayo NE, Vassiliou MC, Fried GM, Feldman LS. Systematic review of outcomes used to evaluate enhanced recovery after surgery. Br J Surg. 2014;101(3):159–70.
14. Napolitano MA, Skancke M, Walters J, Michel L, Randall JA, Brody FJ, Duncan JE. Outcomes and trends in colorectal surgery in U.S. Veterans: a 10-year experience at a Tertiary Veterans Affairs Medical Center. J Laparoendosc Adv Surg Tech A. 2020;30(4):378–82.
15. Eskicioglu C, Forbes SS, Aarts MA, Okrainec A, McLeod RS. Enhanced recovery after surgery (ERAS) programs for patients having colorectal surgery: a meta-analysis of randomized trials. J Gastrointest Surg. 2009;13(12):2321–9.
16. Hoyt D, Ko C, editors. Optimal resources for surgical quality and safety. 1st ed: American College of Surgeons; 2017. ISBN-13: 978-0996826242.
17. Pearsall EA, McLeod RS. Enhanced recovery after surgery: implementation strategies, barriers and facilitators. Surg Clin North Am. 2018;98(6):1201–10.
18. Levy N, Grocott MPW, Lobo DN. Restoration of function: the holy grail of peri-operative care. Anaesthesia. 2020;75(Suppl. 1):e14–7.
19. Sharma A, Deeb A, Ianuzzi J, Rickles A, Monson J, Nad FF. Tobacco smoking and postoperative outcomes after colorectal surgery. Ann Surg. 2013;258(2):296–300.
20. Taylor H, Karahalios A, Bramley D. Long-term effectiveness of the preoperative smoking cessation programme at Western Health. ANZ J Surg. 2017;87(9):677–81.
21. Wischmeyer PE, Carli F, Evans DC, Guilbert S, Kozar R, Pryor A, Thiele RH, Everett S, Grocott M, Gan TJ, Shaw AD, JKM T, Miller TE, Hedrick TL, MD ME, Mythen MG, Bergamaschi R, Gupta R, Holubar SD, Senagore AJ, Abola RE, Bennett-Guerrero E, Kent ML, Feldman LS, Fiore JF Jr, Perioperative Quality Initiative (POQI) 2 Workgroup. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Nutrition Screening and Therapy Within a Surgical Enhanced Recovery Pathway. Anesth Analg. 2018;126(6):1883–95.
22. Shander A, Knight K, Thurer R, Adamson J, Spence R. Prevalence and outcomes of anemia in surgery: a systematic review of the literature. Am J Med. 2004;116 Suppl 7A:58S–69S.2.
23. Beattie WS, Karkouti K, Wijeysundera DN, Tait G. Risk associated with preoperative anemia in noncardiac surgery: a single-center cohort study. Anesthesiology. 2009;110(3):574–81.
24. Warner MA, Shore-Lesserson L, Shander A, Patel SY, Perelman SI, Guinn NR. Perioperative anemia: prevention, diagnosis, and management throughout the spectrum of perioperative care. Anesth Analg. 2020;130(5):1364–80.
25. Kwon S, Thompson R, Dellinger P, Yanez D, Farrohki E, Flum D. Importance of perioperative glycemic control in general surgery: a report from the Surgical Care and Outcomes Assessment Program. Ann Surg. 2013;257(1):8–14.
26. Chen EB, Nooromid MJ, Helenowski IB, Soper NJ, Halverson AL. The relationship of preoperative versus postoperative hyperglycemia on clinical outcomes after elective colorectal surgery. Surgery. 2019;166(4):655–62.
27. Kiran RP, Turina M, Hammel J, Fazio V. The clinical significance of an elevated postoperative glucose value in nondiabetic patients after colorectal surgery: evidence for the need for tight glucose control? Ann Surg. 2013;258(4):599–604.
28. American Diabetes Association. Classification and diagnosis of diabetes: standards of Medical Care in Diabetes. Diabetes Care. 2018;41(Suppl 1):S13–27.
29. Colibaseanu DT, Osagiede O, McCoy RG, Spaulding AC, Habermann EB, Naessens JM, Perry MF, White LJ, Cima RR. Proactive protocol-based management of hyperglycemia and diabetes in colorectal surgery patients. Endocr Pract. 2018;24(12):1073–85.
30. Setji T, Hopkins T, Jimenez M, Manning E, Shaughnessy M, Schroeder R, Mendoza-Lattes S, Spratt S, Westover J, Aronson S, on behalf of the Duke Perioperative Enhancement Team

(POET). Rationalization, development, and implementation of a preoperative diabetes optimization program designed to improve perioperative outcomes and reduce cost. Diabetes Spectr. 2017;30(3):217–23.
31. Evans C, Lee J, Ruhlman M. Optimal glucose management in the perioperative period. Surg Clin N Am. 2015;95(2):337–54.
32. Ljungqvist O, Thorell A, Gutniak M, Häggmark T, Efendic S. Glucose infusion instead of preoperative fasting reduces postoperative insulin resistance. J Am Coll Surg. 1994;178(4):329–36.
33. Shi M, Hu Z, Yang D, Cai Q, Zhu Z. Preoperative oral carbohydrate reduces postoperative insulin resistance by activating AMP-activated protein kinase after colorectal surgery. Dig Surg. 2020;10:1–8.
34. Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration: Application to Healthy Patients Undergoing Elective Procedures: An Updated Report by the American Society of Anesthesiologists Task Force on Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration. Anesthesiology. 2017;126(3):376–93.
35. Migaly J, Bafford A, Francone T, Gaertner W, Eskicioglu C, Bordeianou L, Feingold D, Steele S. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Use of Bowel Preparation in Elective Colon and Rectal Surgery. Dis Colon Rectum. 2019;62(1):3–8.
36. Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, Watcha M, Chung F, Angus S, Apfel CC, Bergese SD, Candiotti KA, Chan MT, Davis PJ, Hooper VD, Lagoo-Deenadayalan S, Myles P, Nezat G, Philip BK, Tramèr MR, Society for Ambulatory Anesthesia. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2014;118(1):85–113.
37. Tateosian V, Champagne K, Gan TJ. What is new in the battle against postoperative nausea and vomiting? Clin Anesth. 2018;32(2):137–48.
38. Scott MJ, McEvoy MD, Gordon DB, Grant SA, Thacker JKM, Wu CL, Gan TJ, Mythen MG, Shaw AD, Miller TE, Perioperative Quality Initiative (POQI) I Workgroup. American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) Joint Consensus Statement on Optimal Analgesia within an Enhanced Recovery Pathway for Colorectal Surgery: Part 2-From PACU to the Transition Home. Perioper Med (Lond). 2017;6:–7.
39. Barletta JF, Asgeirsson T, Senagore AJ. Influence of intravenous opioid dose on postoperative ileus. Ann Pharmacother. 2011;45(7–8):916–23.
40. Kooij F, Schlack W, Preckel B, Hollmann M. Does regional analgesia for major surgery improve outcome? Focus on epidural analgesia. Anesth Analg. 2014;119(3):740–4.
41. Pöpping DM, Elia N, Van Aken HK, Marret E, Schug SA, Kranke P, Wenk M, Tramèr MR. Impact of epidural analgesia on mortality and morbidity after surgery: systematic review and meta-analysis of randomized controlled trials. Ann Surg. 2014;259(6):1056–67.
42. Allen BFS, Jablonski PM, McEvoy MD, Ehrenfeld JM, Shi H, King AB, Wanderer JP. Implementation of an Enhanced Recovery Protocol (ERP) is associated with an increase in the perioperative use of non-opioid multimodal analgesia for non-ERP patients. J Clin Anesth. 2020;62:109694.
43. Weibel S, Jelting Y, Pace NL, Helf A, Eberhart LH, Hahnenkamp K, Hollmann MW, Poepping DM, Schnabel A, Kranke P. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. Cochrane Database Syst Rev. 2018;6:CD009642.
44. Myles PS, Bellomo R, Corcoran T, Forbes A, Peyton P, Story D, Christophi C, Leslie K, McGuinness S, Parke R, Serpell J, Chan MTV, Painter T, McCluskey S, Minto G, Wallace S, Australian and New Zealand College of Anaesthetists Clinical Trials Network and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Restrictive versus liberal fluid therapy for major abdominal surgery. N Engl J Med. 2018;378(24):2263–74.
45. Brandstrup B. Finding the right balance. N Engl J Med. 2018;378:2335–6.
46. Grass F, Lovely JK, Crippa J, Hübner M, Mathis KL, Larson DW. Potential association between perioperative fluid management and occurrence of postoperative ileus. Dis Colon Rectum. 2020;63(1):68–74.
47. Brandstrup B, Beier-Holgersen R, Iversen LH, Starup CB, Wentzel LN, Lindorff-Larsen K, Petersen TC, Tønnesen H. The influence of perioperative fluid therapy on N-terminal-pro-brain natriuretic peptide and the Association with Heart and Lung Complications in Patients Undergoing Colorectal Surgery: Secondary Results of a Clinical Randomized Assessor-blinded Multicenter Trial. Ann Surg. 2020;272(6):941–9.
48. Tolstrup J, Brandstrup B. Clinical assessment of fluid balance is incomplete for colorectal surgical patients. Scand J Surg. 2015;104(3):161–8.
49. Voldby AW, Brandstrup B. Fluid therapy in the perioperative setting-a clinical review. J Intensive Care. 2016;4:27.
50. Vlug MS, Bartels SA, Wind J, Ubbink DT, Hollmann MW, Bemelman WA, Collaborative LAFA Study Group. Which fast track elements predict early recovery after colon cancer surgery? Color Dis. 2012;14(8):1001–8.
51. Nelson R, Edwards S, Tse B. Prophylactic nasogastric decompression after abdominal surgery. Cochrane Database Syst Rev. 2007;3:CD004929.
52. Podda M, Di Saverio S, Davies RJ, Atzeni J, Balestra F, Virdis F, Reccia I, Jayant K, Agresta F, Pisanu A. Prophylactic intra-abdominal drainage following colorectal anastomoses. A systematic review and meta-analysis of randomized controlled trials. Am J Surg. 2020;219(1):164–74.
53. Aarts MA, Rotstein OD, Pearsall EA, Victor JC, Okrainec A, McKenzie M, McCluskey SA, Conn LG, RS ML, iERAS group. Postoperative ERAS interventions have the greatest impact on optimal recovery: experience with implementation of ERAS across multiple hospitals. Ann Surg. 2018;267(6):992–7.
54. Lau C, Phillips E, Bresee C, Fleshner P. Early use of low residue diet is superior to clear liquid diet after elective colorectal surgery: a randomized controlled trial. Ann Surg. 2014;260(4):641–7. discussion 647-9
55. Chough I, Zaghiyan K, Ovsepyan G, Fleshner P. Practice changes in postoperative feeding after elective colorectal surgery: from prospective randomized study to everyday practice. Am Surg. 2018;84(10):1675–8.
56. Fiore JF Jr, Bialocerkowski A, Browning L, Faragher IG, Denehy L. Criteria to determine readiness for hospital discharge following colorectal surgery: an international consensus using the Delphi technique. Dis Colon Rectum. 2012;55(4):416–23.
57. Balvardi S, Pecorelli N, Castelino T, Niculiseanu P, Liberman AS, Charlebois P, Stein B, Carli F, Mayo NE, Feldman LS, Fiore JF Jr. Measuring in-hospital recovery after colorectal surgery within a well-established enhanced recovery pathway: a comparison between hospital length of stay and time to readiness for discharge. Dis Colon Rectum. 2018;61(7):854–60.
58. Cartmell MT, Jones OM, Moran BJ, Cecil TD. A defunctioning stoma significantly prolongs the length of stay in laparoscopic colorectal resection. Surg Endosc. 2008;22(12):2643–7.
59. Munk-Madsen P, Eriksen JR, Kehlet H, Gogenur I. Why still in hospital after laparoscopic colorectal surgery within an enhanced recovery programme? Color Dis. 2019;21(12):1438–44.
60. Forsmo HM, Pfeffer F, Rasdal A, Sintonen H, Korner H, Erichsen C. Pre- and postoperative stoma education and guidance within an enhanced recovery after surgery (ERAS) programme reduces

length of hospital stay in colorectal surgery. Int J Surg. 2016;36(Pt A):121–6.
61. Younis J, Salerno G, Fanto D, Hadjipavlou M, Chellar D, Trickett JP. Focused preoperative patient stoma education, prior to ileostomy formation after anterior resection, contributes to a reduction in delayed discharge within the enhanced recovery programme. Int J Color Dis. 2012;27(1):43–7.
62. Chaudhri S, Brown L, Hassan I, Horgan AF. Preoperative intensive, community-based vs. traditional stoma education: a randomized, controlled trial. Dis Colon Rectum. 2005;48(3):504–9.
63. Hughes MJ, Cunningham W, Yalamarthi S. The effect of preoperative stoma training for patients undergoing colorectal surgery in an enhanced recovery programme. Ann R Coll Surg Engl. 2019:1–5.
64. Hignett S, Parmar CD, Lewis W, Makin CA, Walsh CJ. Ileostomy formation does not prolong hospital length of stay after open anterior resection when performed within an enhanced recovery programme. Color Dis. 2011;13(10):1180–3.
65. Miller D, Pearsall E, Johnston D, Frecea M, McKenzie M. Executive summary: enhanced recovery after surgery: best practice guideline for care of patients with a fecal diversion. J Wound Ostomy Continence Nurs. 2017;44(1):74–7.
66. Lohsiriwat V, Jitmungngan R. Enhanced recovery after surgery in emergency colorectal surgery: review of literature and current practices. World J Gastrointest Surg. 2019;11(2):41–52.
67. Lohsiriwat V. Enhanced recovery after surgery vs conventional care in emergency colorectal surgery. World J Gastroenterol. 2014;20(38):13950–5.
68. Wisely JC, Barclay KL. Effects of an Enhanced Recovery After Surgery programme on emergency surgical patients. ANZ J Surg. 2016;86(11):883–8.
69. Shida D, Tagawa K, Inada K, et al. Modified enhanced recovery after surgery (ERAS) protocols for patients with obstructive colorectal cancer. BMC Surg. 2017;17(1):18.
70. Shang Y, Guo C, Zhang D. Modified enhanced recovery after surgery protocols are beneficial for postoperative recovery for patients undergoing emergency surgery for obstructive colorectal cancer: a propensity score matching analysis. Medicine (Baltimore). 2018;97(39):e12348.
71. Verheijen PM, Vd Ven AW, Davids PH, Vd Wall BJ, Pronk A. Feasibility of enhanced recovery programme in various patient groups. Int J Color Dis. 2012;27(4):507–11.
72. Roulin D, Blanc C, Muradbegovic M, Hahnloser D, Demartines N, Hubner M. Enhanced recovery pathway for urgent colectomy. World J Surg. 2014;38(8):2153–9.
73. Hajibandeh S, Hajibandeh S, Bill V, Satyadas T. Meta-analysis of Enhanced Recovery After Surgery (ERAS) protocols in emergency abdominal surgery. World J Surg. 2020;
74. Lee GC, Hodin RA. Applying enhanced recovery pathways to unique patient populations. Clin Colon Rectal Surg. 2019;32(2):134–7.
75. Bagnall NM, Malietzis G, Kennedy RH, Athanasiou T, Faiz O, Darzi A. A systematic review of enhanced recovery care after colorectal surgery in elderly patients. Color Dis. 2014;16(12):947–56.
76. Rumstadt B, Guenther N, Wendling P, et al. Multimodal perioperative rehabilitation for colonic surgery in the elderly. World J Surg. 2009;33(8):1757–63.
77. Feroci F, Lenzi E, Baraghini M, et al. Fast-track surgery in real life: how patient factors influence outcomes and compliance with an enhanced recovery clinical pathway after colorectal surgery. Surg Laparosc Endosc Percutan Tech. 2013;23(3):259–65.
78. Forsmo HM, Erichsen C, Rasdal A, Korner H, Pfeffer F. Enhanced Recovery After Colorectal Surgery (ERAS) in elderly patients is feasible and achieves similar results as in younger patients. Gerontol Geriatr Med. 2017;3:2333721417706299.
79. Slieker J, Frauche P, Jurt J, et al. Enhanced recovery ERAS for elderly: a safe and beneficial pathway in colorectal surgery. Int J Color Dis. 2017;32(2):215–21.
80. Baek SJ, Kim SH, Kim SY, Shin JW, Kwak JM, Kim J. The safety of a "fast-track" program after laparoscopic colorectal surgery is comparable in older patients as in younger patients. Surg Endosc. 2013;27(4):1225–32.
81. Owodunni OP, Hampton J, Bettick D, et al. High compliance to an enhanced recovery pathway for patients >/=65 years undergoing major small and large intestinal surgery is associated with improved postoperative outcomes. Ann Surg. 2019;270(6):1117–23.
82. Depalma N, Cassini D, Grieco M, et al. Feasibility of a tailored ERAS programme in octogenarian patients undergoing minimally invasive surgery for colorectal cancer. Aging Clin Exp Res. 2020;32(2):265–73.
83. Ban KA, Berian JR, Ko CY. Does implementation of enhanced recovery after surgery (ERAS) protocols in colorectal surgery improve patient outcomes? Clin Colon Rectal Surg. 2019;32(2):109–13.
84. Dai X, Ge X, Yang J, et al. Increased incidence of prolonged ileus after colectomy for inflammatory bowel diseases under ERAS protocol: a cohort analysis. J Surg Res. 2017;212:86–93.
85. D'Andrea AP, Khetan P, Miller R, Sylla P, Divino CM. Outcomes after bowel resection for inflammatory bowel disease in the era of surgical care bundles and enhanced recovery. J Gastrointest Surg. 2020;24(1):123–31.
86. Joliat GR, Hubner M, Roulin D, Demartines N. Cost analysis of enhanced recovery programs in colorectal, pancreatic, and hepatic surgery: a systematic review. World J Surg. 2019;
87. Lee L, Li C, Landry T, et al. A systematic review of economic evaluations of enhanced recovery pathways for colorectal surgery. Ann Surg. 2014;259(4):670–6.
88. Lemanu DP, Singh PP, Stowers MD, Hill AG. A systematic review to assess cost effectiveness of enhanced recovery after surgery programmes in colorectal surgery. Color Dis. 2014;16(5):338–46.
89. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M. Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials. World J Surg. 2014;38(6):1531–41.
90. Roulin D, Donadini A, Gander S, et al. Cost-effectiveness of the implementation of an enhanced recovery protocol for colorectal surgery. Br J Surg. 2013;100(8):1108–14.
91. Lee L, Feldman LS. Enhanced recovery after surgery: economic impact and value. Surg Clin North Am. 2018;98(6):1137–48.
92. Stone AB, Grant MC, Wu CL, Wick EC. Enhanced recovery after surgery for colorectal surgery: a review of the economic implications. Clin Colon Rectal Surg. 2019;32(2):129–33.
93. Joliat GR, Ljungqvist O, Wasylak T, Peters O, Demartines N. Beyond surgery: clinical and economic impact of Enhanced Recovery After Surgery programs. BMC Health Serv Res. 2018;18(1):1008.
94. Sikka R, Morath JM, Leape L. The Quadruple Aim: care, health, cost and meaning in work. BMJ Qual Saf. 2015;24(10):608–10.
95. Khan S, Wilson T, Ahmed J, Owais A, MacFie J. Quality of life and patient satisfaction with enhanced recovery protocols. Color Dis. 2010;12(12):1175–82.
96. Hughes M, Coolsen MM, Aahlin EK, et al. Attitudes of patients and care providers to enhanced recovery after surgery programs after major abdominal surgery. J Surg Res. 2015;193(1):102–10.
97. Li D, Jensen CC. Patient satisfaction and quality of life with enhanced recovery protocols. Clin Colon Rectal Surg. 2019;32(2):138–44.
98. Thacker J. Overview of enhanced recovery after surgery: the evolution and adoption of enhanced recovery after surgery in North America. Surg Clin North Am. 2018;98(6):1109–17.

99. Pearsall EA, Meghji Z, Pitzul KB, et al. A qualitative study to understand the barriers and enablers in implementing an enhanced recovery after surgery program. Ann Surg. 2015;261(1):92–6.
100. Abeles A, Kwasnicki RM, Darzi A. Enhanced recovery after surgery: current research insights and future direction. World J Gastrointest Surg. 2017;9(2):37–45.
101. Tanious MK, Ljungqvist O, Urman RD. Enhanced recovery after surgery: history, evolution, guidelines, and future directions. Int Anesthesiol Clin. 2017;55(4):1–11.
102. Joshi GP, Kehlet H. Enhanced recovery pathways: looking into the future. Anesth Analg. 2019;128(1):5–7.
103. Currie A, Soop M, Demartines N, Fearon K, Kennedy R, Ljungqvist O. Enhanced recovery after surgery interactive audit system: 10 years' experience with an international web-based clinical and research perioperative care database. Clin Colon Rectal Surg. 2019;32(1):75–81.
104. Aziz O, Atallah L, Lo B, et al. Ear-worn body sensor network device: an objective tool for functional postoperative home recovery monitoring. J Am Med Inform Assoc. 2011;18(2):156–9.
105. Dobkin BH, Dorsch A. The promise of mHealth: daily activity monitoring and outcome assessments by wearable sensors. Neurorehabil Neural Repair. 2011;25(9):788–98.
106. Appelboom G, Camacho E, Abraham ME, et al. Smart wearable body sensors for patient self-assessment and monitoring. Arch Public Health. 2014;72(1):28.
107. Alam R, Figueiredo SM, Balvardi S, et al. Development of a patient-reported outcome measure of recovery after abdominal surgery: a hypothesized conceptual framework. Surg Endosc. 2018;32(12):4874–85.
108. Fiore JF Jr, Feldman LS. Tracking postoperative recovery-making a case for smartphone technology. JAMA Surg. 2019;28:28.
109. Williams AM, Bhatti UF, Alam HB, Nikolian VC. The role of telemedicine in postoperative care. mHealth. 2018;4:11.
110. Asiri A, AlBishi S, AlMadani W, ElMetwally A, Househ M. The use of telemedicine in surgical care: a systematic review. Acta Inform Med. 2018;26(3):201–6.
111. Borsuk DJ, AL-Khamis A, Geiser AJ, et al. S128: active post discharge surveillance program as a part of Enhanced Recovery After Surgery protocol decreases emergency department visits and readmissions in colorectal patients. Surg Endosc. 2019;33(11):3816–27.
112. Mandel JC, Kreda DA, Mandl KD, Kohane IS, Ramoni RB. SMART on FHIR: a standards-based, interoperable apps platform for electronic health records. J Am Med Inform Assoc. 2016;23(5):899–908.

General Postoperative Complications

8

Daniel I. Chu and David J. Maron

Key Concepts

- Complications following colorectal surgery are not infrequent, making recognition and treatment an important component of the care of postoperative patients.
- Assessment of risk factors (particularly modifiable factors) can help to estimate and reduce the risk of postoperative complications.
- Gastrointestinal complications are the most frequent complications after major abdominal operations and range from minor nausea/vomiting to ileus and bowel obstruction.
- Postoperative bleeding and transfusions are the second most common complication following colorectal surgery, and additional complications such as venous thromboembolism can have major impacts on patients and healthcare systems.
- Infectious complications following colorectal surgery include surgical site infections (SSIs) – which include both incisional and organ space infections, as well as postoperative urinary tract infections and pseudomembranous colitis.
- Pulmonary complications in colorectal surgical patients include pneumonia, aspiration, and postoperative respiratory failure requiring prolonged ventilation.

Introduction

Every operation carries inherent risks for postoperative complications, and the field of colorectal surgery is certainly no different. Colorectal operations account for nearly 25% of all complications in general surgery [1] and have reported complication rates exceeding 35% [2, 3]. A query of data from the 2012 to 2017 American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) Procedure Targeted Colectomy database shows that the most frequent postoperative complication is ileus followed by bleeding and surgical site infections (Table 8.1). Less common complications include myocardial infarctions, pulmonary embolisms, and strokes (Table 8.1). While agencies such as the Centers for Medicare and Medicaid Services (CMS) view complications such as venous thromboembolism as key performance measures, it is increasingly clear that colorectal-specific complications such as ileus and anastomotic leaks have significant impacts on patients, providers, and healthcare systems [4]. It is therefore critical for colorectal surgeons to be able to recognize, understand, and manage a diverse set of complications as they will happen.

Several classification schemes exist to grade complications. One of the most commonly used is the Clavien-Dindo Classification [5, 6]. This classification scheme, refined since 1992, stratifies complications into seven grades (I, II, IIIa, IIIb, IVa, IVb, and V) with increasing severity from grade I (which represents any deviation from the normal postoperative course without a need for major intervention) to grade V (which represents death of a patient). Other classification schemes also exist including a more recently proposed Comprehensive Complication Index [7] by Clavien and Dindo, the Accordion scale [8], and the ACS-NSQIP classification of complications [9]. Despite the heterogeneity in these classification schemes, it is clear that complications matter, as they are associated with increased risks of patient mortality [4, 10], longer lengths of stay [1], more readmissions [4, 11], higher costs [12], and worse long-term oncologic outcomes [13]. Significant responsibility therefore lies with the colorectal surgeon to be experienced not only with performing the index operation(s) but also with managing postoperative complications.

The aims of this chapter will be to provide an overview of common risk factors for postoperative complications and to

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Table 8.1 Common postoperative complications after colorectal surgery using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) Procedure Targeted for Colectomy (2012–2017)

Complication	Overall frequency (%)	2012	2013	2014	2015	2016	2017
Prolonged postoperative ileus	17.1	15.99	17.07	17.36	17.54	17.28	16.91
Bleeding/transfusion	10.3	12.29	11.67	10.84	10.01	9.13	9.11
Sepsis	5.42	4.77	4.96	5.73	5.51	5.58	5.67
Organ/space SSI	5.07	4.29	4.57	4.99	5.09	5.38	5.63
Superficial incisional SSI	4.96	6.38	5.74	5.4	4.69	4.37	3.99
Septic shock	4.05	3.01	3.98	4.52	4.2	4.16	4.13
On ventilator greater than 48 hours	3.76	4.31	4.15	3.82	3.67	3.6	3.35
Leak	3.38	3.6	3.8	3.41	3.44	3.09	3.23
Pneumonia	3.38	3.15	3.4	3.59	3.46	3.5	3.16
Urinary tract infection	2.53	3.32	2.79	2.71	2.43	2.22	2.12
Unplanned intubation	2.25	2.48	2.45	2.4	2.17	2.11	2.04
DVT requiring therapy	1.47	1.5	1.52	1.44	1.46	1.46	1.45
Wound disruption	1.32	1.51	1.51	1.37	1.32	1.22	1.13
Deep incisional SSI	1.3	1.69	1.76	1.66	1.42	0.86	0.77
C. diff	1.28	–	–	–	0.89	1.55	1.38
Progressive renal insufficiency	0.81	0.78	0.81	0.79	0.8	0.85	0.81
Acute renal failure	0.81	0.86	0.8	0.83	0.81	0.81	0.76
Cardiac arrest requiring CPR	0.79	0.72	0.73	0.82	0.81	0.82	0.79
Myocardial infarction	0.76	0.73	0.64	0.72	0.8	0.81	0.79
Pulmonary embolism	0.67	0.68	0.65	0.71	0.7	0.63	0.68
Stroke/CVA	0.3	0.28	0.32	0.32	0.31	0.27	0.29

Complications listed in order of overall frequency. All numbers expressed as % (frequency)

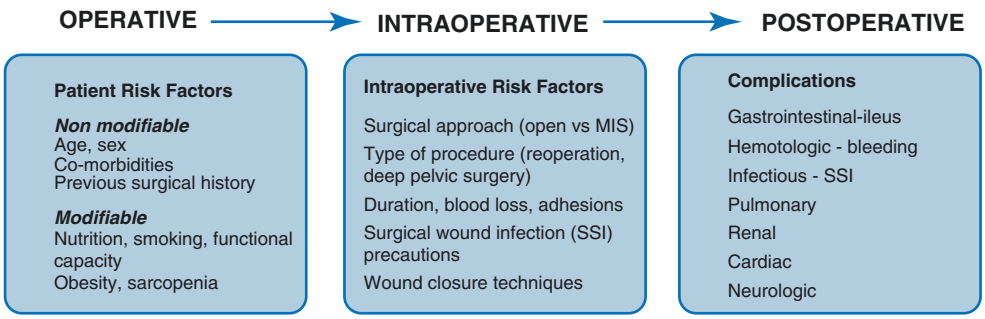

Fig. 8.1 Risk factors for postoperative complications in colorectal surgery

review the management of general complications in colorectal surgery. The discussion will be framed pragmatically in order of frequency of complications using the ACS-NSQIP. Successful acquisition and application of this knowledge will build a foundation for excellence in the care of colorectal surgery patients.

Risk Factors

Successful management of postoperative complications begins with a thorough understanding of the risk factors leading to those complications (Fig. 8.1). Some of these risk factors are non-modifiable (i.e., age and sex/gender), but others are potentially modifiable (i.e., nutrition and smoking). The latter risk factors are prime targets for single-level interventions (i.e., smoking cessation-only) versus more comprehensive interventions (i.e., prehabilitation and enhanced recovery pathways).

Non-modifiable Risk Factors

Age

Older age is a significant risk factor for postoperative complications. The reasons are multifactorial and due to decreased physiologic reserve, worse organ system function(s), cognitive impairment, and increased frailty [14]. Studies have shown that even within the geriatric population, increasing age is a strong independent predictor of mortality and postoperative complications [15, 16]. Among octogenarians [17] and nonagenarians [18], studies have suggested that common operations can be performed safely, but complication rates often exceed 25%. While age is non-modifiable, interventions can target age-associated risk factors such as poor nutrition, sarcopenia, and decreased physiologic reserve. Comprehensive recovery pathways such as Enhanced Recovery Programs (ERPs), for instance, have shown promising early results in improving surgical outcomes and reducing complications for the elderly [19].

Sex

Sex has been shown to be associated with risks of postoperative complications. Recent single-institution studies have associated the male sex with higher risks of complications for laparoscopic and open colorectal operations [15]. Within the ACS-NSQIP database, overall complications were higher for males across many major surgical procedures [20]. Similarly, males have been observed to be at higher risk for anastomotic leaks after colorectal operations [21]. While the underlying mechanism(s) are not clear, complication rates may be higher in males due to sex-based variations in risk prevalence at the patient level (i.e., smoking rates, cardiac disease, etc.) and procedure level (i.e., obesity, narrow pelvis, etc.).

Morbidities

Many patients undergoing colorectal surgery have preexisting comorbidities, and data has consistently shown that comorbidities are linked to the risk of developing a postoperative complication. Patients with American Society of Anesthesiology (ASA) scores of 3–5, for instance, are at significant risk of postoperative complications such as anastomotic leaks [22]. Similarly, patients with a high Charlson Comorbidity Index (CCI) are at increased risk for mortality and morbidities after colorectal operations [23–25]. Additional comorbidities have also been associated with postoperative complications including need for emergency surgery, body weight loss of >10%, use of steroids, congestive heart failure, renal insufficiency, and neurologic deficits [26]. More recent studies have suggested that comorbidities and comorbidity indices should not be considered in isolation. Patients often have "clusters" of comorbidities that in combination drive the risks for complications [27]. While some comorbidities may not be modifiable, a priori knowledge of them can at least provide some knowledge to better educate patients on risks and expected outcomes.

Prior Surgeries and Adhesion Formation

Prior abdominal surgical history is increasingly common, and colorectal surgeons often face reoperative scenarios. For laparoscopic operations, a history of prior abdominal surgery has been shown to be predictive of the need for open conversion, unintentional enterotomies, postoperative ileus, reoperations, and longer operative times [28]. Similarly, the presence of adhesions from prior operations appears to most influence colorectal resections with respect to adhesions-related complications [29]. While past surgical history is considered non-modifiable, experience of the colorectal surgeon is important to help mitigate complications in this circumstance.

Modifiable Risk Factors

Nutrition

Malnutrition is common and may occur in upward of 50% of surgical patients [30]. Several scoring systems such as the Nutrition Risk Screening (NRS) tool [31] and Malnutrition Universal Screening Tool (MUST) have been used effectively to screen patients for malnutrition and help predict outcomes [32]. Early studies since 2002 have demonstrated that preoperative optimization of nutrition benefits malnourished surgical patients [33]. While the optimal content of supplements are still debatable, studies suggests that oral immunonutrition, which often contains arginine and fatty acids, may be one of the key elements [34]. In a large population-based study of 3375 patients in Washington state, significant improvements in length of stay for surgical patients were observed for those on oral immunonutrition with reductions in postoperative complications [35]. Additional evidence suggests that oral supplementation at least 7–10 days prior to an elective operation (and parenteral nutrition only as needed) may improve nutritional status in a malnourished patient to ensure a better surgical outcome [36].

Smoking

Smoking is one of the most significant risk factors for postoperative complications. Multiple studies have associated smoking with complications such as surgical site infections [37], anastomotic leaks [38], and even disease recurrence in inflammatory bowel disease [39]. Smoking risk is modifiable. Randomized trials have shown that smoking abstinence/interventions at 4 weeks before surgery reduces postoperative complications such as wound infections to levels of nonsmokers [40, 41]. In another trial, initiating a preoperative smoking-cessation program 6–8 weeks before the surgical date significantly reduced postoperative complications from 31% to 5% [42]. A recent meta-analysis of 11 randomized controlled trials demonstrated a 44% pooled risk reduction of 30-day postoperative complications with smoking cessation [43]. While the most effective type of smoking-cessation intervention remains unclear, the evidence thus far indicates that preoperative smoking cessation should be a fundamental part of any complication risk-reduction strategy, especially for high-risk specialties such as colorectal surgery [44].

Preoperative Anemia

Anemia is a modifiable risk factor for postoperative complications. In a large ACS-NSQIP study of 23,348 elective open and laparoscopic colorectal operations, preoperative anemia was an independent risk factor for postoperative complica-

tions and longer length of stays [45]. More recent studies have also associated anemia with higher risk of postoperative complications [46]. Building evidence suggest that interventions with iron infusions and oral supplementation are effective and mitigate the risks of postoperative complications [47]. In a study on 95 colorectal cancer patients, correction of preoperative anemia with intravenous/oral iron restored hemoglobin levels to normal and corrected anemia patients required no postoperative transfusions (0% compared to 38% transfusion rates for uncorrected, anemic patients) [47]. Societies such as the American Society of Anesthesiologists have established guidelines on the perioperative management of anemia with interventions recommended if time permits [48]. More recently, the Enhanced Recovery After Surgery (ERAS) Society also incorporated anemia management into the most recent 2018 colorectal guidelines [36].

Sarcopenia

Sarcopenia describes the loss of muscle mass and strength that occurs with aging. It may be further accelerated with the presence of chronic diseases and is a result of multiple physiologic mechanisms including declines in growth hormones, nutritional insufficiency, decreased physical activity, and loss of alpha-motor neurons [49]. Retrospective studies in colorectal cancer have associated sarcopenia with an over 82% increased odds of postoperative complications after colorectal surgery [50, 51]. A recent meta-analysis of 29 studies in gastrointestinal cancers showed that sarcopenia was a consistent risk factor for major complications (risk ratio, 1.40) and overall complications (risk ratio, 1.35). Effective interventions to address sarcopenia have yet to be formalized but will undoubtedly work at multiple levels including improving functional capacity and nutritional status.

Obesity

Over a third of adults in the United States are currently obese, with predictions that over half of the US population will be obese by 2030 [52]. Obesity, defined as a body mass index (BMI) of greater than 30 kg/m^2, is increasingly common in the surgical population, and colorectal surgeons often manage these challenging patients. Studies have shown that obesity increases the risk of surgical complications after colorectal surgery [53, 54]. Data using the ACS-NSQIP has suggested that a dose-dependent relationship exists between BMI and complications with increasing obesity classes leading to increasing risks of complications such as surgical site infections [55]. Taken together, these data suggest that obesity is a modifiable risk factor that may be addressable using weight-loss interventions in the preoperative and elective setting [15].

Functional Exercise Capacity

The functional capacity of a patient is measurable and has been linked to surgical outcomes. Similar to athletic training, improving functional exercise capacity is possible. In one of the first studies on prehabilitation, Carli et al. demonstrated that moderate aerobic and resistance exercise significantly improved scores on walking tests [56]. While these improvements were not yet linkable to measurable reductions in postoperative complications, this study formed the basis for further studies that have suggested benefits of prehabilitation programs [44]. A large international, randomized controlled trial by van Rooijen et al. is currently underway to test the effects of a multimodal rehabilitation program on functional capacity (6-minute walk test) in surgical patients [57].

Open Surgical Approach

Open approaches in colorectal surgery have been associated with higher rates of postoperative complications [58]. In contrast, minimally invasive techniques are significantly associated with improved short-term outcomes including decreased surgical site infections, venous thromboembolism events, and pneumonias [58–60]. These associations are complex as hospital/surgical volume and clinical culture also play important roles in determining surgical outcomes [61]. Doing the best operation in the operating room, however, ensures the best start to surgical recovery, and the benefits of minimally invasive techniques are clear – this technique should therefore be utilized whenever possible and currently remains a central tenant of colorectal ERP pathways [36].

Assessing Risk Factors

Risk calculators use population-level data to quantify the risk of complications for individual patients. The POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) [62] and APACHE (Acute Physiology and Chronic Health Evaluation) [63] scoring systems are two original examples of validated scoring systems that use clinical information to risk stratify. A relatively newer system is the ACS-NSQIP Risk Calculator [64] which was developed to predict risk of postoperative complications, length of stay, mortality, and readmission based on patient- and procedure-level factors (Fig. 8.2). This powerful calculator continues to evolve with the steady accumulation of robust national data annually and identification of new risk factors. In fact, the ACS-NSQIP Risk Calculator was recently updated to include geriatric-specific risk factors to better predict outcomes for the growing geriatric population [65].

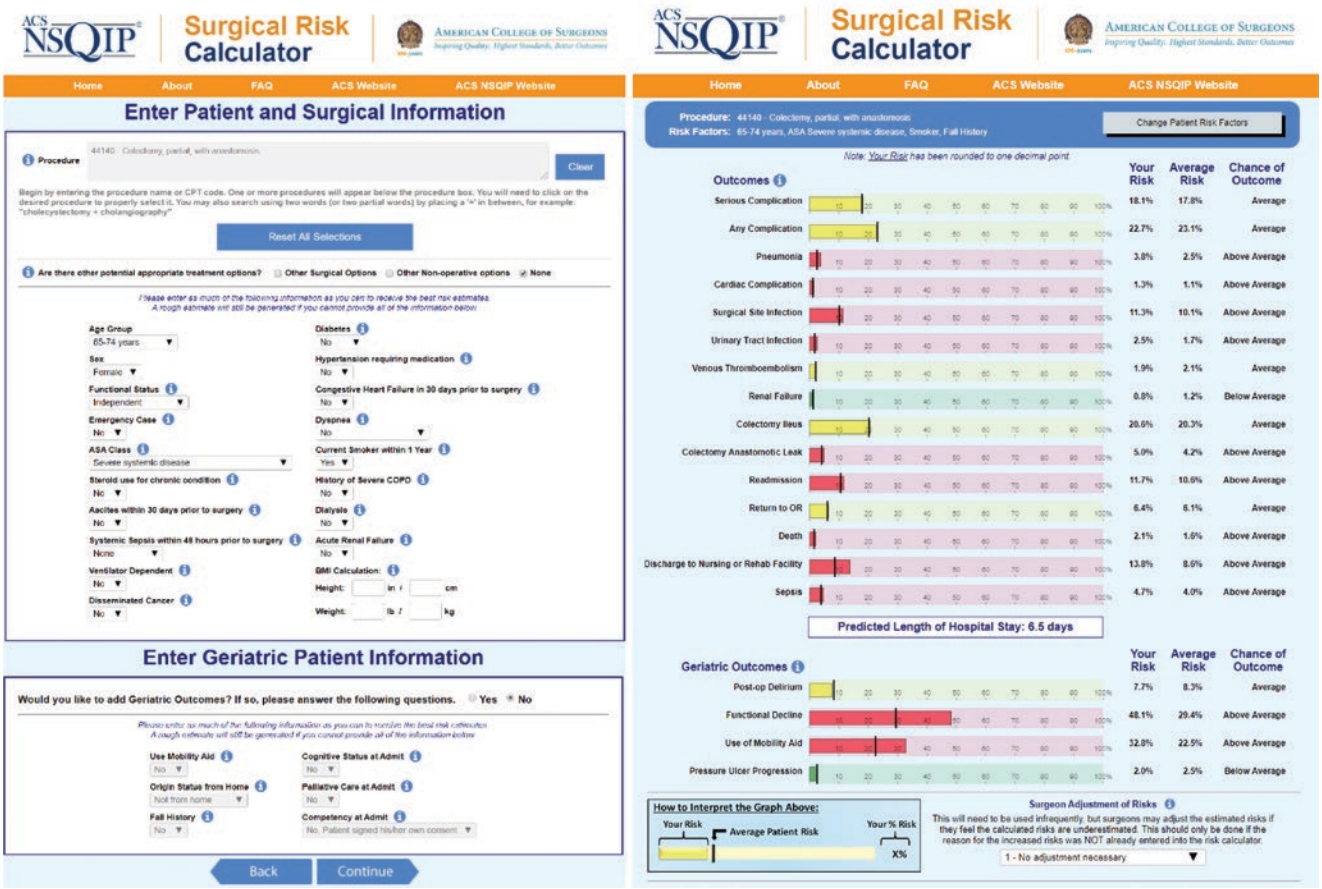

Fig. 8.2 The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) Risk Calculator including new geriatric risk factors

Addressing Risk Factors

Once risk is identified, however, the question remains: What can be done? Single-item interventions to address individual risk factors such as malnutrition and smoking have previously been highlighted, but larger gains may be seen with more comprehensive and multilevel interventions. These include programs that are meant to optimize patients before major surgery such as the STRONG program [66] and comprehensive recovery programs such as Enhanced Recovery Programs which aim to mitigate the surgical stress and organ dysfunction associated with major surgery [36]. Prehabilitation is a relatively newer but synergistic program that has gained attention in addressing the risks of complications by specifically targeting risk factor categories (nutrition, smoking, obesity, and physical activity) before surgery [67]. Data is still limited, however, with the most recent study from Carli et al. (2020) showing no demonstrable improvement in reduction of complications as measured by the CCI [68]. Larger multi-institutional trials will aim to establish the effectiveness of such interventions [57].

Postoperative Complications

According to the 2012–2017 ACS-NSQIP database, the most common postoperative complications in colorectal surgery are (1) gastrointestinal complications (ileus), (2) hematologic complications (bleeding), and (3) infectious complications (surgical site infections [SSIs]) (Table 8.1). Other postoperative complications such as cardiac, renal, and pulmonary complications also occur in colorectal surgery but less frequently. This section will review the most common postoperative complications as guided by the ACS-NSQIP database. In addition, a review of other associated but important complications will be presented in an organ system approach.

Gastrointestinal Complications (#1)

Gastrointestinal complications are the most frequent complications after major abdominal operations and range from minor nausea/vomiting to ileus and obstructions. The sever-

ity of complications is determined by several risk factors including the type of operation performed, the approach (minimally invasive vs. open), and even blood loss during the case (Fig. 8.1) [69].

Ileus (Functional Bowel Obstruction)

Ileus, which is a functional obstruction of the small bowel, is the single most common complication after colorectal surgery. In the ACS-NSQIP, postoperative ileus rates occur in 12–17% of patients after colorectal surgery (Table 8.1) [4]. This complication drives significant lengths of stay and costs for healthcare systems [4]. The pathophysiology of ileus is unclear but is likely a consequence of disturbances to normal peristalsis governed by the enteric nervous system as a result of anesthetic and surgical manipulation [69]. Disturbances in the large bowel are called pseudo-obstruction or Ogilvie's syndrome [70]. Several factors are known to slow return of bowel function including medications (i.e., opioids), electrolyte abnormalities, inflammatory conditions, pain, and degree of operative manipulation. Patients present with symptoms of nausea, vomiting, bloating, burping, and hiccups in the absence of flatus or bowel movements. Abdominal distension and accompanied tympani are usually observed on physical exam. Abdominal radiographs and computed tomography (CT) scans show dilated loops of bowel but with no transition points or concerns for mechanical obstruction.

Studies have suggested that postoperative ileus can be subdivided into severe ileus and non-severe ileus [71]. In a prospective database from 40 international centers in 5 countries, the rates of severe and non-severe ileus were 9.3% and 6.1%, respectively, even under an Enhanced Recovery Program. Non-severe ileus, or a "primary" ileus, was best treated with nonoperative management including nasogastric tube decompression, bowel rest, intravenous fluids, mobilization, and avoidance of opioids. Severe ileus was very different and driven by intraabdominal complications such as abscesses. As a result, management for severe ileus centers on addressing the underlying insult.

Recommendations for treating functional obstruction such as ileus are to (i) ensure there is no mechanical component to the obstruction, (ii) start with nonoperative management with bowel rest and decompression, and (iii) address underlying causes (electrolyte abnormalities for non-severe ileus and intraabdominal pathology for severe ileus).

Postoperative Small Bowel Obstruction (Mechanical Bowel Obstruction)

Mechanical bowel obstructions in the postoperative setting for the small bowel and colon are most often caused by adhesions. For the small bowel, these obstructions are termed early postoperative small bowel obstructions (ESBO) and occur in upward of 9.5% of abdominal operations [72, 73]. ESBO clinically mimics postoperative ileus, and the differentiating the two can be difficult. Making the correct diagnosis is critical as there is an 8–9% strangulation risk with ESBO [72]. Compared to laparoscopic approaches, open cases are at increased risk for developing this complication. Diagnosis can be made through abdominal radiographs, which may show air-fluid levels in loops of small bowel, and CT scans, which may show a transition point. Strangulation is uncommon from the adhesions themselves, but increasing distension leads to bowel necrosis as mural tension leads to decreased mucosal perfusion. Treatment is usually initially nonoperative with nasogastric decompression, and success rates have been reported as high as 87% [73]. However, if the obstruction does not resolve, then the patient may require operative intervention. The time to wait remains controversial with reports showing safe waiting times from 24 hours to 7 days [74–76], but these decisions are complex and individualized. Reoperations are not without risk as there are increased risks for complications especially for those patients who had an index open operation [72].

Hematologic Complications (#2)

Colorectal operations affect the hematologic system directly and through the coagulation pathway. The 2012–2017 ACS-NSQIP data show that postoperative bleeding and transfusions are the second most common complication following colorectal surgery (Table 8.1). Additional complications such as venous thromboembolism occur less frequently but have major impacts on patients and healthcare systems.

Postoperative Bleeding and Transfusions

Bleeding requiring reoperation is rare after colorectal surgery, but bleeding requiring transfusions may occur in up to 10% of colorectal operations [77]. Risk factors for bleeding include intraoperative factors and medical coagulopathies such as hemophilia A (factor VIII deficiency), hemophilia B (factor IX deficiency), von Willebrand's disease, warfarin therapy, and platelet disorders [78]. One unique intraoperative factor that may lead to significant bleeding in colorectal surgery includes operations in the pelvis. The presacral space is lined by a presacral venous plexus that can be easily disrupted during proctectomy. Trauma to these veins may lead to massive hemorrhage [78].

All postoperative bleeding requires an assessment, resuscitation, and ultimately control. Mild bleeding with no systemic symptoms is often self-limited. Withholding anticoagulants and antiplatelet agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) is first-line and effective step. Severe bleeding with systemic changes such as tachycardia and hypotension requires more aggressive interventions. While radiographic techniques such as CT angiography may be used to identify bleeding sources, delay may be fatal.

In a study of 196 reoperations for bleeding, 77% of takebacks occurred within 24 hours of the index operation with a 28% mortality rate [79]. An expeditious return to the operating room must always be considered if the patient demonstrates signs of exsanguination. Intraoperatively, the source needs to be localized and controlled, clots evacuated, and the peritoneal cavity carefully examined. It is not uncommon to find no active source of bleeding, especially after operations that require significant adhesiolysis and mobilization of retroperitoneal structures. In these situations, a reoperation is still useful as evacuation of the clot may help with achieving final hemostasis.

Presacral bleeding is a challenging situation that all colorectal surgeons must be able to manage. The algorithms are well-established and focus on initial control with packing, resuscitation, and then further action if bleeding persists. These additional actions include suture ligation, sterile thumbtacks, rectus muscle welding, and hemostatic agents [78]. The principles of damage control surgery are also relevant to massive presacral bleeding. In the situation where bleeding control cannot be established, patients should be temporized, packed, and taken back to the ICU to correct acidosis, coagulopathies, and hypothermia. A second operation is usually performed in 24–48 hours with the goal of restoring intestinal continuity, removing packing, and achieving final closure [78]. A related complication is abdominal compartment syndrome, a life-threatening condition that results from massive uncontrolled hemorrhage and/or aggressive resuscitation leading to increased abdominal pressure [80]. When pressures exceed 20 mmHg [78], the compartment must be rapidly decompressed to reestablish flow to the viscera, usually via an abdominal laparotomy. With decompression, symptoms tend to resolve. Complications are high, however, with multi-organ dysfunction and mortality rates approaching 50% [81].

Venous Thromboembolism

Venous thromboembolisms (VTEs) include deep vein thrombosis (DVT) and pulmonary embolism (PE). Colorectal surgery patients are at high risk for developing VTEs because many colorectal diseases such as cancer and inflammatory bowel disease create hypercoagulable states. Among colorectal surgical patients, VTE rates are reported from 1.1% to 2.5% [82]. While not as prevalent as complications such as ileus, VTEs are a common cause of preventable deaths. Many risk factors have been identified including obesity, steroid use, sepsis, reoperations, ASA class 3, and having another postoperative complication [82]. Based on these factors, the American College of Chest Physicians (ACCP) has published important guidelines on risk stratification to guide VTE prophylaxis [83]. These stratifications use validated scoring systems (Caprini Score and the Roger Score) to stratify patients to early ambulation, mechanical prophylaxis, or chemical prophylaxis with low-molecular-weight heparin (LMWH) or low-dose unfractionated heparin (LDUH). Diagnosis for VTEs can be made by (i) ultrasound scanning and D-dimer testing for DVTs and (ii) CT pulmonary angiography and/or D-dimer testing for PEs [84]. Ventilation perfusion scanning (V/Q scan) and V/Q SPECT are reserved for patients with contrast allergies or renal impairment. Prevention of VTEs is more effective than treatment of this complication. Once a VTE is diagnosed, treatment relies upon systemic anticoagulation with chemical agents such as LMWH, coumadin, or newer oral anticoagulants such as dabigatran, apixaban, or edoxaban. In cases where anticoagulation is contraindicated, inferior vena cava (IVC) filters need to be considered to prevent development of a fatal PE.

Infectious Complications (#3)

Infectious-related complications occur frequently after colorectal operations. These complications are usually related to the surgical site. However, infectious complications can occur well away from the surgical bed including urinary tract infections and *Clostridium difficile* infections.

Surgical Site Infection (SSI)

In the United States, an estimated 500,000 cases of surgical site infections (SSIs) are reported each year [85]. As the leading cause of nosocomial infections after surgery, SSIs add over 3.7 million excess hospital days and $10 billion in excess costs per year to the healthcare system [86]. SSIs also add significant morbidity with a 2–11 times higher risk of death for patients who experience an SSI [87]. Importantly, most SSIs are thought to be preventable [88]. Colorectal operations have one of the highest rates of SSIs with reported rates from 15% to over 30% [89].

SSIs are infections in areas where surgery was performed. Classically, SSIs are categorized to (1) superficial incisional (limited to skin/subcutaneous tissues), (2) deep incisional (involves muscle/fascia), and (3) organ space. Risk factors for SSIs include patient factors (i.e., age, nutritional status, diabetes, smoking, obesity, coexistent infection at another site, microorganism colonization, altered immune response, and duration of postoperative stay) and operative factors (i.e., preoperative antiseptic preparation, antimicrobial prophylaxis, duration of operation, operation room venting, use of foreign materials, surgical site, and surgical technique) (Fig. 8.1).

The WHO [90, 91], ACS/SIS [92], and CDC [93] guidelines are major publications that represent the consensus of multidisciplinary experts on SSI prevention strategies. The ACS/SIS, WHO, and CDC reviewed 17, 29, and 42 individual SSI reduction processes, respectively. Interestingly, only a minority of reviewed processes were recommended at the

Table 8.2 Centers for Disease Control and Prevention (CDC) recommendations on prevention of postoperative surgical site infections [93]

Evidence level	#	Specific recommendations	Level of recommendation
Category IA	8	1. Administer IV ABX before skin incision in all C-section procedures 2. In clean and clean-contaminated, do not administer additional IV ABX after incision closed, even in presence of a drain 3. Perioperative glycemic control and target <200 mg/d 4. Maintain perioperative normothermia 5. For patients with normal pulm function under GETA, administer increased FiO2 during surgery and after extubation in immediate postop period 6. Perform intraoperative skin prep with alcohol-based antiseptic agent 7. For prosthetic joint arthroplasty on immunosuppressive therapy, follow #2 8. For prosthetic joint arthroplasty, follow #2	Strong recommendation/ high-quality evidence
Category 1B	4	1. Administer ABX when indicated based on guidelines and time to incision 2. Do not apply antimicrobial agents to incision (topicals) for SSI prevention 3. Advise patients to shower or bathe (full body) with soap (antimicrobial or nonantimicrobial) or an antiseptic agent on at least the night before OR day 4. Do not withhold transfusion of necessary blood products to prevent SSI	Strong recommendation/ accepted practice
Category 2	5	1. Application of autologous platelet-rich plasma is not necessary 2. Consider use of triclosan-coated sutures for SSI prevention 3. Application of a microbial sealant after intraop skin prep is not necessary 4. Use of plastic adhesive drapes with or without antimicrobial properties is not necessary 5. Consider intraop irrigation of deep/subcut tissues with iodophor solution	Weak recommendation
No recommendation	25	1. No RCTs evaluating benefit/harms of weight-adjusted IV ABX dosing and effect 2. … [continues for 24 other parameters]	No recommendations

highest level of evidence. The CDC, for example, noted that only 12 processes had high-quality evidence to support their implementation and 25 processes had no recommendations whatsoever due to the lack of evidence (Table 8.2) [93]. The framework to approaching these guidelines, however, is to consider that there are "core" measures and "supplementary" measures. The former has the most evidence to back their use. The supplementary measures have limited evidence but are in-practice at many institutions.

When comparing the three guidelines, five core themes emerge. These include effective antibiotic prophylaxis, proper preparation of patients and surgeon skin, maintenance of normothermia, glycemic control, and FiO2 of >80% intraoperatively and postoperatively. Antibiotic prophylaxis remains the core of any SSI reduction bundle, as originally championed by SIP/SCIP, and focuses on administering the proper antibiotic within 1–2 hours before incision. Skin preparation focuses on alcohol-based antiseptics combined with agents such as chlorhexidine. Normothermia (≥36 °C) is recommended throughout the operation in addition to perioperative glycemic control, although specific glucose ranges vary across guidelines. Finally, maintaining high FiO2 (>80%) is the most consistent recommendation across all three guidelines. These five elements represent the core components of any effective SSI reduction bundle. Additional elements should be considered supplementary but left to the discretion of the institution to include with consideration of cost-effectiveness. Bowel preparation with a combination of mechanical and oral antibiotics, for example, is recommended by the American Society for Enhanced Recovery (ASER) to reduce the risk of SSIs after colorectal operations [94].

Treatments of SSIs are based on source control. For superficial infections, the treatment typically involves opening the incision, exploring the space, irrigating, and debriding the wound with subsequent regular wound care. Deep incisional and organ space infections may be amenable to percutaneous drainage under image guidance. Those that cannot be adequately drained, in the manner, necessitate a return to the operation room for exploration, washout, drainage, and debridement. Should implanted material be involved (i.e., infected synthetic mesh after a parastomal hernia repair), then it must be removed. Antibiotics alone do not usually address the underlying nidus of infection for deep incisional and organ space infections.

Anastomotic Leaks

Anastomotic leaks are perhaps the most feared complication in colorectal surgery and can occur with any intestinal reconstruction. This complication will be discussed extensively in Chap. 10 and will not be further covered here.

Wound Dehiscence

Wound dehiscence is a partial or complete disruption of any or all layers of the operative wound. Disruption with extrusion of abdominal viscera is evisceration, which requires immediate operation. Long-term effect of wound disruptions manifest as incisional hernias. Wound dehiscence is rare and occurs in 1–3% of colorectal surgeries [95]. Systemic and local factors contribute to the development of this complica-

tion. Systemic factors include any comorbid conditions that lead to poor wound healing (i.e., diabetes mellitus, uremia, impaired immune function, steroid use, poor nutritional status, cancer, obesity, and smoking). Local factors include inadequate closure, increased intra-abdominal pressure, and poor wound healing. In a Swedish population-based study of 30,050 patients in 2007–2013, wound dehiscence requiring reoperation occurred in 2.9% of patients after colorectal cancer surgery. While these complications were rare, adjusted mortality risk was significantly increased by 26% [95].

Proper wound closure is one of the most important and modifiable factors to prevent wound dehiscence. Key principles include a clean initial incision, appropriate tissue handling/suture material, and adequate spacing of the sutures. The STITCH trial was a multicenter randomized controlled trial that compared small bites (5 mm of fascia every 5 mm of advancement) to large bites (1 cm of fascia every 1 cm of advancement) with respect to the development of incisional hernia [96]. The small bite technique was more effective than the large bite technique with lower rates of incisional hernia (13% vs. 21%). Placement of retention stitches should be considered in high-tension wounds or patients with increased risk factors. In a randomized controlled trial of 300 high-risk surgical patients randomized to closure with retention sutures versus standard continuous fascia closure-only, wound dehiscence and evisceration occurred significantly less in the retention group (4% vs. 13.3% and 0.7% vs. 2.7%, respectively) [97].

Other Infectious Complications

Urinary tract infections (UTIs) are the most frequently acquired nosocomial infection. The incidence of postoperative UTI after colorectal operations approaches 4% [98]. Risk factors include preexisting contamination of the urinary tract, urinary retention, and instrumentation such as indwelling urinary catheters. In a large retrospective study of the 2005–2012 ACS-NSQIP database, patients with postoperative UTIs had significantly longer length of stays (+5 days), higher reoperation rates (11.9% vs. 5.1%), higher 30-day mortality (3.3% vs. 1.7%), and more concurrent complications such as sepsis [98]. Diagnosis of UTI is made by examination of the urine with confirmation by cultures. Prevention involves treating urinary tract contamination before surgery, prevention or prompt treatment of urinary retention, and careful instrumentation when needed. Treatment includes adequate hydration, proper drainage of the bladder, and urine-specific antibiotics.

Clostridium difficile Colitis

Clostridium difficile (*C. diff*) is one of the most common nosocomial pathogens and the cause of 10–20% of antibiotic-associated colitis and diarrhea [99]. Postoperative *C. diff* infections occur at an incidence of 0.2–8.4% after major surgeries [99]. While infrequent, the overall incidence of *C. diff* infection is increasing in the United States [100] with significant morbidity for affected patients. Risk factors include antibiotic use, PPI use, low albumin, and prior hospitalization [99]. The history, physical exam, and laboratory testing should all be used to aid in the workup and diagnosis of *C. diff* colitis. Stool testing should follow protocols to ensure the highest specificity and sensitivity while remaining practical and time-sensitive. Depending on patient presentation, radiographic and endoscopic testing can complement the workup to determine the most appropriate and effective treatment plan. Treatment options range from oral antibiotic therapy (oral vancomycin) to consideration of fecal transplantation to urgent/emergent surgery.

Pulmonary Complications (#4)

Pulmonary complications may occur after any major surgery. In colorectal surgery, pulmonary complications include postoperative respiratory failure requiring prolonged ventilation, pneumonia, and aspiration. Each of these complications drives longer hospitalizations and often leads to further serious complications.

Postoperative Respiratory Failure

Postoperative respiratory failure is defined as postoperative ventilation for >48 hours or patient reintubation. In the 2012–2017 ACS-NSQIP database, prolonged ventilation occurred in 3.3–4.3% of colorectal patients with reintubation rates around 2.3% (Table 8.1). Risk factors include poor preoperative lung function, age, concomitant comorbidities (i.e., obstructive sleep apnea, pulmonary hypertension, and cardiovascular disease), smoking, and aspiration. Preventative measures include fast-track extubation, effective pain therapy, breathing training, physiotherapy, noninvasive ventilation, use of bronchodilators, and appropriate volume resuscitation. Studies using ERPs have demonstrated positive results in reducing the occurrence of these pulmonary complications by standardizing best practices for pulmonary function [101]. In a retrospective analysis of 1298 patients under an ERP, minimally invasive approaches and >70% compliance with ERP processes prevented pulmonary complications. Patients who did have pulmonary complications had a significantly longer hospital length of stay (+15 days) [101]. Treatment of respiratory failure is primarily supportive and includes early tracheostomy (to decrease dead space), protective ventilation, lowered peak pressures (<30 mmHg), increased positive end-expiratory pressure (PEEP 10–20 mmH_2O), early patient mobilization, and bronchoscopy as needed. Critical cases may lead to use of extracorporeal membrane oxygenation (ECMO).

Pneumonia

Pneumonia is the most common pulmonary complication among patients who die after surgery. Mortality rates for postoperative pneumonia vary from 20% to 40% and include both hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) [102, 103]. In colorectal surgery, the incidence of postoperative pneumonia has been reported from 1% to 4% [104]. The etiology of postoperative pneumonia is multifactorial. Atelectasis, aspiration, and secretions are important predisposing factors. Patients may also be exposed to nosocomial infections such as *Pseudomonas aeruginosa* and *Klebsiella* in the ICUs [105]. Clinical findings suggestive of postoperative pneumonia include fever, tachypnea, increased secretions, and physical exam suggestive of pulmonary consolidation. Chest X-rays and CT scans of the chest may show patchy opacification and/or localized consolidation. Several strategies may be used to decrease the risk of postoperative pneumonia. Respiratory exercises, deep breathing, coughing, and mobilization may help prevent atelectasis, which is a precursor of pneumonia. It is important to stress that control of postoperative pain is important for these actions to occur – one of the many focuses of ERPs [36]. Subglottic secretion suctioning on ventilated patients has also been shown to reduce ventilator-associated pneumonias [106]. The benefits of minimally invasive approaches may also extend to prevention of pneumonia [107] and to the elderly [108]. Treatment is supportive and based on aggressive ventilatory support and parenteral antibiotics.

Pulmonary Aspiration

Postoperative aspiration occurs in 1–2% of surgical cases [109] with mortality rates exceeding 30% [110]. Normal protective reflexes are often compromised in the postanesthetic state, with depressed mental status and the presence of a foreign body (i.e., nasogastric or endotracheal tubes). Additional risk factors include older age, pulmonary disease, need for intraoperative blood transfusions, dementia, and malignancy [110]. Aspiration of orogastric contents leads to severe pneumonia and pulmonary compromise with resultant prolonged hospital lengths of stays, costs, and death [109]. Prevention of aspiration includes preoperative fasting, proper positioning, careful intubation, and use of histamine-2 blockers [111]. Effective aspiration prevention protocols have been further developed that focus on bedside swallowing evaluations and stepwise advancement of oral intake [112]. Treatment of aspiration involves reestablishing patency of the airway and preventing further damage to the lung. Endotracheal bronchoscopy may be required to remove solid matter. Fluid resuscitation and antibiotics should be started concomitantly with aggressive management to prevent death and development of other complications.

Renal Complications (#5)

Renal complications affect the urinary tract and include acute kidney injury and postoperative urinary retention. While often reversible, these complications increase the risk of having long-term damage such as chronic kidney injury requiring dialysis.

Acute Kidney Injury

Acute kidney injury (AKI) describes a decrease in renal function over a course of hours to days that may range from a minor decrease in glomerular filtration to complete renal failure. The ACS-NSQIP defines AKI as a change in serum creatinine >2 mg/dl or a need for acute renal replacement therapy [64]. Postoperative AKI is a common complication in surgery and may affect up to 40% of the surgical population [113] and 14% of the colorectal population [114]. Development of postoperative AKI is associated with significant risks of both short- and long-term mortality, chronic kidney disease, and hemodialysis [113]. Risk factors include hypovolemia, bleeding, nephrotoxic agents, and cardiovascular failure. Preventative measures include avoidance of hypoperfusion and careful administration of nephrotoxic drugs including contrast agents. Treatment is supportive and based on volume replacement, preventing further renal damage and alleviating any obstructive pathologies.

Postoperative Urinary Retention

The inability to void postoperatively is common after anorectal and pelvic operations. Postoperative urinary retention (POUR) rates may occur in up to 25% of colorectal patients [115]. Even under modern ERP pathways, POURs still occur. In a study of 513 ERP patients in Switzerland, POUR occurred in 14% of patients [116]. These patients had worse surgical recovery including slower mobilization rates, more pain, and more UTIs. In that study, independent risk factors for POUR include male gender and thoracic epidural analgesia [116]. The treatment of POUR requires catheterization of the bladder and subsequent removal based on voiding ability. Efforts have recently been made in preventing POUR by administrating tamsulosin in the days before and after surgery. In one study, a threefold decrease in POUR rates was observed (25–6.7%) after administration of tamsulosin 3 days before surgery and 3 days after surgery [115].

Cardiac Complications (#6)

Cardiac complications following colorectal surgery are rare but life-threatening. Patients with risk factors of cardiac disease need to undergo appropriate cardiovascular testing and intervention prior to surgical intervention. Important guidelines from the American College of Cardiology (ACC) and

American Heart Association (AHA), supported by the ACS, exist that provide evidence-based recommendations for risk stratification and optimization of patients before major surgery including colorectal surgeries [117].

Myocardial Infarction

Approximately 1.5% of all patients undergoing a colorectal operation in the United States experience a postoperative myocardial infarction (MI) with mortality rates exceeding 28.5% [118]. Nearly 16% of all surgical patients, however, may experience a myocardial injury, and even these mortality rates are high (8.9%) [119]. Risk factors for postoperative MI include history of congestive heart failure, chronic renal disease, age >70 years old, peripheral vascular disorders, cancer, valvular disease, and hypertension [118]. Risk stratification and perioperative optimization are critical for colorectal patients as avoidance of this complication is the best strategy. The most cited and comprehensive guideline for stratification and optimization is the 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery [117]. These guidelines provide stepwise approaches to preoperative cardiac assessments including (i) initial clinical risk stratification of patients to low (<1% risk of major adverse cardiac event, MACE) and elevated (>1% MACE) risk categories, (ii) functional capacity assessment by metabolic equivalent of task (MET) for elevated risk patients (<4 MET = poor, 5–10 MET = moderate/good, and ≥11 MET = excellent), (iii) pharmacological stress testing for elevated risk patients with poor (<4 MET) or unknown functional capacity, and (iv) coronary revascularization for those with abnormal stress testing [117]. Treatment for MIs and other MACEs is supportive, and immediate consultations with cardiology (and potentially cardiac surgery) should be made to best individualize care and rescue these patients.

Dysrhythmias

Dysrhythmias such as atrial fibrillation occur after colorectal surgery. In a study of 571 colorectal patients, the incidence of postoperative atrial fibrillation (POAF) was 6.6% within 30 days of surgery [120]. This complication was closely associated with development of other complications including pneumonia, abdominal fluid collections, and sepsis. Patients with POAF were at higher risk for in-hospital mortality (9.1% vs. 2.6%) and 1-year mortality (33.3% vs. 8.8%) [120]. Preventative strategies to POAF include pharmacologic therapies (e.g., continuing beta-blockers), fluid optimization, and minimizing risk of other complications [121]. Treatment for POAF necessitates the involvement of cardiologists as there are both short- and long-term management strategies using rate-control medications (beta-blockers) and cardioversion [122].

Neurological Complications (#7)

Neurological complications in colorectal surgery include those complications that are captured by ACS-NSQIP (cerebrovascular accidents such as strokes) and those that are not but are equally important to identify (sexual dysfunction, delirium, etc.). While these complications can be devastating, significant improvements have been made in preventing them and managing them.

Perioperative Cerebrovascular Accidents

Perioperative strokes occur infrequently (0.3% rate from 2012 to 2017 ACS-NSQIP database) (Table 8.1) but are associated with significant perioperative morbidity and mortality. Most are thromboembolic events and occur within the initial 72 hours postoperative period. Risk factors include the type of surgery performed, intraoperative hypotension, history of previous stroke, cardiac issues (atrial fibrillation, valvular heart disease, mechanical valves, etc.), hypertension, peripheral vascular disease, age, neoplastic disease, and smoking [123]. Cerebrovascular events usually present with an acute neurologic change (i.e., weakness, facial droop, slurred speech). Workup involves getting an initial non-contrasted CT of the head to differentiate whether the stroke is ischemic or hemorrhagic. Treatment is dependent on the type of stroke, and neurology consultations are recommended for individualized management.

Sexual Dysfunction

Colorectal operations carry a risk of postoperative sexual dysfunction, typically due to injury to the nerves during pelvic dissection [124]. The pudendal nerves are not typically damaged during proctectomy; however, the nerves which are important in coordinating erection (nervi erigentes) and ejaculation (hypogastric nerves) may be affected. The hypogastric nerves include pre- and postganglionic sympathetic fibers from vertebral levels of T10-L2 and descend in the retroperitoneal space at the level of the sacral promontory. Injury to these nerves can occur during the posterior dissection of a total mesorectal excision or during transection of the inferior mesenteric artery and can result in ejaculatory dysfunction. The nervi erigentes (or pelvic splanchnic nerves) arise from the anterior rami of S2-S4 and enter the sacral plexus along the anterolateral wall of the rectum. Erectile dysfunction may occur due to avulsion from excessive traction of the rectum during proctectomy or by direct injury of the nerves during dissection near the seminal vesicles and prostate.

The incidence of postoperative sexual dysfunction in males varies widely in the medical literature (from 5% to 90%), and a significant number of patients may suffer from preoperative dysfunction [124]. In a prospective study of 169

patients who underwent proctectomy for rectal cancer, Adam et al. [125] found that 71% of males reported erectile dysfunction after surgery (vs. 24% preoperative) and 78% reported ejaculatory dysfunction (vs. 32%) ($p < 0.001$). Stage T3 or T4 tumors and low rectal tumors were independent risk factors of worse sexual function. Similarly, Dulskas and Samalavicius reported postoperative erectile dysfunction in 63.9% of patients; however, the incidence of preoperative dysfunction was 41.7% [126]. Sexual dysfunction may be higher in patients who undergo abdominoperineal resection than those who undergo low anterior resection.

Psychological evaluation and support of the patient and his/her partner are important and can improve the response to pharmacologic therapy [127]. Among the medications available, the efficacy of sildenafil was demonstrated in a study where 32 patients who had undergone proctectomy were randomized to treatment or placebo [128]. Erectile function improved in 80% of patients treated with sildenafil compared to only 17% of patients treated with placebo.

Determining significant changes in sexual function in older women following proctectomy can be more difficult, as a high percentage of women report baseline preoperative genitourinary dysfunction [4]. Younger female patients who undergo pelvic surgery for benign disease may be at risk of fertility problems, likely due to extensive dissection leading to intra-abdominal and pelvic adhesions. Waljee et al. reported a threefold increase in the risk of infertility following total proctocolectomy in patients with ulcerative colitis (48% vs. 15%) [129]. In a more recent meta-analysis, Rajaratnam et al. showed that the risk of infertility is almost four times higher following IPAA [130]. While it would seem that a laparoscopy would reduce adhesion formation and therefore reduce the risk of infertility, a recent retrospective comparison of 161 patients did not demonstrate a difference in infertility rates between open and minimally invasive approaches [131].

Postoperative Delirium

Postoperative delirium (POD) is a form of delirium that occurs after a surgical procedure and may occur at rates as high as 87% [132]. Risk factors include reduced cognitive reserve from preexisting comorbidities (i.e., dementia and age), sensory impairment, dehydration, substance abuse, withdrawal of certain types of medications (anticholinergics, benzodiazepines, etc.), sleep-wake cycle disturbances, and environmental change (i.e., prolonged hospitalization or ICU stay) [133]. Patients with delirium are at increased risk for adverse outcomes including higher mortality, longer hospital stays, and discharge to nursing facility [134]. Preventative measures include frequent and deliberate orientation of patient to place/time, early postoperative mobilization, and consistent use of home devices while hospitalized (i.e., hearing aids and glasses). In the ICU, sedative medication should be titrated between patient comfort and oversedation. Treatment is supportive and includes supervision/reorientation, removal of inciting agents, and pharmacologic therapies.

Conclusion

Postoperative complications are an inherent part of colorectal surgery. All lead to increased risks of mortality, prolonged hospital length of stays, readmissions, and other adverse outcomes. The most common complications in colorectal surgery include ileus, bleeding, and surgical site infections. It is critical for colorectal surgeons to be aware of the many risk factors for these complications and to optimize patients preoperatively. When complications occur, surgeons need to recognize them early, respond in an expedient manner, and administer the appropriate treatment to rescue the patient and achieve the best possible outcome.

References

1. Schilling PL, Dimick JB, Birkmeyer JD. Prioritizing quality improvement in general surgery. J Am Coll Surg. 2008;207(5):698–704.
2. Longo WE, et al. Risk factors for morbidity and mortality after colectomy for colon cancer. Dis Colon Rectum. 2000;43(1):83–91.
3. Tevis SE, Kennedy GD. Postoperative complications: looking forward to a safer future. Clin Colon Rectal Surg. 2016;29(3):246–52.
4. Scarborough JE, et al. Associations of specific postoperative complications with outcomes after elective colon resection: a procedure-targeted approach toward surgical quality improvement. JAMA Surg. 2017;152(2):e164681.
5. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–13.
6. Clavien PA, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187–96.
7. Slankamenac K, et al. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg. 2013;258(1):1–7.
8. Strasberg SM, Linehan DC, Hawkins WG. The accordion severity grading system of surgical complications. Ann Surg. 2009;250(2):177–86.
9. Khuri SF, et al. The Department of Veterans Affairs' NSQIP: the first national, validated, outcome-based, risk-adjusted, and peer-controlled program for the measurement and enhancement of the quality of surgical care. National VA Surgical Quality Improvement Program. Ann Surg. 1998;228(4):491–507.
10. Khuri SF, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg. 2005;242(3):326–41; discussion 341–3.
11. Lawson EH, et al. Association between occurrence of a postoperative complication and readmission: implications for quality improvement and cost savings. Ann Surg. 2013;258(1):10–8.
12. Zogg CK, et al. Rethinking priorities: cost of complications after elective colectomy. Ann Surg. 2016;264(2):312–22.
13. Tevis SE, et al. Postoperative complications in patients with rectal cancer are associated with delays in chemotherapy that lead

to worse disease-free and overall survival. Dis Colon Rectum. 2013;56(12):1339–48.
14. Yang R, Wolfson M, Lewis MC. Unique aspects of the elderly surgical population: an anesthesiologist's perspective. Geriatr Orthop Surg Rehabil. 2011;2(2):56–64.
15. Kirchhoff P, Dincler S, Buchmann P. A multivariate analysis of potential risk factors for intra- and postoperative complications in 1316 elective laparoscopic colorectal procedures. Ann Surg. 2008;248(2):259–65.
16. Aquina CT, et al. The impact of age on complications, survival, and cause of death following colon cancer surgery. Br J Cancer. 2017;116(3):389–97.
17. Weerink LBM, et al. Long-term survival in octogenarians after surgical treatment for colorectal cancer: prevention of postoperative complications is key. Ann Surg Oncol. 2018;25(13):3874–82.
18. Kunitake H, et al. Caring for octogenarian and nonagenarian patients with colorectal cancer: what should our standards and expectations be? Dis Colon Rectum. 2010;53(5):735–43.
19. Ostermann S, et al. Randomized controlled trial of enhanced recovery program dedicated to elderly patients after colorectal surgery. Dis Colon Rectum. 2019;62(9):1105–16.
20. Al-Taki M, et al. Effect of gender on postoperative morbidity and mortality outcomes: a retrospective cohort study. Am Surg. 2018;84(3):377–86.
21. Lipska MA, et al. Anastomotic leakage after lower gastrointestinal anastomosis: men are at a higher risk. ANZ J Surg. 2006;76(7):579–85.
22. Tan WP, et al. American Society of Anesthesiologists class and Charlson's comorbidity index as predictors of postoperative colorectal anastomotic leak: a single-institution experience. J Surg Res. 2013;184(1):115–9.
23. Tian Y, et al. Age-adjusted charlson comorbidity index score as predictor of prolonged postoperative ileus in patients with colorectal cancer who underwent surgical resection. Oncotarget. 2017;8(13):20794–801.
24. Ouellette JR, Small DG, Termuhlen PM. Evaluation of Charlson-Age Comorbidity Index as predictor of morbidity and mortality in patients with colorectal carcinoma. J Gastrointest Surg. 2004;8(8):1061–7.
25. Krarup PM, et al. Association of comorbidity with anastomotic leak, 30-day mortality, and length of stay in elective surgery for colonic cancer: a Nationwide Cohort Study. Dis Colon Rectum. 2015;58(7):668–76.
26. Kozol RA, et al. Minimizing risk in colon and rectal surgery. Am J Surg. 2007;194(5):576–87.
27. Hahn EE, et al. Understanding comorbidity profiles and their effect on treatment and survival in patients with colorectal cancer. J Natl Compr Cancer Netw. 2018;16(1):23–34.
28. Franko J, et al. The influence of prior abdominal operations on conversion and complication rates in laparoscopic colorectal surgery. JSLS. 2006;10(2):169–75.
29. Parker MC. Epidemiology of adhesions: the burden. Hosp Med. 2004;65(6):330–6.
30. Beattie AH, et al. A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. Gut. 2000;46(6):813–8.
31. Kondrup J, et al. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003;22(3):321–36.
32. Almasaudi AS, et al. The relation between Malnutrition Universal Screening Tool (MUST), computed tomography-derived body composition, systemic inflammation, and clinical outcomes in patients undergoing surgery for colorectal cancer. Am J Clin Nutr. 2019;110(6):1327–34.
33. Braga M, et al. Preoperative oral arginine and n-3 fatty acid supplementation improves the immunometabolic host response and outcome after colorectal resection for cancer. Surgery. 2002;132(5):805–14.
34. Gianotti L, et al. A randomized controlled trial of preoperative oral supplementation with a specialized diet in patients with gastrointestinal cancer. Gastroenterology. 2002;122(7):1763–70.
35. Thornblade LW, et al. Preoperative immunonutrition and elective colorectal resection outcomes. Dis Colon Rectum. 2017;60(1):68–75.
36. Gustafsson UO, et al. Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS((R))) Society Recommendations: 2018. World J Surg. 2019;43(3):659–95.
37. Agodi A, et al. Risk of surgical site infection in older patients in a cohort survey: targets for quality improvement in antibiotic prophylaxis. Int Surg. 2015;100(3):473–9.
38. Baucom RB, et al. Smoking as dominant risk factor for anastomotic leak after left colon resection. Am J Surg. 2015;210(1):1–5.
39. Bolckmans R, et al. Does smoking cessation reduce surgical recurrence after primary ileocolic resection for Crohn's disease? Dis Colon Rectum. 2020;63(2):200–6.
40. Lindstrom D, et al. Effects of a perioperative smoking cessation intervention on postoperative complications: a randomized trial. Ann Surg. 2008;248(5):739–45.
41. Sorensen LT, Karlsmark T, Gottrup F. Abstinence from smoking reduces incisional wound infection: a randomized controlled trial. Ann Surg. 2003;238(1):1–5.
42. Moller AM, et al. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. Lancet. 2002;359(9301):114–7.
43. Thomsen T, Tonnesen H, Moller AM. Effect of preoperative smoking cessation interventions on postoperative complications and smoking cessation. Br J Surg. 2009;96(5):451–61.
44. van Rooijen SJ, et al. Making patients fit for surgery: introducing a four pillar multimodal prehabilitation program in colorectal cancer. Am J Phys Med Rehabil. 2019;98(10):888–96.
45. Leichtle SW, et al. Does preoperative anemia adversely affect colon and rectal surgery outcomes? J Am Coll Surg. 2011;212(2):187–94.
46. Wilson MJ, et al. The role of preoperative iron deficiency in colorectal cancer patients: prevalence and treatment. Int J Color Dis. 2017;32(11):1617–24.
47. Quinn EM, et al. Correction of iron-deficiency anaemia in colorectal surgery reduces perioperative transfusion rates: a before and after study. Int J Surg. 2017;38:1–8.
48. American Society of Anesthesiologists Task Force on Perioperative Blood, M. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management*. Anesthesiology. 2015;122(2):241–75.
49. Roubenoff R. Sarcopenia: a major modifiable cause of frailty in the elderly. J Nutr Health Aging. 2000;4(3):140–2.
50. Nakanishi R, et al. Sarcopenia is an independent predictor of complications after colorectal cancer surgery. Surg Today. 2018;48(2):151–7.
51. Yang J, et al. A new diagnostic index for sarcopenia and its association with short-term postoperative complications in patients undergoing surgery for colorectal cancer. Color Dis. 2019;21(5):538–47.
52. Wang Y, et al. Has the prevalence of overweight, obesity and central obesity levelled off in the United States? Trends, patterns, disparities, and future projections for the obesity epidemic. Int J Epidemiol. 2020;
53. Hussan H, et al. Morbid obesity is associated with increased mortality, surgical complications, and incremental health care utilization in the peri-operative period of colorectal cancer surgery. World J Surg. 2016;40(4):987–94.

54. Pikarsky AJ, et al. Is obesity a high-risk factor for laparoscopic colorectal surgery? Surg Endosc. 2002;16(5):855–8.
55. Wahl TS, et al. The obese colorectal surgery patient: surgical site infection and outcomes. Dis Colon Rectum. 2018;61(8):938–45.
56. Gillis C, et al. Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. Anesthesiology. 2014;121(5):937–47.
57. van Rooijen S, et al. Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: the first international randomized controlled trial for multimodal prehabilitation. BMC Cancer. 2019;19(1):98.
58. Wilson MZ, Hollenbeak CS, Stewart DB. Laparoscopic colectomy is associated with a lower incidence of postoperative complications than open colectomy: a propensity score-matched cohort analysis. Color Dis. 2014;16(5):382–9.
59. Kennedy GD, et al. Laparoscopy decreases postoperative complication rates after abdominal colectomy: results from the national surgical quality improvement program. Ann Surg. 2009;249(4):596–601.
60. Bilimoria KY, et al. Laparoscopic-assisted vs. open colectomy for cancer: comparison of short-term outcomes from 121 hospitals. J Gastrointest Surg. 2008;12(11):2001–9.
61. Ghaferi AA, Birkmeyer JD, Dimick JB. Complications, failure to rescue, and mortality with major inpatient surgery in medicare patients. Ann Surg. 2009;250(6):1029–34.
62. Copeland GP, Jones D, Walters M. POSSUM: a scoring system for surgical audit. Br J Surg. 1991;78(3):355–60.
63. Knaus WA, et al. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818–29.
64. Bilimoria KY, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. J Am Coll Surg. 2013;217(5):833–42 e1–3.
65. Hornor MA, et al. Enhancing the American College of Surgeons NSQIP Surgical Risk Calculator to Predict Geriatric Outcomes. J Am Coll Surg. 2020;230(1):88–100. e1
66. Lee MJ. Optimizing the safety of surgery, before surgery. Clin Orthop Relat Res. 2014;472(3):809–11.
67. Scheede-Bergdahl C, Minnella EM, Carli F. Multi-modal prehabilitation: addressing the why, when, what, how, who and where next? Anaesthesia. 2019;74 Suppl 1:20–6.
68. Carli F, et al. Effect of multimodal prehabilitation vs postoperative rehabilitation on 30-day postoperative complications for frail patients undergoing resection of colorectal cancer: a randomized clinical trial. JAMA Surg. 2020;155(3):233–42.
69. Artinyan A, et al. Prolonged postoperative ileus-definition, risk factors, and predictors after surgery. World J Surg. 2008;32(7):1495–500.
70. Chudzinski AP, Thompson EV, Ayscue JM. Acute colonic pseudoobstruction. Clin Colon Rectal Surg. 2015;28(2):112–7.
71. Venara A, et al. Incidence and risk factors for severity of postoperative ileus after colorectal surgery: a prospective registry data analysis. World J Surg. 2019;
72. Goussous N, et al. Early postoperative small bowel obstruction: open vs laparoscopic. Am J Surg. 2015;209(2):385–90.
73. Ellozy SH, et al. Early postoperative small-bowel obstruction: a prospective evaluation in 242 consecutive abdominal operations. Dis Colon Rectum. 2002;45(9):1214–7.
74. Chu DI, et al. Early versus late adhesiolysis for adhesive-related intestinal obstruction: a nationwide analysis of inpatient outcomes. J Gastrointest Surg. 2013;17(2):288–97.
75. Bauer J, et al. Adhesive small bowel obstruction: early operative versus observational management. Am Surg. 2015;81(6):614–20.
76. Teixeira PG, et al. Early operation is associated with a survival benefit for patients with adhesive bowel obstruction. Ann Surg. 2013;258(3):459–65.
77. Chen D, et al. Postoperative bleeding risk prediction for patients undergoing colorectal surgery. Surgery. 2018;164(6):1209–16.
78. Hammond KL, Margolin DA. Surgical hemorrhage, damage control, and the abdominal compartment syndrome. Clin Colon Rectal Surg. 2006;19(4):188–94.
79. Hirshberg A, et al. Reoperation for bleeding in trauma. Arch Surg. 1993;128(10):1163–7.
80. Kirkpatrick AW, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med. 2013;39(7):1190–206.
81. De Waele JJ, Hoste EA, Malbrain ML. Decompressive laparotomy for abdominal compartment syndrome–a critical analysis. Crit Care. 2006;10(2):R51.
82. Emoto S, et al. Venous thromboembolism in colorectal surgery: incidence, risk factors, and prophylaxis. Asian J Surg. 2019;42(9):863–73.
83. Gould MK, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e227S–77S.
84. Tenna AM, Kappadath S, Stansby G. Diagnostic tests and strategies in venous thromboembolism. Phlebology. 2012;27 Suppl 2:43–52.
85. Anderson DJ, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014;35 Suppl 2:S66–88.
86. Zimlichman E, et al. Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. JAMA Intern Med. 2013;173(22):2039–46.
87. Kirkland KB, et al. The impact of surgical-site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. Infect Control Hosp Epidemiol. 1999;20(11):725–30.
88. Umscheid CA, et al. Estimating the proportion of healthcare-associated infections that are reasonably preventable and the related mortality and costs. Infect Control Hosp Epidemiol. 2011;32(2):101–14.
89. Zywot A, et al. Bundles prevent surgical site infections after colorectal surgery: meta-analysis and systematic review. J Gastrointest Surg. 2017;21(11):1915–30.
90. Allegranzi B, et al. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis. 2016;16(12):e276–87.
91. Allegranzi B, et al. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis. 2016;16(12):e288–303.
92. Ban KA, et al. American College of Surgeons and Surgical Infection Society: Surgical Site Infection Guidelines, 2016 Update. J Am Coll Surg. 2017;224(1):59–74.
93. Berrios-Torres SI, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surg. 2017;152(8):784–91.
94. Holubar SD, et al. American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) joint consensus statement on prevention of postoperative infection within an enhanced recovery pathway for elective colorectal surgery. Perioper Med (Lond). 2017;6:4.
95. Soderback H, et al. Incidence of wound dehiscence after colorectal cancer surgery: results from a national population-based register for colorectal cancer. Int J Color Dis. 2019;34(10):1757–62.
96. Deerenberg EB, et al. Small bites versus large bites for closure of abdominal midline incisions (STITCH): a double-

blind, multicentre, randomised controlled trial. Lancet. 2015;386(10000):1254–60.
97. Khorgami Z, et al. Prophylactic retention sutures in midline laparotomy in high-risk patients for wound dehiscence: a randomized controlled trial. J Surg Res. 2013;180(2):238–43.
98. Sheka AC, Tevis S, Kennedy GD. Urinary tract infection after surgery for colorectal malignancy: risk factors and complications. Am J Surg. 2016;211(1):31–9.
99. Southern WN, et al. Postoperative Clostridium difficile-associated diarrhea. Surgery. 2010;148(1):24–30.
100. Zilberberg MD, Shorr AF, Kollef MH. Increase in adult Clostridium difficile-related hospitalizations and case-fatality rate, United States, 2000-2005. Emerg Infect Dis. 2008;14(6):929–31.
101. Jurt J, et al. Respiratory complications after colorectal surgery: avoidable or fate? World J Surg. 2018;42(9):2708–14.
102. Nagle RT, et al. Pneumonia is associated with a high risk of mortality after pancreaticoduodenectomy. Surgery. 2017;161(4):959–67.
103. McGillicuddy EA, et al. Factors predicting morbidity and mortality in emergency colorectal procedures in elderly patients. Arch Surg. 2009;144(12):1157–62.
104. Chughtai M, et al. The incidence of postoperative pneumonia in various surgical subspecialties: a dual database analysis. Surg Technol Int. 2017;30:45–51.
105. Sader HS, et al. Frequency and antimicrobial susceptibility of Gram-negative bacteria isolated from patients with pneumonia hospitalized in ICUs of US medical centres (2015–2017). J Antimicrob Chemother. 2018;73(11):3053–9.
106. Damas P, et al. Prevention of ventilator-associated pneumonia and ventilator-associated conditions: a randomized controlled trial with subglottic secretion suctioning. Crit Care Med. 2015;43(1):22–30.
107. Schwenk W, et al. Pulmonary function following laparoscopic or conventional colorectal resection: a randomized controlled evaluation. Arch Surg. 1999;134(1):6–12. discussion 13
108. Milone M, et al. Pulmonary complications after surgery for rectal cancer in elderly patients: evaluation of laparoscopic versus open approach from a multicenter study on 477 consecutive cases. Gastroenterol Res Pract. 2017;2017:5893890.
109. Kozlow JH, et al. Epidemiology and impact of aspiration pneumonia in patients undergoing surgery in Maryland, 1999–2000. Crit Care Med. 2003;31(7):1930–7.
110. Studer P, et al. Risk factors for fatal outcome in surgical patients with postoperative aspiration pneumonia. Int J Surg. 2016;27:21–5.
111. Agnew NM, et al. Gastroesophageal reflux and tracheal aspiration in the thoracotomy position: should ranitidine premedication be routine? Anesth Analg. 2002;95(6):1645–9, table of contents.
112. Starks B, Harbert C. Aspiration prevention protocol: decreasing postoperative pneumonia in heart surgery patients. Crit Care Nurse. 2011;31(5):38–45.
113. Bihorac A. Acute kidney injury in the surgical patient: recognition and attribution. Nephron. 2015;131(2):118–22.
114. Wiener JGD, et al. The Association of Enhanced Recovery Pathway and Acute Kidney Injury in Patients Undergoing Colorectal Surgery. Dis Colon Rectum. 2020;63(2):233–41.
115. Poylin V, et al. Perioperative use of tamsulosin significantly decreases rates of urinary retention in men undergoing pelvic surgery. Int J Color Dis. 2015;30(9):1223–8.
116. Grass F, et al. Postoperative urinary retention in colorectal surgery within an enhanced recovery pathway. J Surg Res. 2017;207:70–6.
117. Fleisher LA, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130(24):2215–45.
118. Moghadamyeghaneh Z, et al. Risk factors of postoperative myocardial infarction after colorectal surgeries. Am Surg. 2015;81(4):358–64.
119. Puelacher C, et al. Perioperative myocardial injury after noncardiac surgery: incidence, mortality, and characterization. Circulation. 2018;137(12):1221–32.
120. Quinn R, et al. Morbidity and mortality with atrial fibrillation following colorectal surgery. ANZ J Surg. 2018;88(10):1003–7.
121. Frendl G, et al. 2014 AATS guidelines for the prevention and management of perioperative atrial fibrillation and flutter for thoracic surgical procedures. J Thorac Cardiovasc Surg. 2014;148(3):e153–93.
122. Joshi KK, et al. Postoperative atrial fibrillation in patients undergoing non-cardiac non-thoracic surgery: a practical approach for the hospitalist. Hosp Pract (1995). 2015;43(4):235–44.
123. Vlisides P, Mashour GA. Perioperative stroke. Can J Anaesth. 2016;63(2):193–204.
124. Walsh PC, Schlegel PN. Radical pelvic surgery with preservation of sexual function. Ann Surg. 1988;208(4):391–400.
125. Adam JP, et al. Prospective and longitudinal study of urogenital dysfunction after proctectomy for rectal cancer. Dis Colon Rectum. 2016;59(9):822–30.
126. Dulskas A, Samalavicius NE. A prospective study of sexual and urinary function before and after total mesorectal excision. Int J Color Dis. 2016;31(6):1125–30.
127. Eveno C, et al. Sexual and urinary dysfunction after proctectomy for rectal cancer. J Visc Surg. 2010;147(1):e21–30.
128. Lindsey I, et al. Randomized, double-blind, placebo-controlled trial of sildenafil (Viagra) for erectile dysfunction after rectal excision for cancer and inflammatory bowel disease. Dis Colon Rectum. 2002;45(6):727–32.
129. Waljee A, et al. Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. Gut. 2006;55(11):1575–80.
130. Rajaratnam SG, et al. Impact of ileal pouch-anal anastomosis on female fertility: meta-analysis and systematic review. Int J Color Dis. 2011;26(11):1365–74.
131. Gorgun E, et al. Does laparoscopic ileal pouch-anal anastomosis reduce infertility compared with open approach? Surgery. 2019;166(4):670–7.
132. Robinson TN, Eiseman B. Postoperative delirium in the elderly: diagnosis and management. Clin Interv Aging. 2008;3(2):351–5.
133. Kang SY, Seo SW, Kim JY. Comprehensive risk factor evaluation of postoperative delirium following major surgery: clinical data warehouse analysis. Neurol Sci. 2019;40(4):793–800.
134. Raats JW, et al. Postoperative delirium in elderly after elective and acute colorectal surgery: a prospective cohort study. Int J Surg. 2015;18:216–9.

Anastomotic Construction

9

H. David Vargas and David A. Margolin

Key Concepts

- Anastomotic construction represents a fundamental and essential skill restoring intestinal continuity and preserving bowel function and continence.
- It encompasses a broad range of methods and configurations and can be performed utilizing a spectrum of operative platforms.
- While anastomosis may be a heterogeneous endeavor, consistent fundamental principles must be preserved in all its forms.
- Stapling technologies represent a challenge for surgeon knowledge and understanding their use in clinical practice given the numerous innovations and specific tissue–device interactions.
- Colonic mobilization techniques bringing bowel into proximity to the distal limb while preserving blood supply represents an essential and critical skill for anastomotic construction. Surgeons must be familiar with advanced techniques for mobilization to achieve anastomosis.

Introduction

Anastomotic construction represents one of the fundamental activities of the intestinal surgeon. Following closely behind the principal goal of resection of the pathologic condition, restoration of a functional intestinal tract invariably remains an important aspect of a patient's sense of well-being and health as well as their perception of a successful operation. Fortunately, a healed and functional anastomosis is common, and the inability to perform an anastomosis remains a relatively rare phenomenon. This current perspective belies the early history of surgery of the intestinal tract where anastomotic failure and mortality were exceedingly high (Fig. 9.1) [1]. Advances in surgical technique and scientific discovery were critical to safe anastomotic construction.

Intestinal anastomosis encompasses a broad range of surgical activity: the multitude of pathologic conditions requiring resection, the variety of anatomic segments that can be resected, the numerous permutations of suture materials, and the array of anastomotic configurations. Adding to the complexity of this topic, we must also consider the different means of access to the peritoneal cavity, including laparotomy or minimally invasive approaches such as laparoscopy or robotic surgery.

In spite of remarkable technological advances, anastomotic leak continues to plague our best efforts even 20 years into the twenty-first century. It continues to be a most feared complication. The morbidity of leak is far reaching, often involving reoperation, lengthy hospital stay, loss of function, poorer oncologic outcomes, or even operative mortality [2]. Unfortunately, anastomosis outcomes vary, in part based on surgeon performance [3, 4]. This is particularly sobering as perhaps there are few operative outcomes that affect a surgeon's personal measure of competence and self-esteem. As individual surgeons, we are acutely aware of the dire implications for our patients who suffer an anastomotic leak. Therefore, the topic of anastomotic construction represents an audacious and humbling endeavor for the authors to embark upon.

The objective is pragmatic and straight forward: to discuss general principles and technical options for anastomotic construction. Going forward, we trust and will rely upon the reader's tolerance and understanding where philosophies and techniques may differ from their own. In the end, we hope that author and reader alike will have subjected themselves and their operative technique to scrutiny and honest appraisal, and will consider the following with intellectual rigor and openness.

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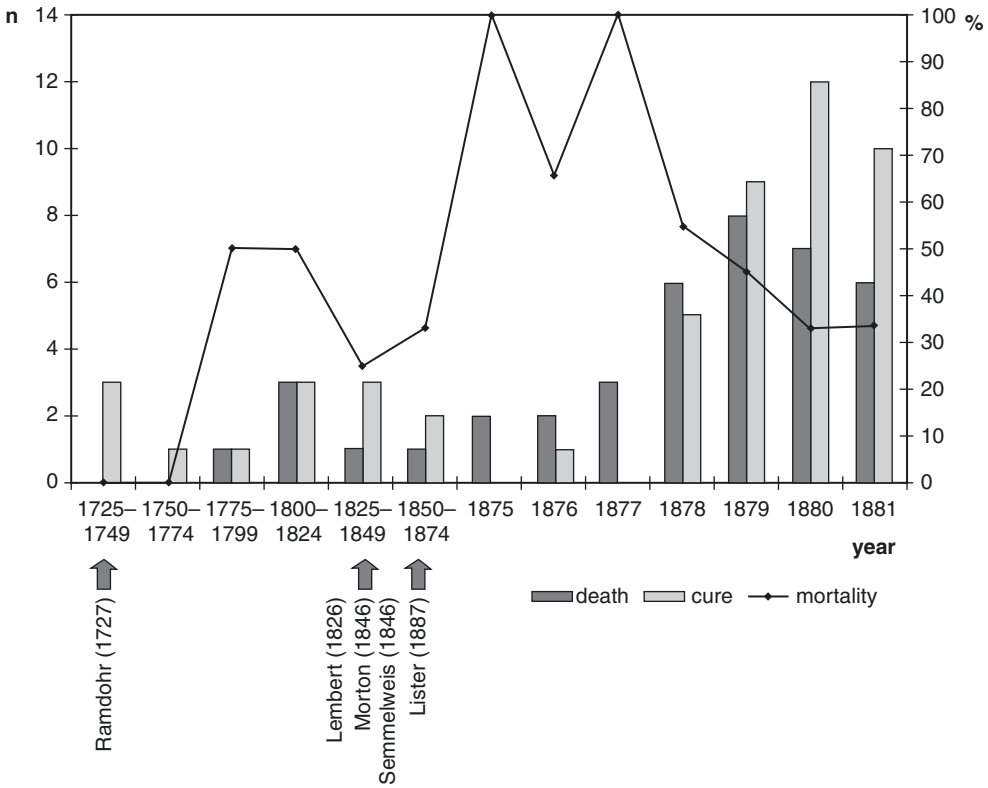

Fig. 9.1 Mortality of gastrointestinal anastomoses performed between 1727 and 1881. Reused with permission [1]. (Copyright © 2005 Springer Nature)

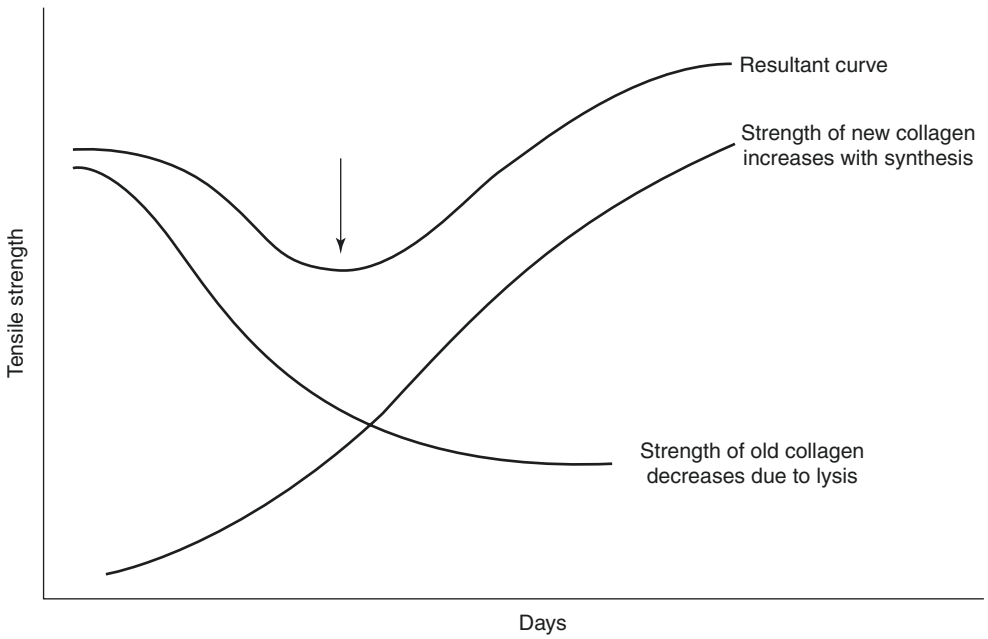

Fig. 9.2 Wound healing in gastrointestinal tract is the fine balance during "lag" phase between collagen synthesis and collagenolysis. Line labeled "resultant curve" shows this balance. Weak time period depicted on graph (arrow) can be prolonged or exacerbated by local or systemic factors that upset equilibrium. (Reused with permission [6]. Copyright © 2006 John Wiley and Sons)

Physiology of Anastomotic Healing

Intestinal anastomotic healing proceeds through the well-elucidated phases described for other models of tissue injury and repair [5, 6]. The status of collagen and tensile strength is critical to anastomotic integrity (Fig. 9.2). However, differences exist as a result of the unique anatomic and physiologic properties of the intestinal tract. Anatomically, the intestinal tract has four layers with characteristics that play unique role in anastomotic healing. The exceptions to this are importantly, the esophagus and the lower aspect of the rectum, both of which notably are lacking serosal layers. Anastomoses involving these specific organs prove more challenging and are marked by higher leak rates [6].

The importance of the serosa was highlighted by Lembert [1, 7, 8]. He popularized the critical idea that apposition of the serosa and inversion of the mucosa was critical to anastomotic healing. Halsted's canine investigations revealed that the submucosal layer contained the highest concentration of collagen and possessed the greatest tensile strength. He emphasized the role of submucosal purchase during intestinal suturing, and the Halsted stitch actually omitted the mucosa. The incorporation of the submucosa provides the initial tensile strength to an anastomosis during *the lag or inflammatory phase* when collagen degradation predominates. During this inflammatory phase, the clotting cascade is activated by platelets and release of inflammatory mediators, causing a fibrin plug to occur at the mucosal defect and assisting in hemostasis. Neutrophils migrate to the wound and essentially clean up the necrotic tissues. Collagenolysis liberates amino acids, especially proline and lysine, which become available for later collagen synthesis. Therefore, the anastomosis is weakest during the first 2 days after surgery, as integrity of the anastomosis relies entirely upon the suture material approximating the submucosa until collagen synthesis occurs [5, 6].

At day 2–4, the proliferative phase begins. This phase is marked by collagen synthesis. Fibroblasts are generally responsible for this activity, but unique to healing in the intestinal tract, smooth muscle cells also contribute to collagen synthesis [6]. Smooth muscle cells from the muscularis mucosae and the muscularis propria contribute to this production. Tensile strength develops as a result, and compared to soft tissue repair, this occurs much more rapidly in the gastrointestinal tract. Similar to cutaneous healing, neither process achieves pre-injury tensile strength. It is estimated that at 1-week small bowel anastomoses achieve nearly 100% of the expected strength. Colonic anastomoses obtain about 50% of their ultimate anastomotic strength in the same time frame [5, 6]. Finally, the remodeling phase of healing is marked by collagen maturation and cross-linking, increasing the tensile strength of the anastomosis.

Epithelial repair, otherwise known as g*astrointestinal restitution*, occurs rapidly as a result of migration of crypt cells from adjacent unwounded epithelium. The integrity of the epithelial layer can be complete by day 3 if mucosal apposition occurs [5]. Critical to this process is restoration of the inner mucus layer. Crypt goblet cells secrete a viscous mucus layer that serves as an important inner protective layer of the mucus layer of the intestinal tract separating the commensal bacterial flora of the microbiome from the epithelium and healing anastomosis [9–11]. One of the major concepts recently introduced regarding anastomotic healing has been the revelation of local changes in the microbiome. The development of pathogenic intestinal bacteria results in collagenolytic activity that undermines tensile strength and anastomotic healing [10–12]. The importance of commensal bacteria and potential deleterious local effects such as these highlight the critical aspect of gastrointestinal restitution and restoration of the mucus layer barrier to the healing of intestinal anastomosis.

In summary, gastrointestinal anastomoses progress through the various phases of healing with important specific differences resulting in rapid restoration of tensile strength and restitution. Anastomotic construction techniques should minimize parameters prolonging the inflammatory phase and collagenolysis: avoidance of tension, minimize necrosis, airtight closure, approximation of the submucosa, and preservation of perfusion. These parameters give rise to the basic tenets of anastomotic construction.

Fundamental Principles for Anastomotic Construction

Anastomotic construction depends on joining two ends of bowel that are healthy and well-perfused. The physical union is airtight and without any tension. Operative technique should involve anatomic mobilization by dividing named vessels and preserving blood supply, minimally traumatic dissection, precise and secure approximation, all while maintaining aseptic technique. Importantly, these fundamental concepts must be preserved across the various operative platforms—open and minimally invasive—knowing that potential advantages and challenges exist for each approach and for specific steps. Regardless of platform, the anastomosis generally represents one of the final operative steps and, independent of the time required for the preceding steps, requires focused attention to detail and meticulous technique.

Operative Planning

Operative decision making necessitates preoperative planning. One of the keys to successful operations depends on the preparation of the surgeon and team so that each step has been imagined, contemplated, and specific details considered. In particular, the principal objective –surgical treatment of the pathologic condition and the planned appropriate extent of resection – must be clearly defined. Localization of pathology preoperatively is a critical item for anticipating segmental or extended resection. Endoscopic description of the segment can be inaccurate and tattoos are potentially helpful in intraoperative localization, but not in preoperative planning. Endoscopic clip placement with X-ray can be helpful (Fig. 9.3). The plan for mesenteric resection and division/preservation of named vessels is dependent on precise localization, and therefore should be a major part of preoperative planning.

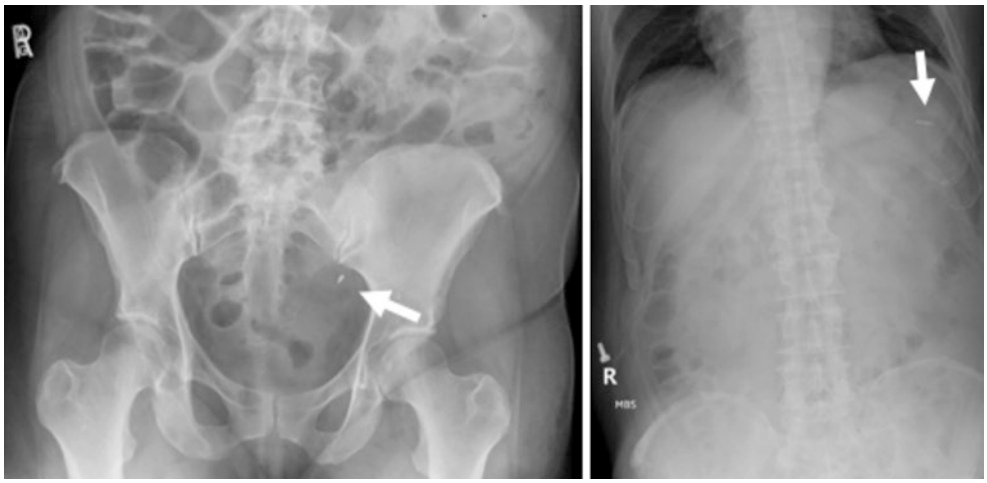

Fig. 9.3 Note white arrows indicating endoscopic clip placed at 60 cm from anal verge seen on plain X-ray in two different patients. Clip placement with radiograph can provide accurate preoperative localization for purposes of specific operative planning

After appropriate resection has been defined, one can then turn attention to the anticipated anastomosis. Several issues must be considered. Are the two bowel ends mobile or is one fixed (rectal or anal)? [13] Is there significant physical distance separating the ends? What specific techniques need consideration to enable adequate mobilization for tension-free anastomosis? How are the respective mesenteries oriented in relation to one another, and how will the anastomosis configuration be affected? Finally, what specific methods for actual bowel anastomosis will be used?

Successful healed anastomoses depend on careful preoperative planning, and a critical aspect of this preparation includes anticipation of obstacles and contingency strategies. Familiarity with multiple operative methods and the ability to adapt to variances in anatomy, pathologic findings, or operative conditions is critical. One must possess versatility or "surgical agility."

Mobilization

While remaining cognizant of the steps of anastomotic construction, the operative team must conduct the planned resection for the specific pathologic condition. Resection extent should not be influenced or potentially compromised by the anticipated anastomosis and potential concerns of bowel length and reach. One should not succumb to the allure of what is technically expedient. The savvy surgeon acknowledges that only after appropriate resection should one be concerned with the task of anastomosis, confident that he or she possesses the skill to mobilize the residual bowel and achieve a tension-free anastomosis.

Proximity refers to bringing the two segments in space for tension-free anastomosis. Tension threatens the initial anastomotic integrity, which for several days is entirely dependent upon the tensile strength of sutures or staples [6]. Tension also leads to ischemia that diminishes conditions for healing [14]. One of the fundamental aspects of anastomotic construction therefore is a tension-free anastomosis.

Small Bowel Mobilization

Small bowel resections represent the simplest bowel resection and typically do not require any significant mobilization given the intraperitoneal nature of the bowel and attached mesentery. The two limbs of bowel for anastomosis can be brought into proximity easily for a tension-free anastomosis.

Small bowel mobilization can be important in certain situations. One should be aware of the particular challenge of an extracorporeal anastomosis during right colectomy. Exteriorization of the proximal transverse colon will be affected by omental adhesions and gastrocolic adhesions. The entire hepatic flexure should be mobilized, by dividing the gastrocolic ligament and dissection off the sweep of the duodenum. Other features that affect the ability to perform this anastomosis in proper fashion include: the size of the omentum especially in the obese patient, a large specimen, shortened mesentery, and increased abdominal wall thickness. Each of these factors must be taken into account when considering specimen extraction site and size of incision.

Small bowel mobilization techniques, however, are critical when performing ileoanal anastomosis [15–17]. The root of the mesentery must be dissected to the pancreas and proximal aspect of the superior mesenteric artery. Relaxing incisions, or "step ladder incisions," can be made anterior and posterior in the mesentery or windows within the mesentery (Fig. 9.4) [18]. Finally, transillumination of the mesentery can identify arcades providing points of safe mesenteric vessel transection, again enabling further lengthening of the mesentery for additional reach of the ileal reservoir for anal anastomosis [19]. A recent cadaveric and angiographic study using fresh human cadavers examined various mobilization techniques and mesenteric division strategies for gaining length for ileal pouch anastomotic construction. This study validated the effectiveness of step ladder incisions technique [20].

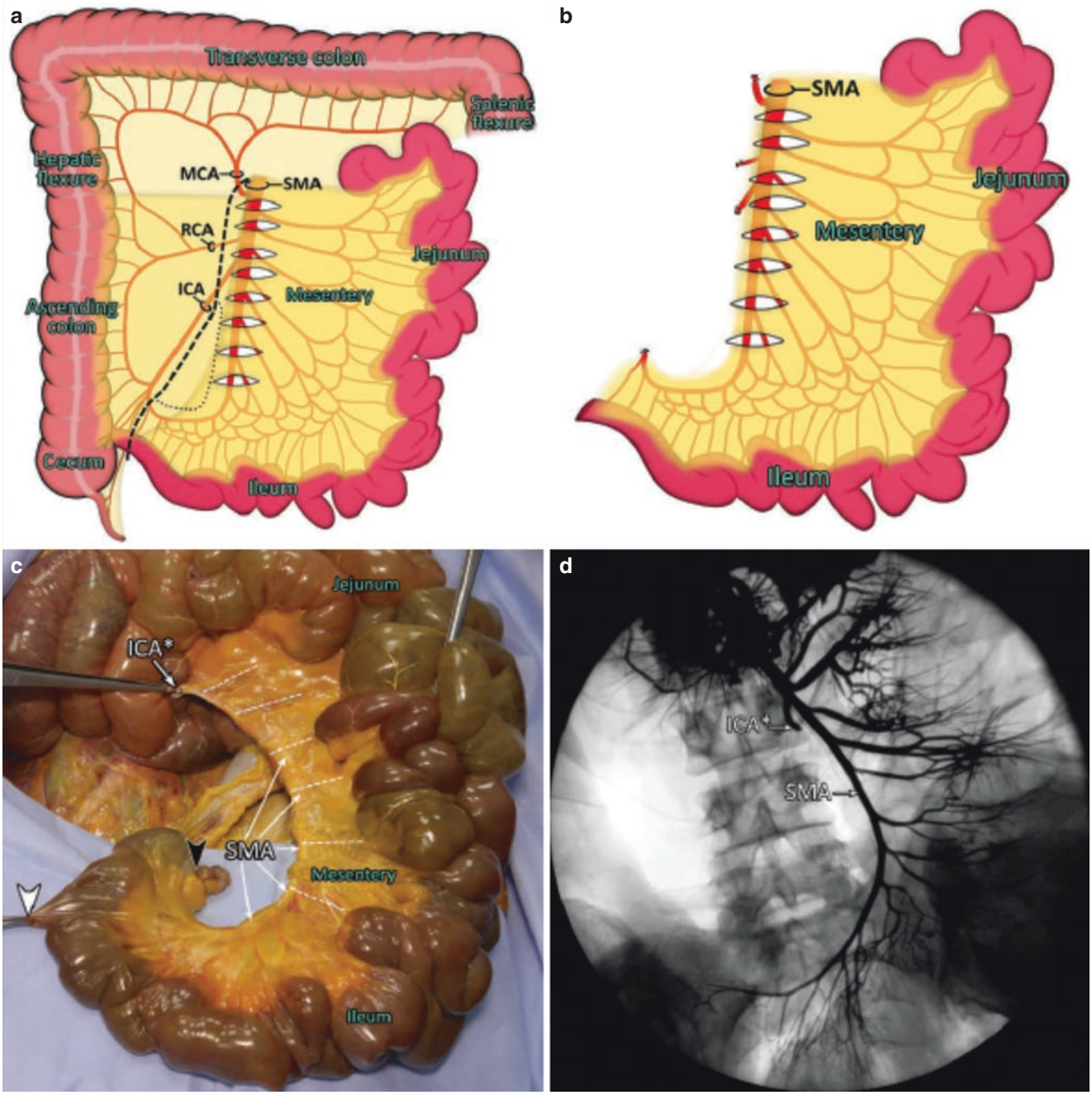

Fig. 9.4 Mesenteric lengthening 1. (**a**) incision of mesocolon and ligation levels of colic vessels during proctocolectomy are included by dashed line. Stepladder incisions are shown on the mesentery. (**b**) Appearance of the small intestine mesentery after proctocolectomy, and mesenteric lengthening is demonstrated. (**c**) Relaxing transverse incisions made on the small intestine mesentery are shown on the cadaver by dashed lines. The SMA and its ileal/jejunal branches in the mesentery were visualized by injecting diluted barium sulfate (white arrowhead, apex of the pouch; black arrowhead, transection point of the terminal ileum). (**d**) Angiographic image of the SMA and branches after mesenteric lengthening is shown. *Ligated vessels; ICA, ileocolic artery; MCA, middle colic artery; RCA, right colic artery; SMA, superior mesenteric artery. (Reused with permission from Ismail et al. [18]. Copyright © 2018 Wolters Kluwer)

Colonic Mobilization

Mobilization is a central issue for resections involving the left side of the colon and rectum. This is because one end of the anastomosis is essentially anatomically fixed [13]. A critical skill for the intestinal surgeon must be mastery of proximal mobilization of the residual left and more proximal colon following left-sided or rectal resection. Essentially, anastomotic construction requires full anatomic dissection and mobilization of the left colon. Whether or not splenic flexure mobilization is necessary for left-sided colonic resec-

tion or low anterior resection is often debated. What should not be debated, however, is the necessity of mastering this maneuver so that when called upon one can perform precise execution with proficiency.

Splenic Flexure Mobilization

This requires sophisticated knowledge of and operative technique for dissection of the anatomic tissue planes and division of embryologic adhesions (Fig. 9.5). The major steps include dissection of the left colon and transverse colon mesenteries completely off the retroperitoneum back to the midline aorta. Attachments to the kidney, stomach, spleen, and inferior border of the pancreas are divided, mobilizing the mesentery back to the inferior mesenteric vein.

High ligation of the inferior mesenteric artery provides upwards of 10 cm of additional length when compared to low ligation [21]. Division of the inferior mesenteric vein at the base of the pancreas produces substantial length [21]. This is an essential step to obtain adequate mobilization and mesenteric length for low pelvic anastomosis (Fig. 9.6).

Maximal mobilization can be further gained by mobilization of attachments to the pancreas beyond the inferior mesenteric vein, as the axis can be further shifted well to the right of the ligament of Treitz to where the middle colic artery arises (Figs. 9.7 and 9.8a, b). Complete dissection of the omentum off of the transverse colon—essentially separating the gastrocolic ligament—enhances release.

Finally, there often exists a hinge-like embryologic conformation of the mesentery of the splenic flexure that must be divided or released to straighten the mesentery (Fig. 9.9). This "unhinges" the angled conformation of the bowel at the splenic flexure (Figs. 9.10, 9.11, and 9.12) and creates a straightened mesentery and splenic flexure that can then descend (Figs. 9.13 and 9.14a, b) in a straight line from the middle colic vessels. This enables the descending colon conduit to reach well below the symphysis pubis to achieve a tension-free anal anastomosis.

Again, while some may choose to debate its necessity in all cases of low anterior resection [22], it would be folly to question the value of possessing the skill to perform full mobilization of the splenic flexure and familiarity with specific details for straightening the left colon [23]. While it is generally accepted that anastomotic leak following low anterior resection appears to correlate with decreasing anastomotic height—that is, the lower the anastomosis the higher the leak rate—master surgeons are able to defy such trends. Remarkably low rates of leak with left-sided anastomoses can be achieved consistently irrespective of anastomotic level [24], and the senior author of this series suggests that the key to low pelvic anastomosis is complete splenic flexure mobilization (personal communication).

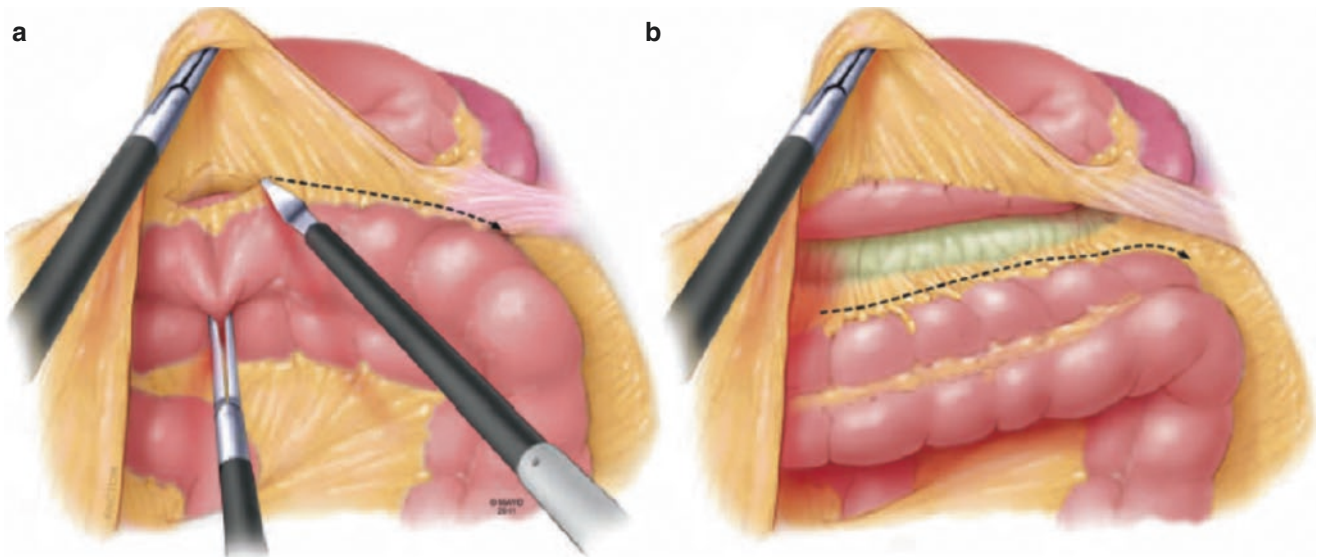

Fig. 9.5 Mobilization of splenic flexure, medial to lateral approach. The greater omentum is reflected superiorly and a transverse incision is made along the gastrocolic ligament releasing the transverse colon and entering the lesser sac. Care must be taken to avoid dissection posterior to the pancreas, where troublesome bleeding may occur. As dissection continues laterally, the renocolic and splenocolic ligaments are divided, as well as any other retroperitoneal attachments of the flexure. The spleen often remains out of view with this approach. (Reused with permission Merchea et al. [93]. Copyright © 2012 John Wiley and Sons)

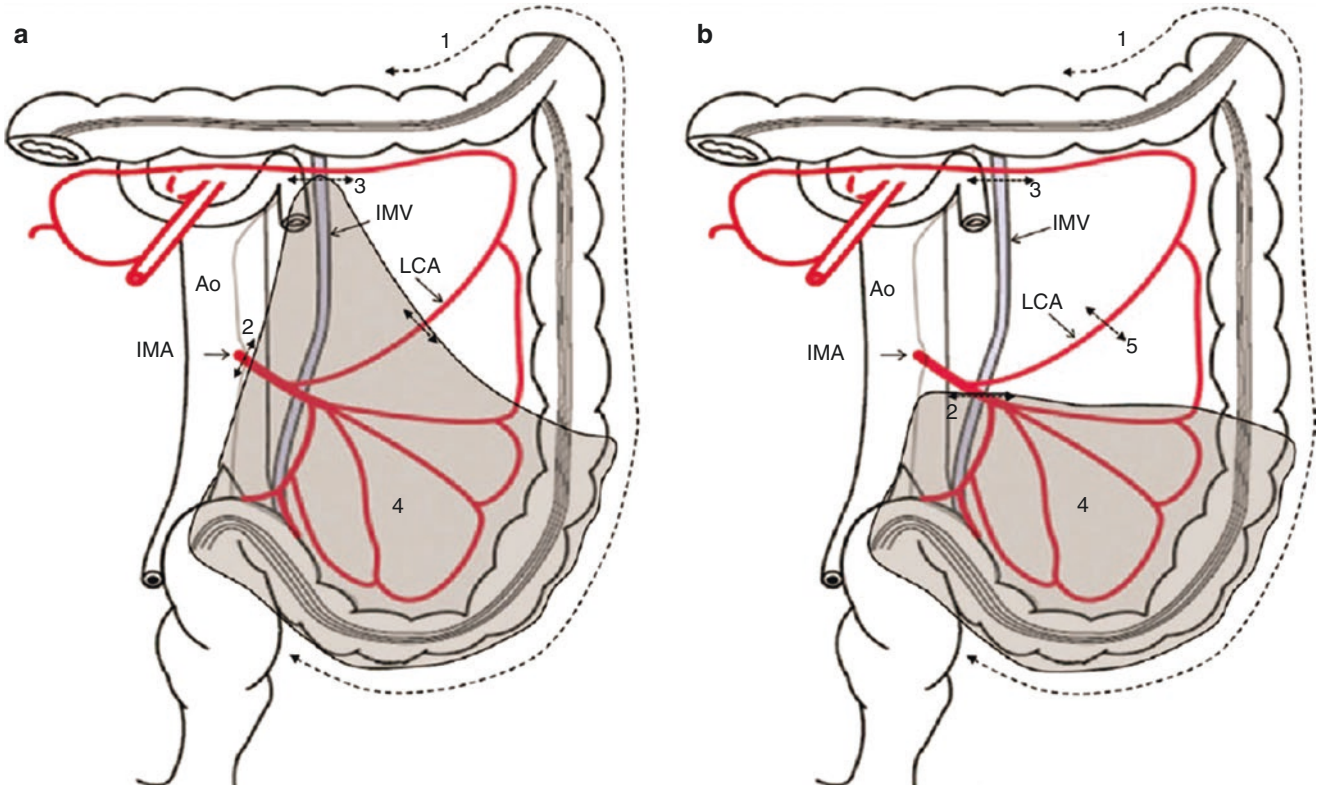

Fig. 9.6 View of the two procedures performed. High tie on left (**a**). Low tie on right (**b**). A, HT. Step 1, mobilization of the splenic flexure, descending colon, and sigmoid to the rectosigmoid junction; step 2, IMA division at its origin 1 cm distant from the aorta; step 3, IMV division at the lower part of the pancreas; step 4, sigmoidectomy with appropriate lymphadenectomy, including section of LCA. B, LT. Step 1, mobilization of the splenic flexure, descending colon, and sigmoid to the rectosigmoid junction; step 2, division of the IMA and IMV 1 cm distally to the origin of the LCA; step 3, IMV division at the lower part of the pancreas; step 4, sigmoidectomy with appropriate lymphadenectomy; step 5, secondary division of LCA; HT, high tie; LT, low tie; Ao, aorta; IMA, inferior mesenteric artery; LCA, left colic artery; IMV, inferior mesenteric vein; dimmed area, extent of resection. (Reused with permission [21]. Copyright © 2012 Wolters Kluwer)

Special Mobilization Techniques

In some instances involving extended resections of the left and transverse colon, or in cases of reoperation where prior left-sided resections have previously taken place, advanced mobilization techniques are available to bring bowel ends into proximity for anastomotic construction. Repeat low anterior resection often requires consideration for extraordinary mobilization to achieve anastomotic construction [25].

Retroileal Anastomosis or Ileal Mesenteric Window

First described by Toupet, the transverse colon can go underneath the small bowel through a surgically created "window" in the small bowel mesentery between the superior mesenteric artery and the ileocolic artery (Fig. 9.15) [26]. The maneuver requires complete splenic flexure mobilization to the root of the middle colic artery, dissecting the transverse colon mesentery at its root allowing the mesentery to pivot at the most proximal extent. This occasionally requires the cecum to be mobilized off the retroperitoneum as well as the root of the small bowel mesentery to facilitate the mesenteric window creation. Transillumination of the mesentery can be performed to identify the major vessels of the small bowel mesentery [27–29]. There is a bare area between the superior mesenteric artery and the ileocolic artery. A 4–5 cm long defect should easily accommodate the transverse colon and attached mesentery (Fig. 9.15). The mesentery should be straight and parallel to the longitudinal axis of the colon with a preserved marginal artery. The "cut edge" or divided edge of the mesentery of the transverse colon points left as the bowel descends to the right of the aorta through the mesenteric window toward the pelvis (Fig. 9.15a–d). This maneuver has also been performed using the laparoscopic platforms [30–32].

Right Colon De-Rotation (Deloyer's Procedure)

Infrequently, following extended resection, the right colon may be chosen as the conduit for anastomosis to the rectum or anal canal. The conduit blood supply is based upon the ileocolic artery and necessitates dissection to the origin of the ileocolic artery. This provides mobility of the mesentery to rotate without acute kinking of the vessel [33]. The de-rotation can also be described as an inversion of the cecum and terminal ileum [34]. The cecum and attached terminal ileum are rotated along the axis of the ileocolic artery in the sagittal plane, with the cecum moving superiorly and the ascending colon caudally (Figs. 9.16 and 9.17) The dorsal surface of the mesentery and ascending colon become ventral in position following de-rotation (Figs. 9.18, 9.19, and 9.20). Mobility of the mesentery and length of the ileocolic artery can enable reach of the conduit to the low pelvis and even the anal canal for ultra-low anastomosis. Functionally, preservation of colonic reservoir, water-absorptive surface area, and maintenance of the ileocecal valve improves post-operative function [34]. In a series of 48 patients, 67% of patients reported fewer than three bowel movements per day [35]. The maneuver has also been described laparoscopically [36]. In terms of safety, anastomotic leak rates in this series indicate predictable safe anastomotic healing. Appendectomy should be performed given the new location of the cecum in the mid-right side of the abdomen.

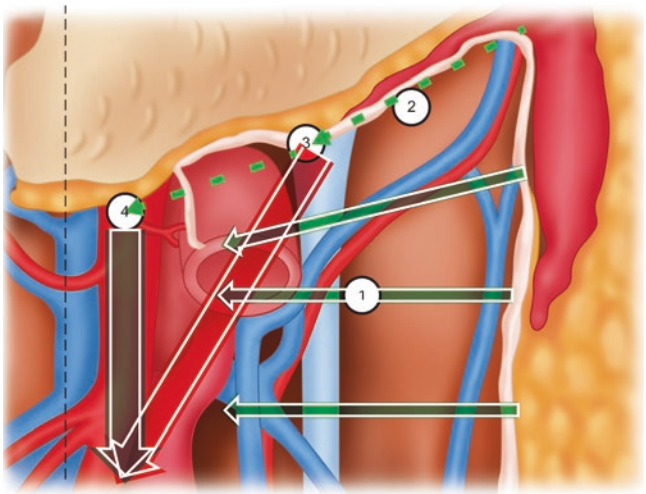

Fig. 9.7 More length obtained after additional mobilization from IMV to the middle colic artery. 1 Mobilize off Gerota's fascia to aorta; 2 Mobilize off inferior border pancrease; 3 Divide IMV; 4 Dissect to the middle colic vessel

Perfusion

One of the central principles of anastomotic construction remains preservation of blood supply and tissue perfusion following mobilization. Again, like tension, this fundamental concept seems empirical. Mastery of mesenteric anatomy, precise identification of named vessels, and meticulous dissection technique enable mobilization resulting in well-perfused bowel ends for anastomotic construction. Clinical assessment of bowel for anastomosis is therefore a critical skill. Color, motility, and visible bleeding from the mucosa represent basic means for assessment of the bowel perfusion and viability.

One approach in the case of left colectomy or low anterior resection, for example, is to purposefully dissect and skeletonize the marginal artery at the distal descending colon. The vessel is transected in order to observe brisk pulsatile arterial bleeding prior to precisely performing proximal resection (Fig. 9.21). This clinical assessment of adequate blood supply provides reliable information for anastomotic construction [24]. If such bleeding is not present, one proceeds proximally on the mesentery until brisk arterial inflow is

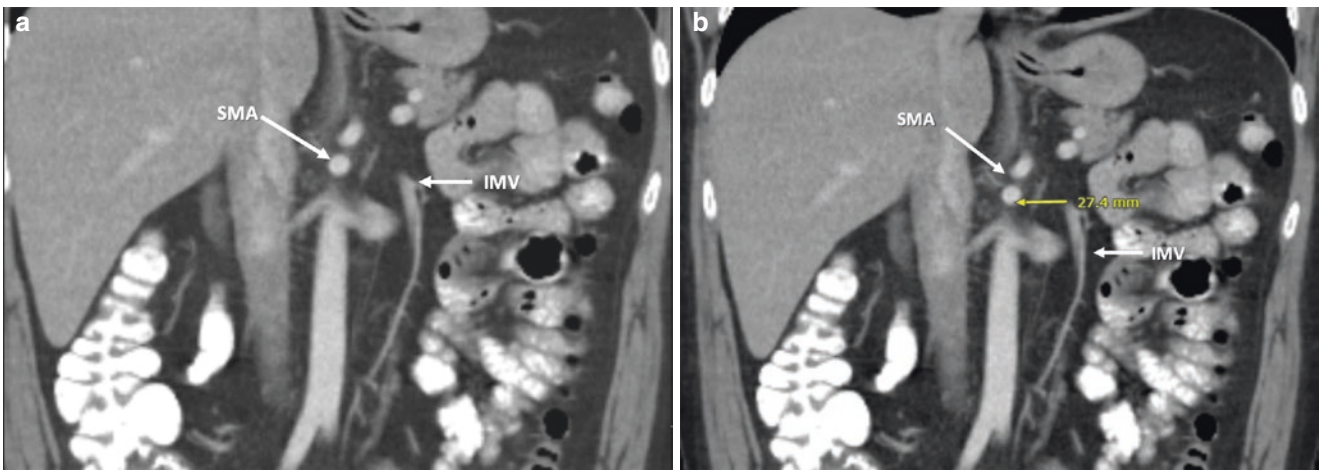

Fig. 9.8 (**a**, **b**) Additional distance mobilizing to the SMA/middle colic vessels

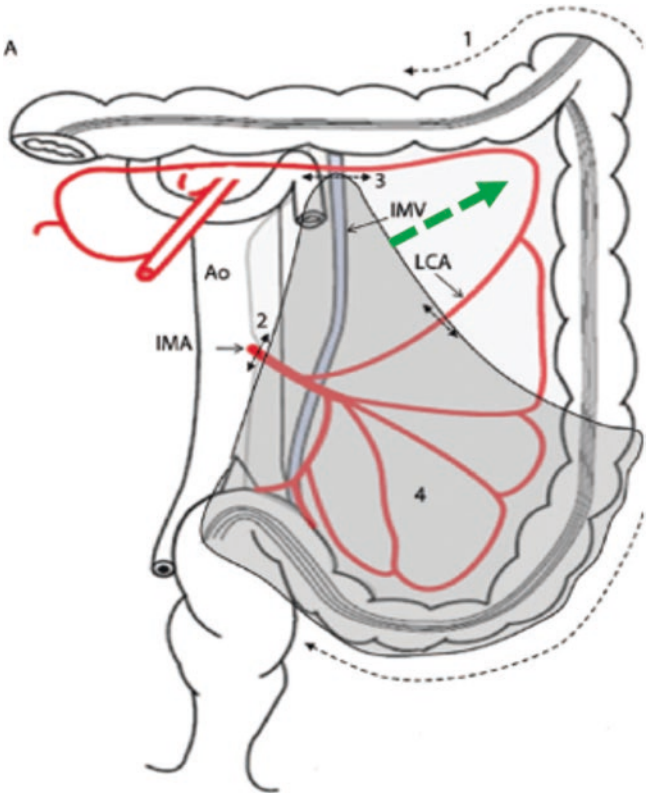

Fig. 9.9 LT. Step 1, mobilization of the splenic flexure, descending colon, and sigmoid to the rectosigmoid junction; step 2, division of the IMA and IMV 1 cm distally to the origin of the LCA; step 3, IMV division at the lower part of the pancreas; step 4, sigmoidectomy with appropriate lymphadenectomy; step 5, secondary division of LCA. Green arrow indicates incision of mesentery releases splenic embryologic conformation and straightens distal transverse colon and left colon; HT, high tie; LT, low tie; Ao, aorta; IMA, inferior mesenteric artery; LCA, left colic artery; IMV, inferior mesenteric vein; dimmed area, extent of resection. (Reused with permission [21]. Copyright © 2012 Wolters Kluwer). Schematic correlating to images in Figs. 9.10, 9.11, and 9.12

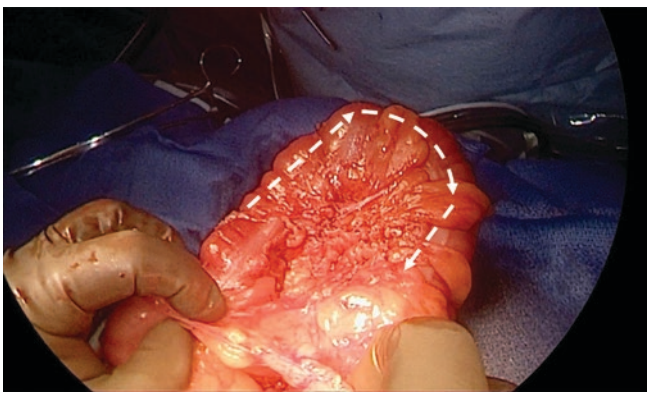

Fig. 9.10 Splenic flexure 180-degree conformation – due to residual omental adhesion. (Photos courtesy of HDV)

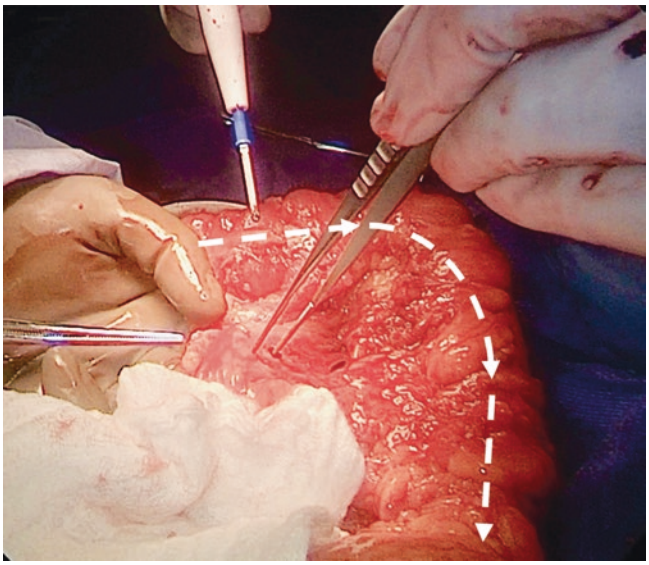

Fig. 9.11 Splenic flexure 90-degree conformation

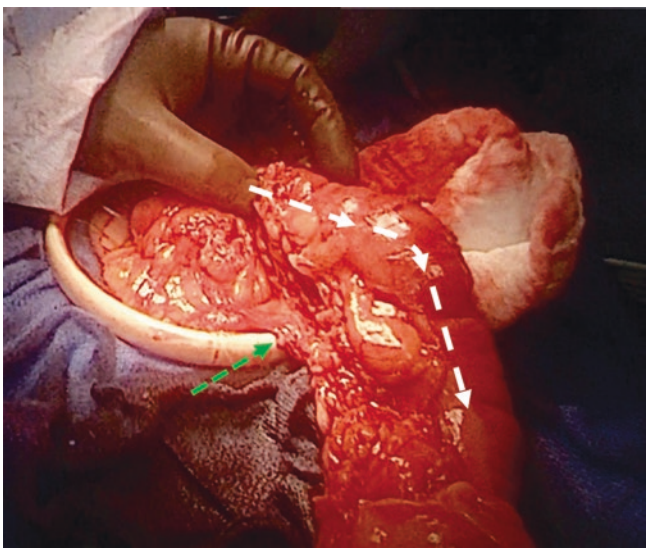

Fig. 9.12 Splenic flexure released and straightened. Green arrow indicates point of relaxing incision of mesentery up to marginal artery

present; this would identify the appropriate point of proximal bowel division. The value of clinical assessment cannot be overstated, and experience would indicate that it is reliable for anastomotic construction [24].

Indocyanine green fluorescence angiography is an intraoperative technique that is increasingly used to assess viability of the intestinal bowel during anastomotic construction (Fig. 9.22) [37–39]. ICG absorbs near-infrared (NIR) light at 800 nm and emits fluorescence. As ICG binds extensively to plasma proteins and is confined to the intravascular com-

partment, tissue microperfusion is indicated by the presence of fluorescence [40]. This technique has been employed during both open and minimally invasive surgery operations. Although the test is a subjective assessment and not yet routinely quantitative, additional information can be obtained to assess perfusion. The PILLAR II trial was a prospective multicenter clinical trial evaluating the utility of ICG fluorescence. Decisions regarding proximal resection were altered in 8% of cases [41]. Additional studies are necessary to determine if anastomotic leak can be reduced based on its use [42]. ICG may prove to be a useful adjunct to clinical assessment and provide means for confirming more precise resection of nonviable bowel, thereby confirming surgical decision making critical to anastomotic construction.

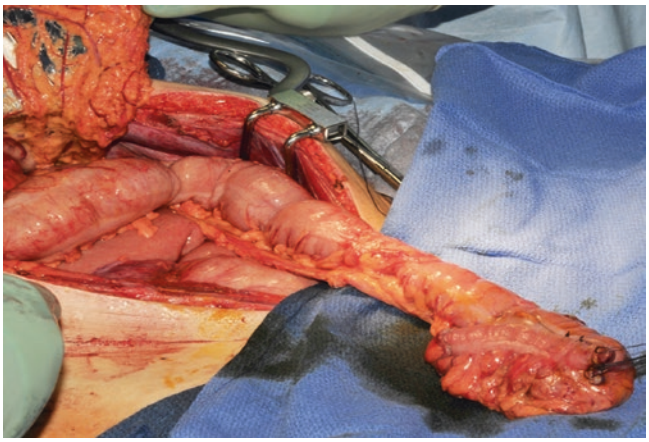

Fig. 9.13 Straight descent of colon with attached mesentery—arrow denotes relaxation of mesentery of the splenic flexure. (Photo courtesy of HDV)

Anastomosis Configuration

The configuration of anastomosis refers to the form in which the bowel ends relate to one another. End-to-end anastomosis, end-to-side, side-to-end, and side-to-side anastomoses are the general anastomotic configurations described. Choice of configuration is often a matter of pragmatism. Certain configurations are technically practical, physically sensible, and aesthetically more pleasing. The configuration should restore continuity in a manner that does not create tension on the mesentery or on the physical union of the bowel ends. It is important to consider that anastomoses are constructed with the patient supine. In the upright position, the mesentery and attached bowel will be affected by gravity, thereby impacting anastomotic construction and possibly tension.

Small bowel anastomosis can be performed end-to-end or side-to-side. The side-to-side anastomosis can be in the configuration of the traditional antiperistaltic functional end-to-end or it can be made in isoperistaltic fashion.

Following right colectomy, size discrepancy of the bowel must be addressed if an end-to-end anastomosis is chosen. This can be accommodated by performing a Cheatle slit along the antimesenteric aspect of the smaller bowel to then match the size of the larger bowel for end-to-end anastomosis (Fig. 9.23). Another way to compensate for size discrepancy is to perform a side-to-side anastomosis. An example of this is anastomosis between the ileum and the transverse colon following right colectomy. Classically, the two ends of bowel are aligned in antiperistaltic fashion (Fig. 9.24a–d) with anastomosis performed at the antimesenteric aspect of the bowel. Side-to-side can also be performed in isoperistaltic configuration (Fig. 9.25), and this method has been gaining popularity with minimally invasive surgical techniques.

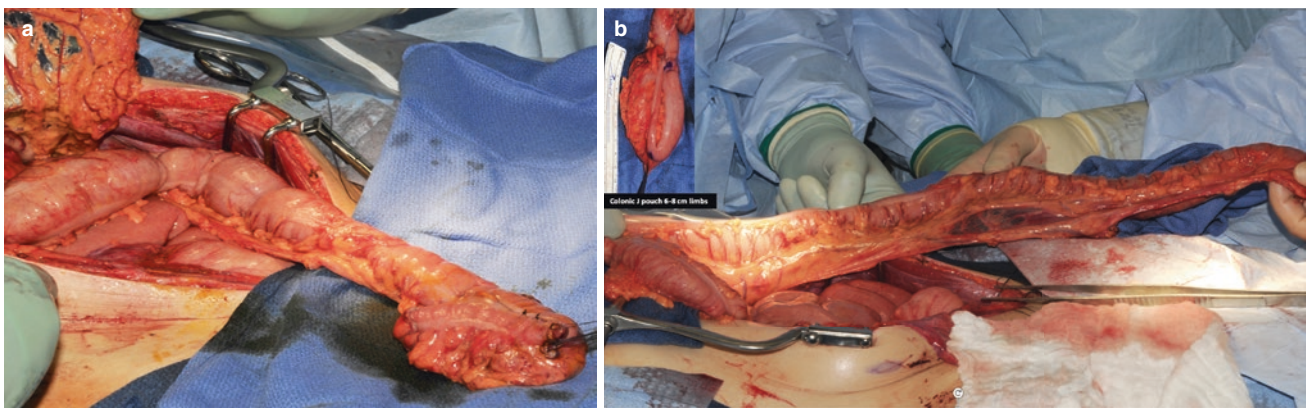

Fig. 9.14 (**a**) After resection, a straight length of colon from transverse colon to descending colon after resection easily resulting in (**b**) colon J-pouch and hand-sewn anastomosis. (Photo courtesy of HDV)

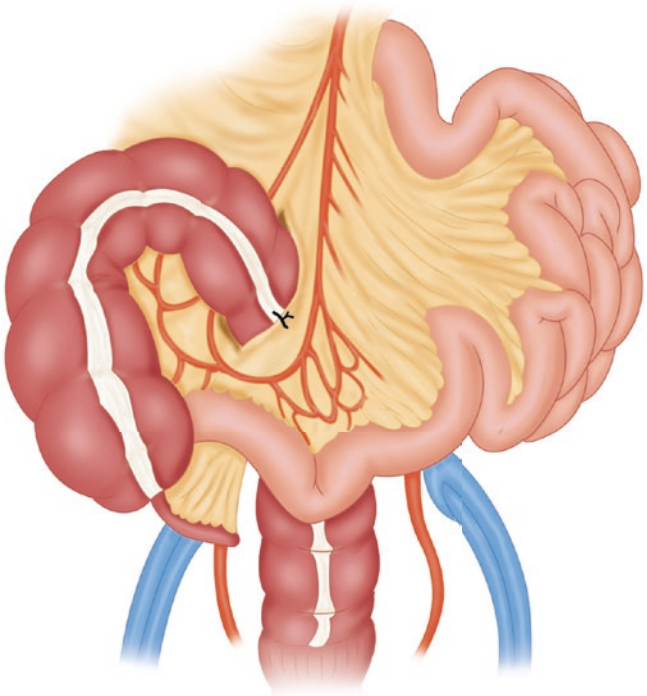

Fig. 9.15 Illustration of the Ileal mesenteric window between the superior mesenteric artery and the ileocolic artery

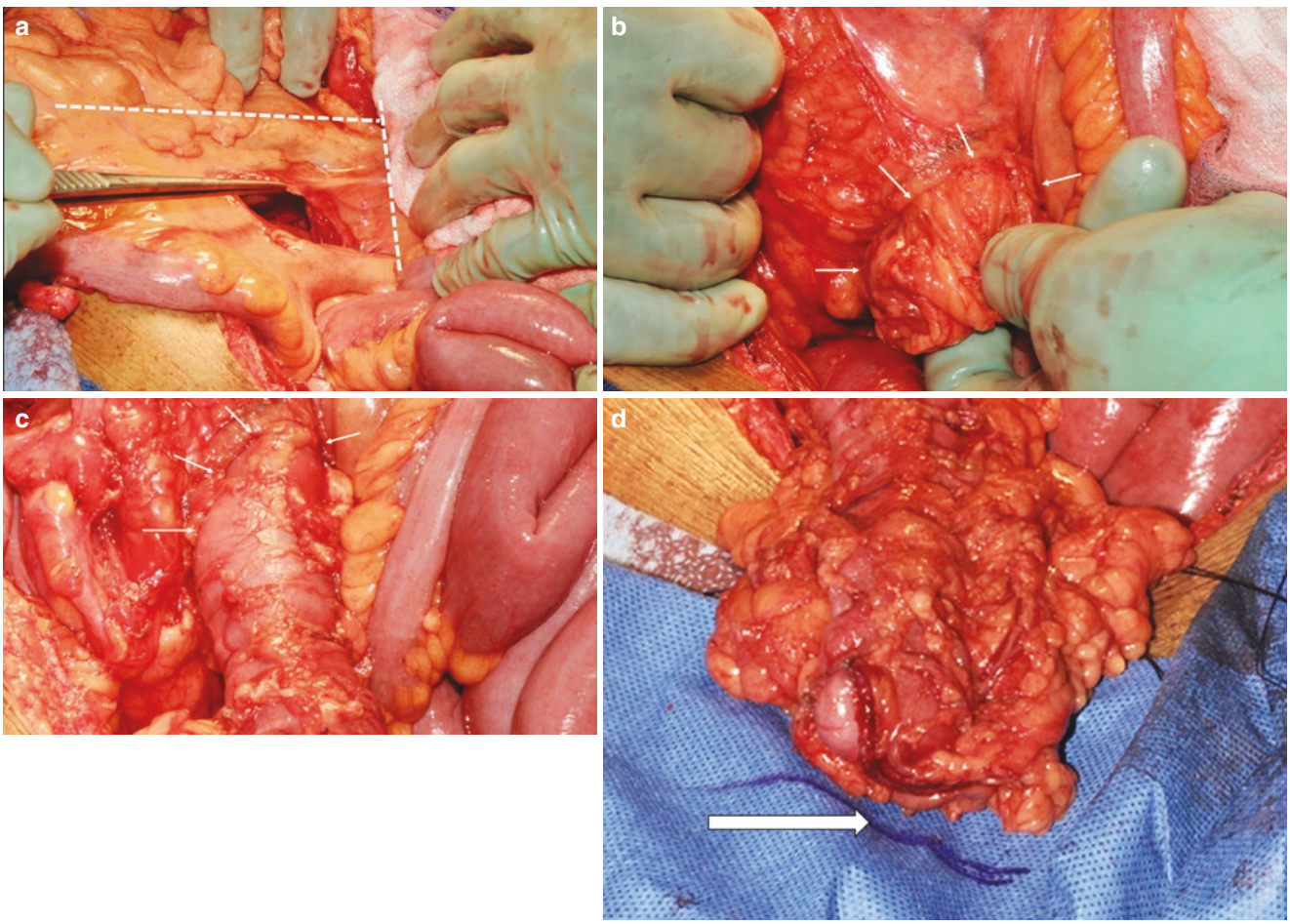

Fig. 9.16 (**a**) Mesenteric window. (**b**) Transverse colon. Arrows delineates mesenteric defect through which transverse colon passes. (**c**) Transverse colon traverses window. Arrows delineates mesenteric defect through which transverse colon traverses. (**d**) Transverse colon after retroileal window. Arrow denotes inferior aspect of symphysis pubis for coloanal anastomosis. (Photos courtesy of HDV)

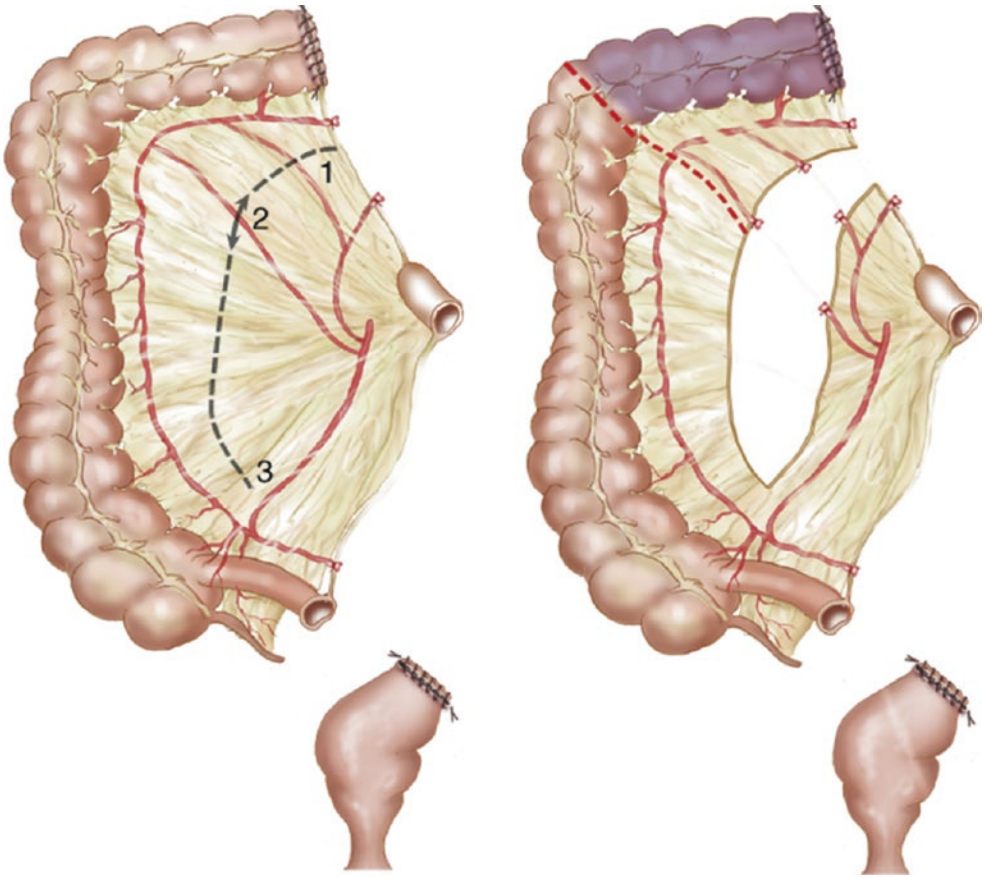

Fig. 9.17 Middle colic and right colic arteries divided likely requiring sacrifice additional portion transverse colon. Ascending colon supplied by ileocolic artery. Dissection of right colon mesentery off retroperitoneum to SMA. (Reused with permission [33]. Copyright © 2018 Elsevier)

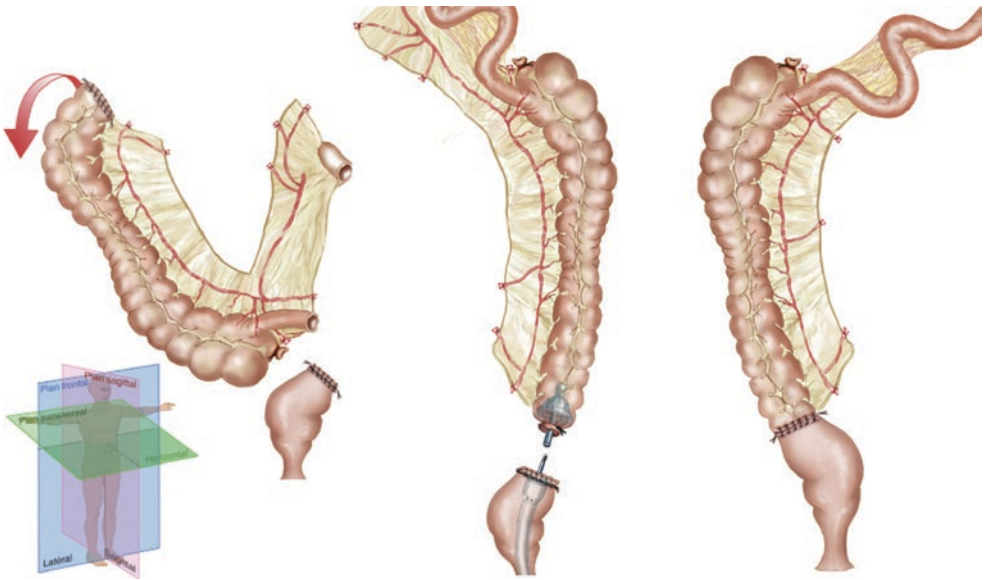

Fig. 9.18 Appendectomy performed. Right colon mesentery rotated in the sagittal plane counterclockwise with cecum placed in the right upper quadrant and ventral surface of right colon now dorsal. Ileum enters cecum from left to right. (Reused with permission [33]. Copyright © 2018 Elsevier)

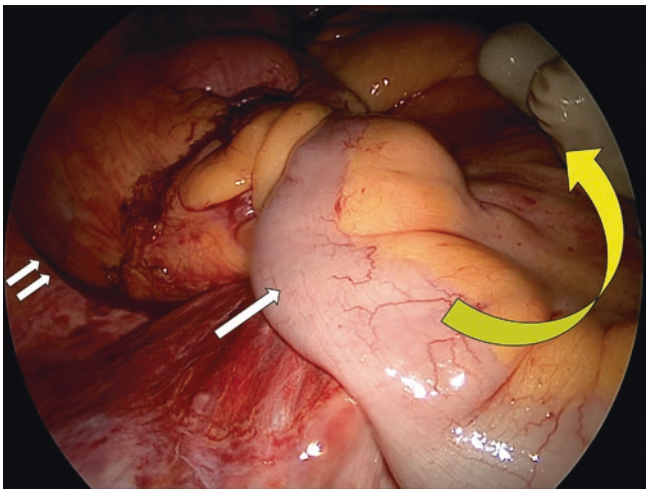

Fig. 9.19 Double arrow – cecum. Single arrow – terminal ileum. View of ileocolic junction prior to de-rotation. Yellow arrow denotes anticipated movement upon de-rotation in sagittal plane. (Photo courtesy of HDV)

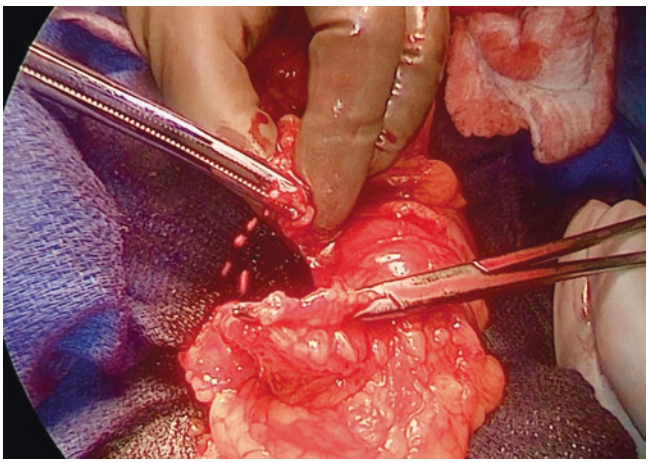

Fig. 9.21 Clinical assessment of perfusion of bowel for anastomosis. Pulsatile arterial bleeding from divided marginal artery. (Photo courtesy HDV)

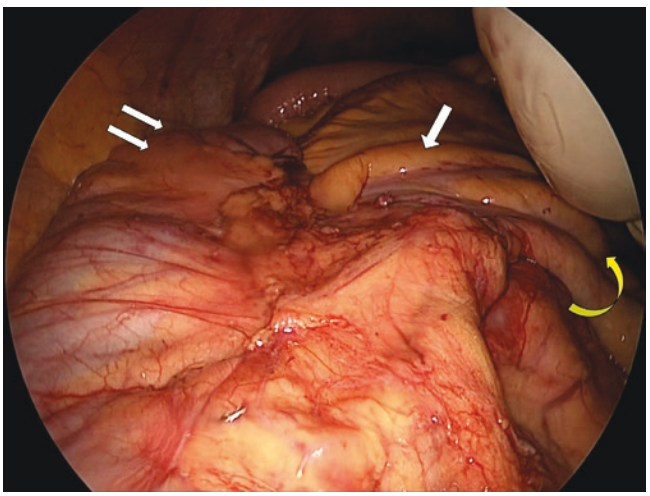

Fig. 9.20 Dorsal surface of colon and mesentery now ventral following de-rotation in sagittal plane. Double arrow – cecum now in right upper quadrant. Single arrow – terminal ileum. Yellow arrow – denotes rotation of ileocolic pedicle and mesentery in sagittal plane. (Photo courtesy HDV)

Finally, size discrepancy can be addressed by an end-to-side or side-to-end configuration (Fig. 9.26). The advantage to an end ileum to side of transverse colon is that this can be performed utilizing circular stapler without any intersecting staple lines (Figs. 9.27, 9.28, and 9.29).

A relatively recent novel anastomotic configuration is the Kono-S anastomosis configuration. This technique was described as a specific method for anastomosis in the treatment of Crohn's disease. It is a variation of a side-to-side configuration that involves the antimesenteric side of both portions of bowel. The bowel is divided proximally and distally resecting the involved Crohn's disease. The mesentery of the bowel to be resected is divided directly adjacent to the mesenteric edge of the bowel, thereby preserving blood supply and enteric nerves [43]. The bowel is transected with staplers placed transversely across the intestine wall perpendicular to the mesentery. The ends of the divided bowel are sutured together acting as a "column," excluding the anastomosis from the mesentery. The antimesenteric aspect of each portion of bowel is opened longitudinally and the anastomosis is performed transversely in Heineke-Mikulicz fashion (Figs. 9.30 and 9.31). Cohort studies demonstrate acceptable safety when compared to traditional side-to-side anastomosis and this technique has been associated with a lower incidence of recurrent disease [44, 45].

In the case of extended right colectomy with anastomosis to the distal third of the transverse colon, mobilization of the splenic flexure reduces the distance the ileum must traverse in spite of the mobility of the intraperitoneal ileum. In this case, isoperistaltic side-to-side appears to be advantageous. When subtotal colectomy is performed, one can mobilize the sigmoid colon and transpose it to the right lower quadrant and hypogastrium. Then, ileal to sigmoid colon anastomosis side-to side-configuration can be performed with the ileum resting in the native or in vivo position (Figs. 9.32 and 9.33).

Colocolonic anastomosis is rare. Splenic flexure tumors can present technical challenge in terms of extent of resection and

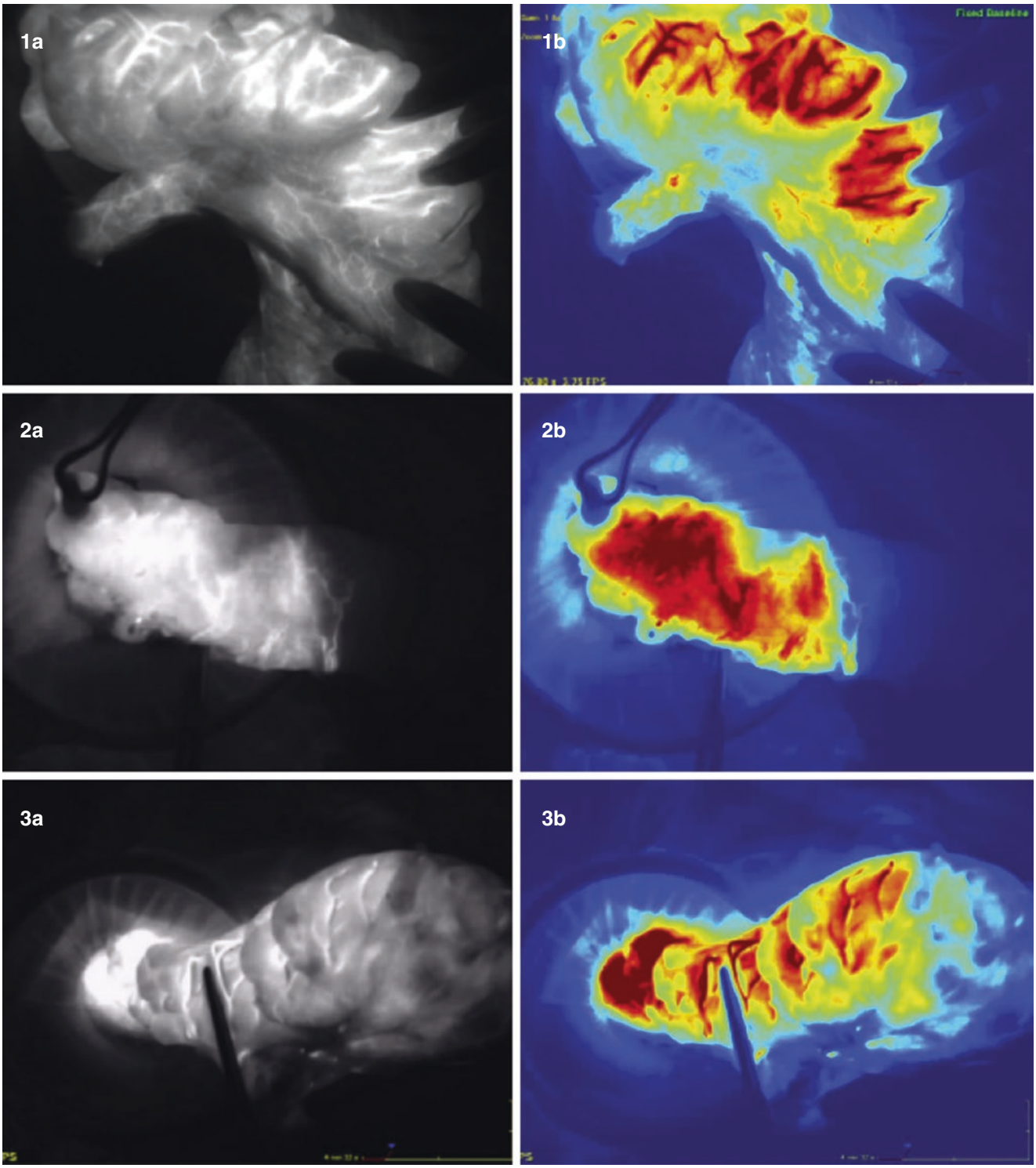

Fig. 9.22 Panels (1**a** and **b**) showed a typical well-perfused left colon during ICG fluorescence angiogram perfusion assessment of the exteriorized left colon without division of the marginal artery. Panels (2**a** and **b**) showed a demarcation of perfusion at where the marginal artery was divided. Panels (3**a** and **b**) showed a perfusion gradient across the exteriorized left colon. (Reused with permission [40]. Copyright © 2019 Elsevier)

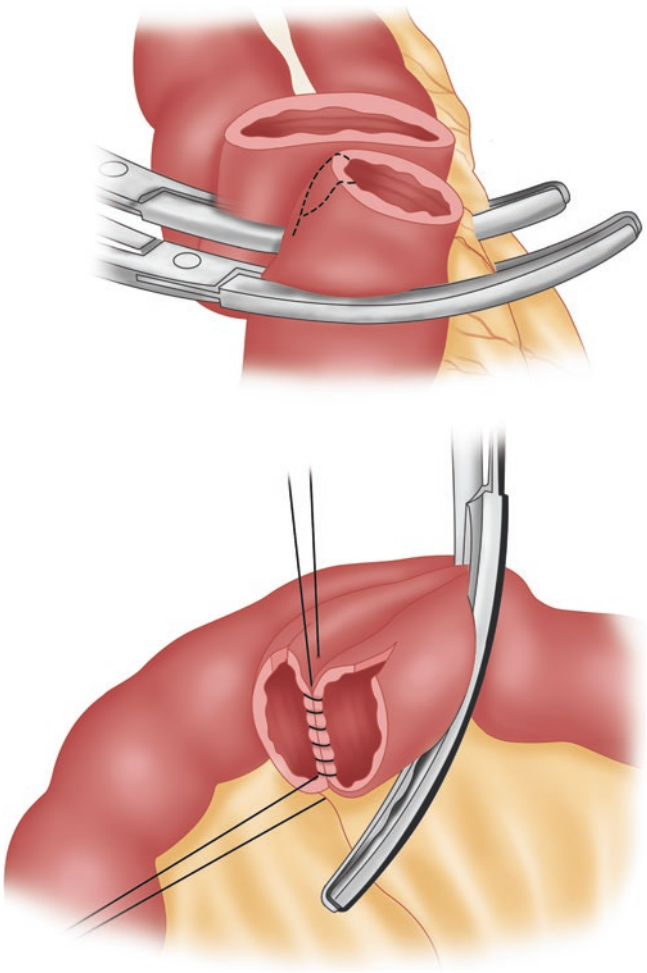

Fig. 9.23 Cheatle slit (anastomotic technique, suture). (Photo courtesy HDV)

the residual bowel present for anastomosis [46, 47]. While the optimal resection may be debatable, splenic flexure resection has been described leaving mid-transverse colon and sigmoid colon for anastomosis. In this instance, side-to-side anastomosis can be performed, but the mesenteric mobility and the more rigid nature of bowel wall do not lend itself well to side-to-side anastomosis. The authors prefer an end-to-end anastomosis as it appears to lay neatly (Fig. 9.34). This can be performed with circular or linear staplers or can be hand-sewn.

Pelvic anastomoses are considered the most challenging technically and can be influenced by unique considerations that may dictate anastomotic configuration. A pelvic end-to-end anastomosis may be necessary as a result of bowel length or surgeon preference. While pelvic reservoirs may be the preference of the surgeon, a narrow pelvic inlet can limit the size of the conduit or proximal bowel that can traverse the pelvic floor for anastomosis. This is most commonly found in the male pelvis or obese individuals. Conversely, that being said, a wide pelvis may easily accommodate either a colonic J-pouch or a side-to-end anal anastomosis should a pelvic reservoir be desired.

Anterior resection or sigmoid colectomy with anastomosis to the upper rectum generally is performed in an end-to-end fashion (Fig. 9.35). Occasionally, size mismatch can make side of colon to end of rectum technically appealing. The same is true for ileorectal anastomosis where one can choose side-to-end versus end-to-end reconstruction.

Low Pelvic Anastomosis

Low pelvic anastomosis can occasionally be limited by reach or size of pelvic inlet. However, functional challenges can result from straight coloanal anastomosis prompting use of reservoir reconstruction. Low anterior resection syndrome can be a debilitating functional consequence of low colorectal or coloanal anastomosis, affecting quality of life of patients following treatment for mid to low rectal cancer.

Pelvic reservoirs such as the colonic pouch (Fig. 9.36) or the side-to-end anastomosis with 5 cm efferent colonic end (Fig. 9.37) appear to provide functional benefit in regard to stool frequency and urgency [48–51, 52]. Some argue that by 2 years after surgery, the function of a straight anastomosis ultimately will approximate that of a colonic J-pouch [53, 54]. Other series indicate that colonic pouch continues to provide functional advantage even at 5 years [6, 48, 55]. Even if a straight anastomosis achieves equivalency at 24 months, a patient suffering from LAR syndrome for 24 months can be so discouraged that they elect to return to a stoma. Poor function is second only to anastomotic leak as a cause for conversion from an existing low pelvic anastomosis to permanent colostomy [56, 57]. In any case, a colonic reservoir like a J-pouch does not by itself obviate the possibility of LAR syndrome and upwards of 30% of patients may still experience increased frequency and urgency.

Some have concerns about the increased complexity of reconstruction with a colonic pouch and the additional staple line. A recent ACS-NSQIP study revealed that colonic J-pouch compared to straight anastomosis was associated with fewer reoperations, organ space infection, and increased ICU usage [58]. In general, in regard to anastomotic leak colonic J-pouch anal anastomosis compares favorably to straight anastomosis in spite of the perception of a more complex anastomosis [50, 59, 60]. The anastomosis is side-

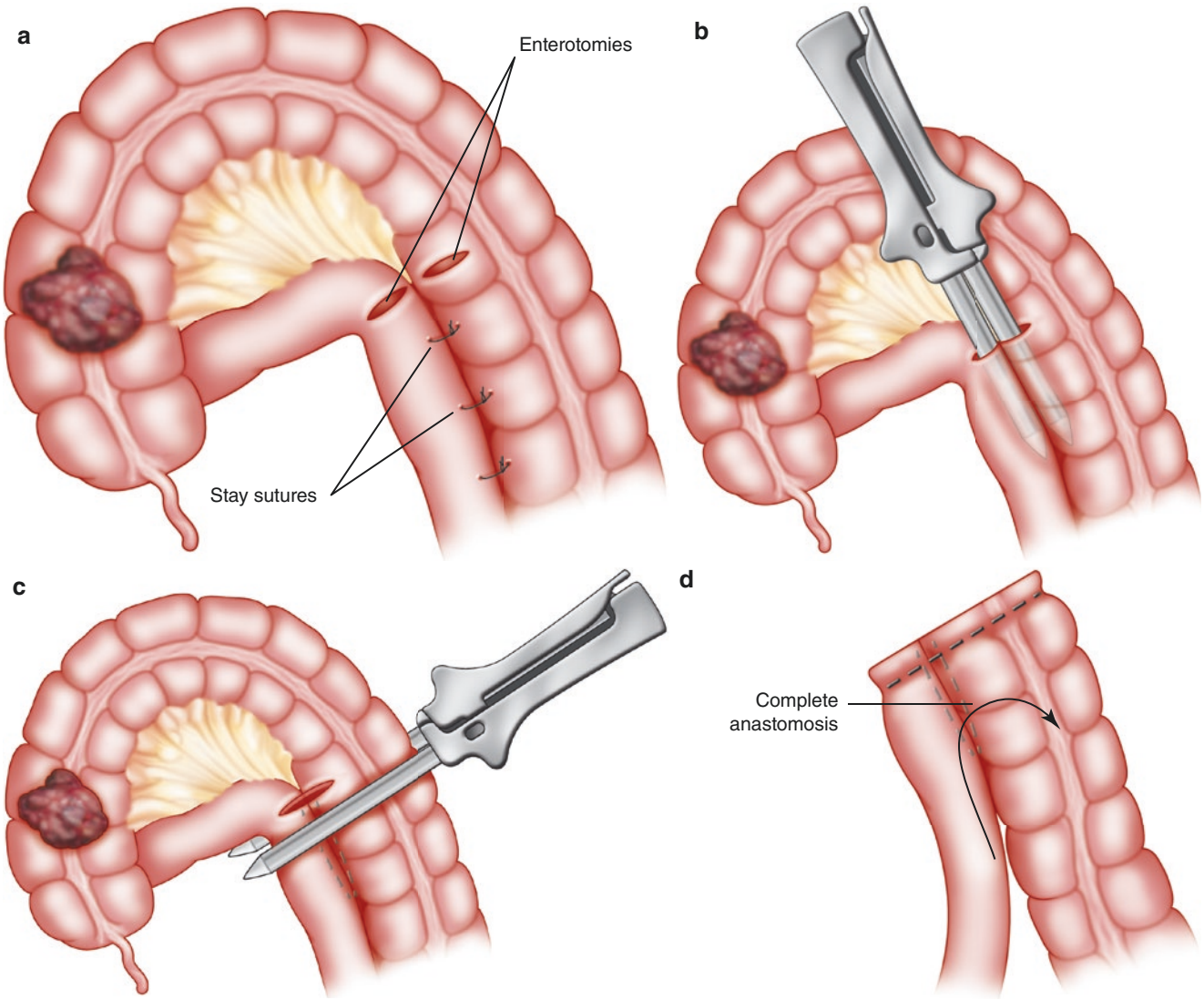

Fig. 9.24 Barcelona anastomosis: (**a**) Stay sutures are placed and two antimesenteric enterotomies are made. (**b**) A linear stapler is used to construct the common wall. (**c**) An additional firing of the linear stapler is used to complete the anastomosis and resect the specimen. (**d**) Completed anastomosis. (Reused with permission from Hunt SR, Silviera ML. Anastomostic construction. Steele et al. [94]. Copyright © 2016 Springer Nature)

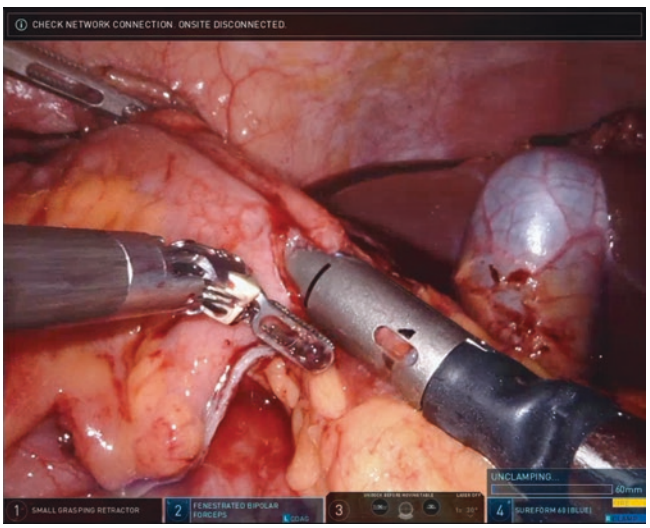

Fig. 9.25 Robotic isoperistaltic side-to-side ileal—transverse colon anastomosis. (Photo courtesy of Drew Gunnells, MD)

to-end with more reliable perfusion of the proximal aspect of colon conduit compared to the end of colon. The mass of the mesentery resulting from the side-to-side pouch construction fills the dead space of the presacral area of the pelvis, further reducing areas for fluid accumulation, which theoretically assists in reducing pelvic sepsis.

All of these features are shared by the side of colon to end of anorectum reconstruction (STE; "Baker-type anastomosis"). A technical aspect is that the efferent limb distal to the STE anastomosis should be 5–6 cm long. Compared to a colonic J-pouch, the bowel function appears equivalent [61, 62] and is superior to a straight anastomosis [60]. In terms of morbidity, there is no difference when compared to a colonic J-pouch. STE, however, may be faster to perform than a colonic pouch [61, 62]. The additional time to construct a neorectal reservoir should be balanced against the potential long-term benefits.

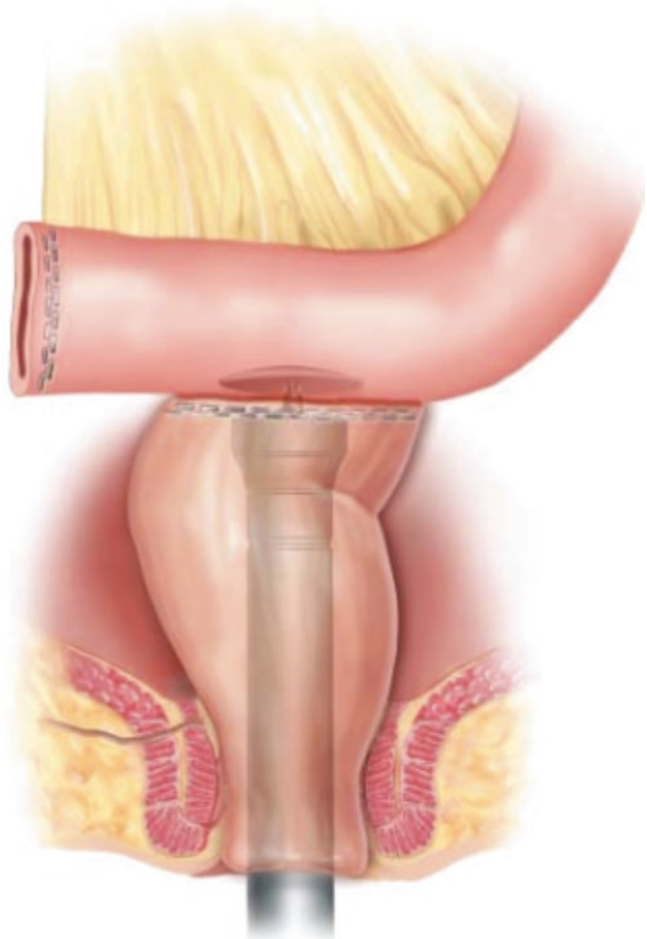

Fig. 9.26 Stapled end-to-side ileorectal anastomosis. (Reused with permission from Wexner SD, Fleshman JW, eds. Colon and Rectal Surgery: Abdominal Operations. Wolters Kluwer, 2018. Copyright © 2018 Wolters Kluwer)

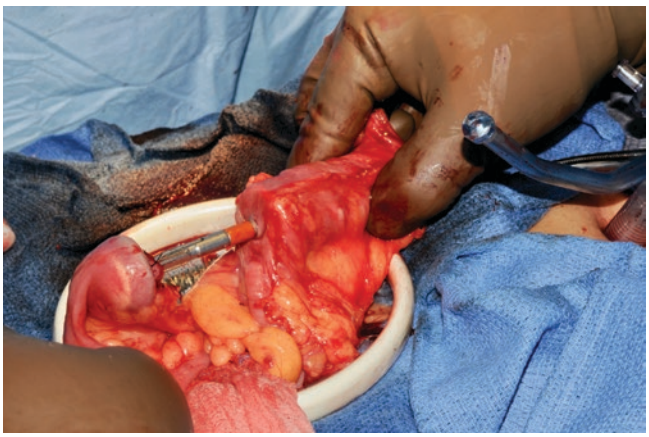

Fig. 9.27 End-to-side ileocolonic anastomosis after right colectomy. (Photos courtesy of HDV)

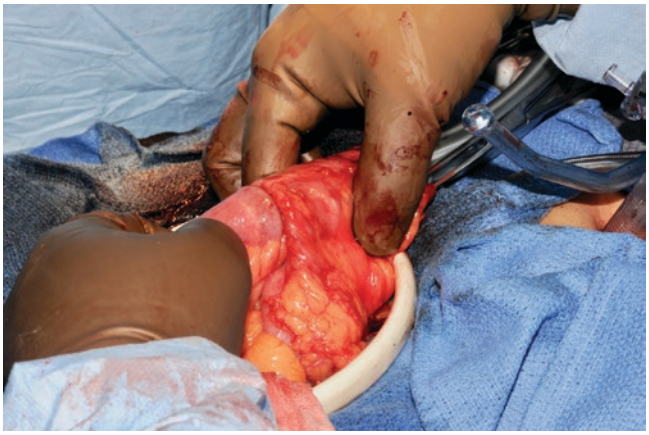

Fig. 9.28 End-to-side ileocolonic anastomosis after right colectomy. (Photos courtesy of HDV)

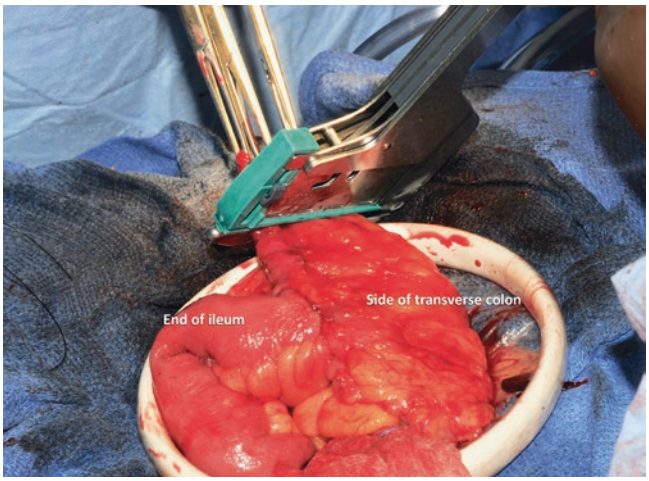

Fig. 9.29 Completed end-to-side ileocolonic anastomosis after right colectomy. (Photo courtesy of HDV)

Methods for Anastomotic Construction

Multiple methods of anastomotic construction exist but can be broadly divided into hand sewn or stapled. In some respect, this is naïve as more often than not both major methods are combined to greater or lesser degrees. A two-layered hand-sewn intestinal anastomosis may first be preceded by bowel transection with linear cutting staplers. Similarly, a robotic isoperistaltic side-to-side small bowel to colon anastomosis following right colectomy often involves hand-suturing the common defect closed. While technique and method often can seem to be polarized, the reality is that anastomotic construction techniques require understanding and mastery of both major categories.

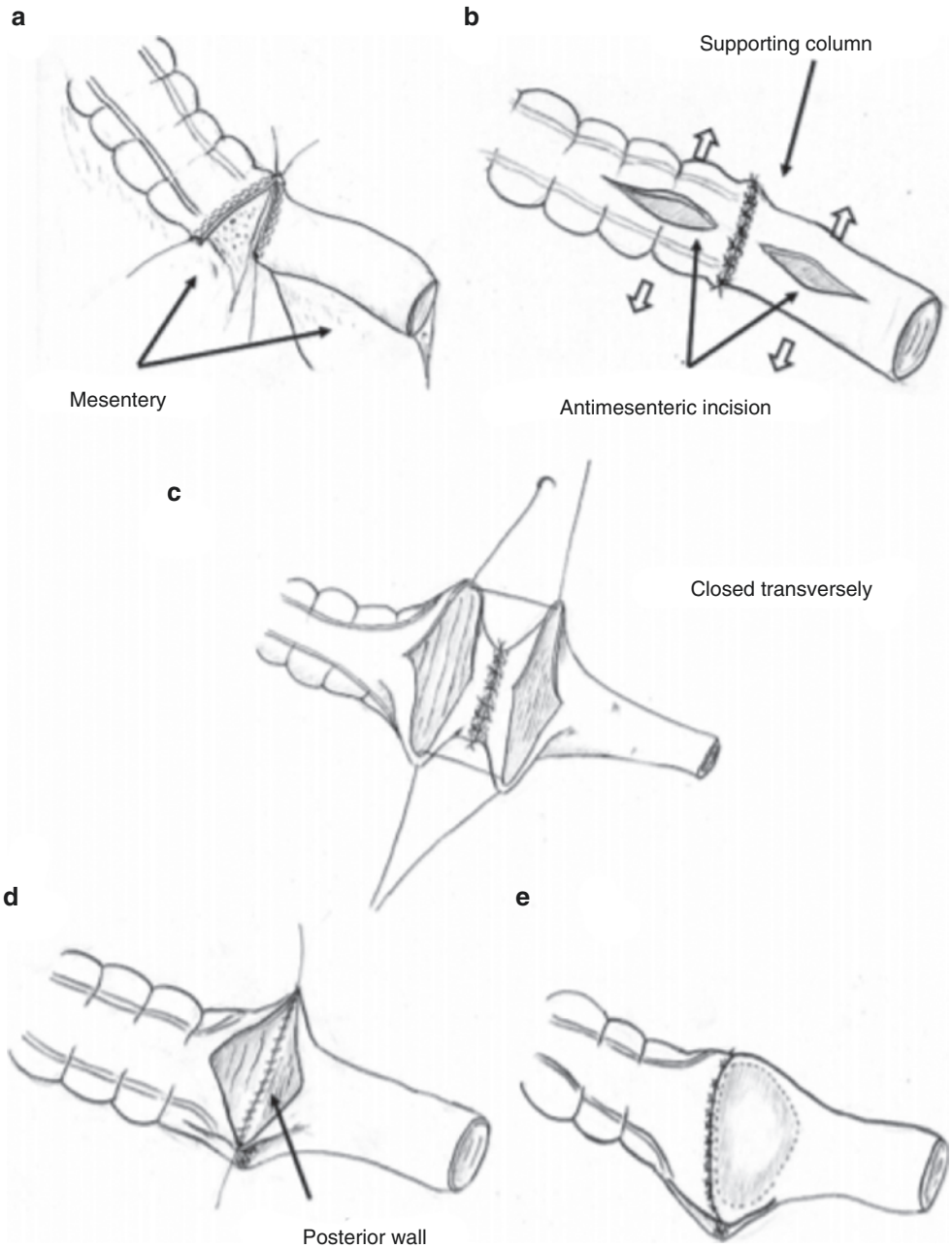

Fig. 9.30 Kono-S anastomosis for Crohn's disease. (**a**) The bowel was divided with a linear stapler perpendicular to the mesentery. Each stapled line was connected and reinforced (supporting column). (**b**) Antimesenteric longitudinal incisions (7–8 cm) were performed on each stump, starting within 0.5–1 cm away from the staple line. (**c**) Antimesenteric orifice was closed transversely. (**d**) Single layer running suture was used as posterior wall. (**e**) Anterior wall was closed in two layers with running and interrupted sutures. (Reused with permission [15]. Copyright © 2018 Springer Nature)

Sutured Anastomosis

Hand-sutured anastomoses historically represent the earliest form of intestinal anastomotic construction [1, 7, 8]. It continues to be a mainstay of surgical practice. The ability to consistently perform the precise technique requires tremendous technical discipline, concentration, and manual dexterity, given the fact that tissues are neither uniform nor static. Certainly, proficiency and skill range from workmanlike to that of an artisan depending on surgeon traits: innate dexterity, meticulous attention to detail, and intense concentration. To do it well requires practice and experience. The technique has evolved over time and can be applied for any potential type of anastomosis involving small or large bowel, rectum or anus, and performed using any configuration. Thus, the hand-sewn method for anastomotic construction must be considered a fundamental and dependable technique, and intestinal surgeons must be unwavering in their commitment to mastering this technique.

Specific aspects of sutured anastomosis have been examined and investigated including: suture material, inverted versus everted technique, continuous versus interrupted, single- versus two-layered, and importance of tissue pur-

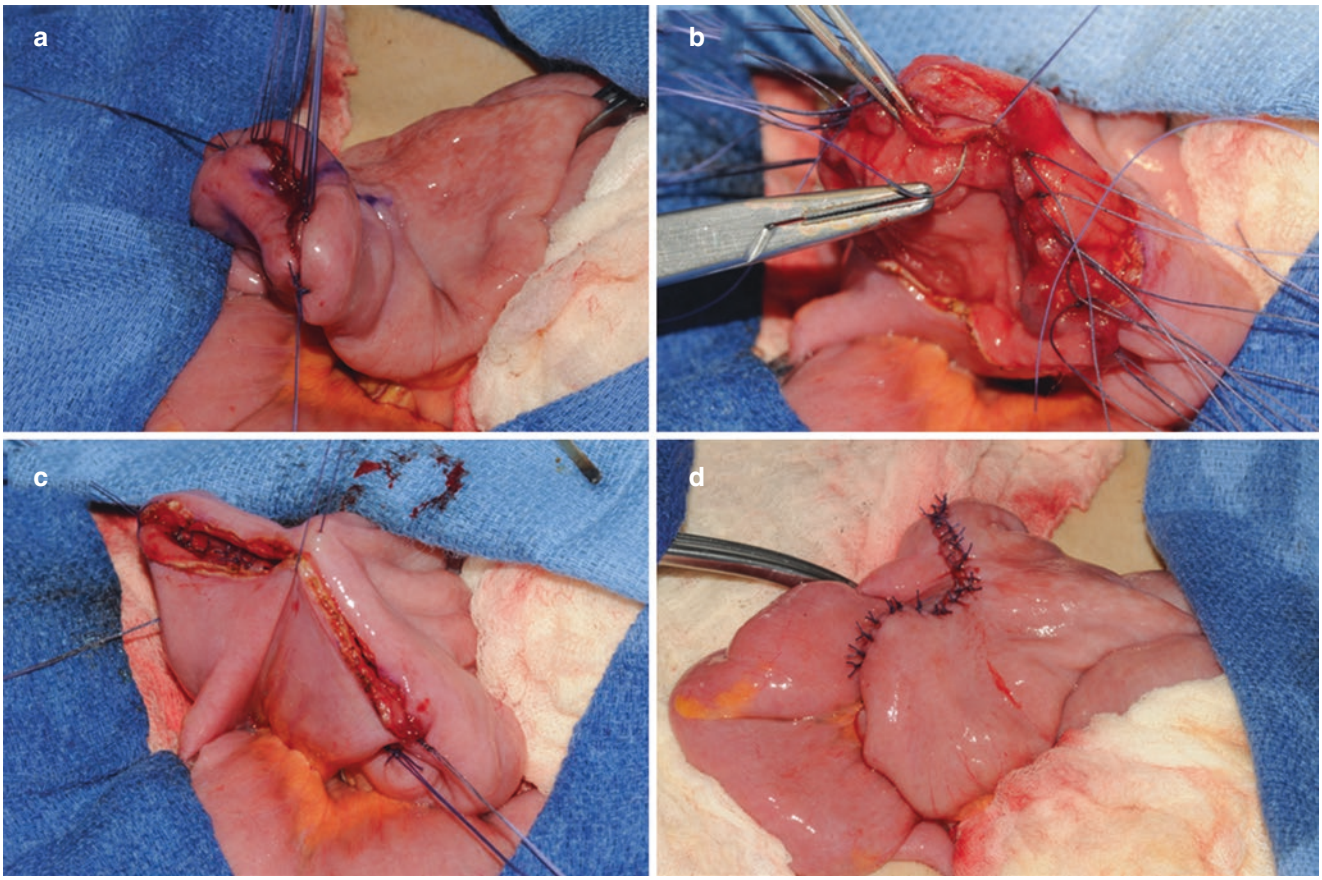

Fig. 9.31 Kono-S anastomosis. (**a**) Column of staple lines approximated. (**b**) Back wall of single layered interrupted simple sutures. (**c**) Anterior layer stay sutures. (**d**) Completed Kono-S hand-sewn anastomosis. (Photos courtesy of HDV)

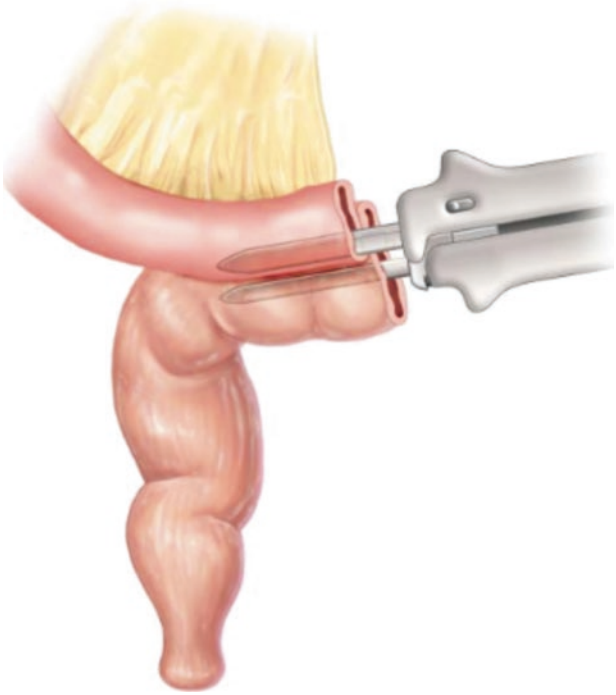

Fig. 9.32 Side-to-side functional end-to-end ileocolic anastomosis. (Reused with permission from Wexner SD, Fleshman JW, eds. Colon and Rectal Surgery: Abdominal Operations. Wolters Kluwer, 2018. Copyright © 2018 Wolters Kluwer)

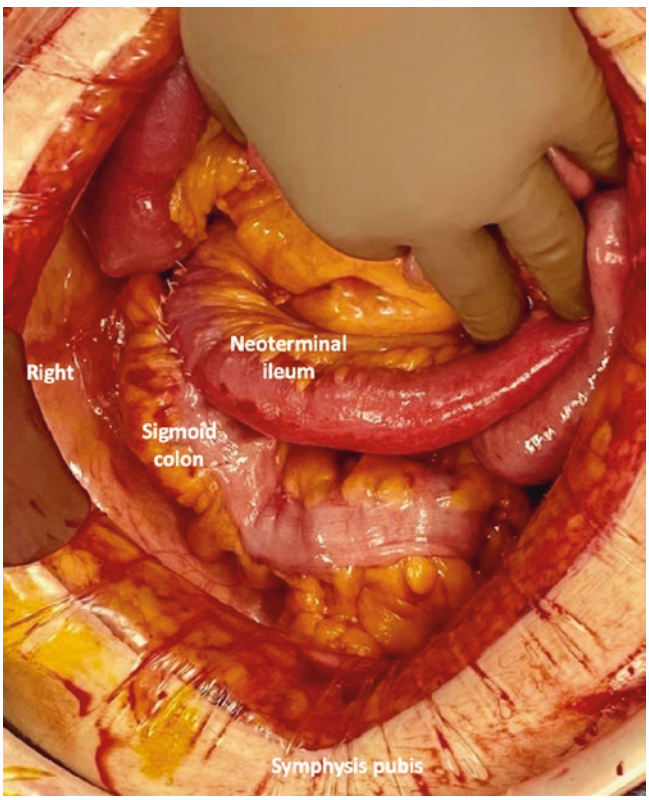

Fig. 9.33 Ileosigmoid side-to-side anastomosis configuration following transposition of sigmoid colon to right lower quadrant. (Photo courtesy of HDV)

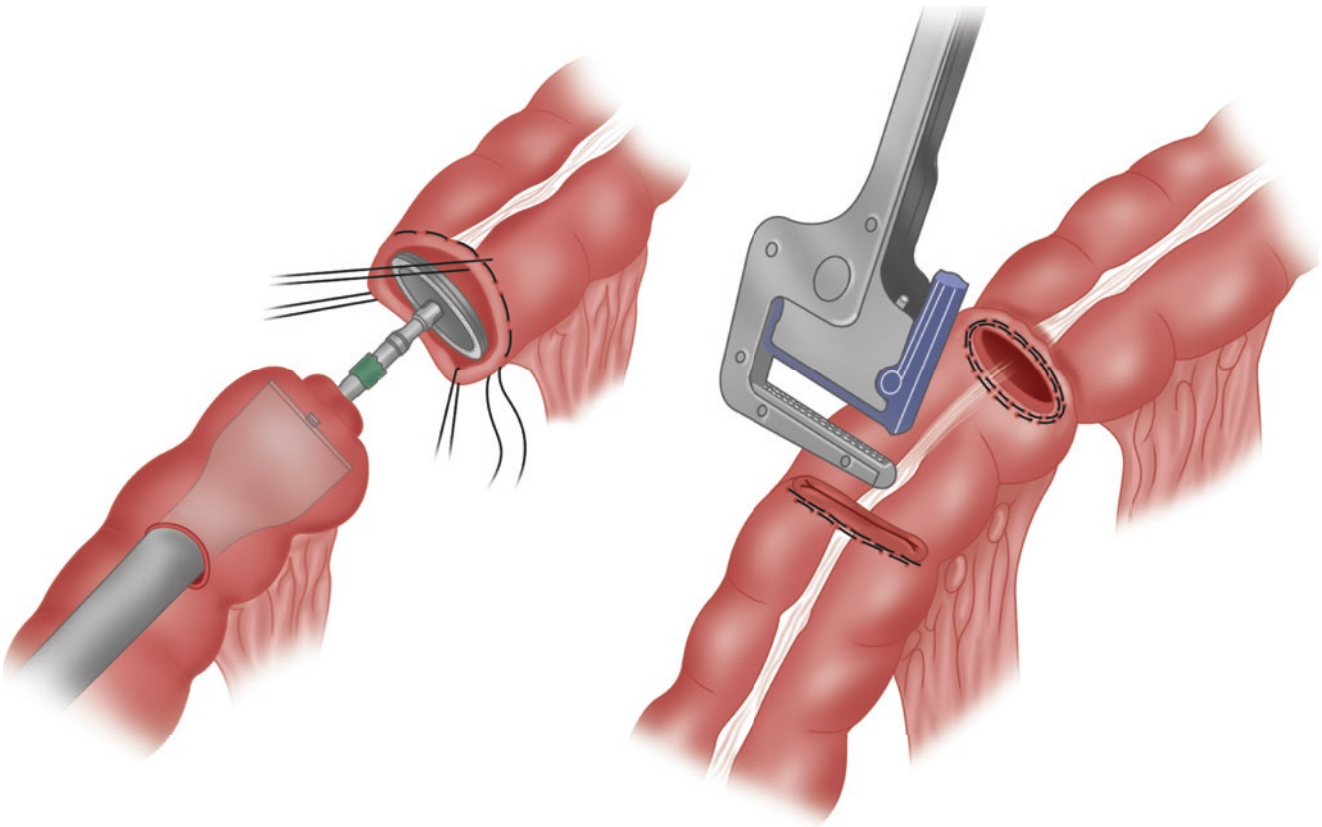

Fig. 9.34 Colocolonic end-to-end anastomosis

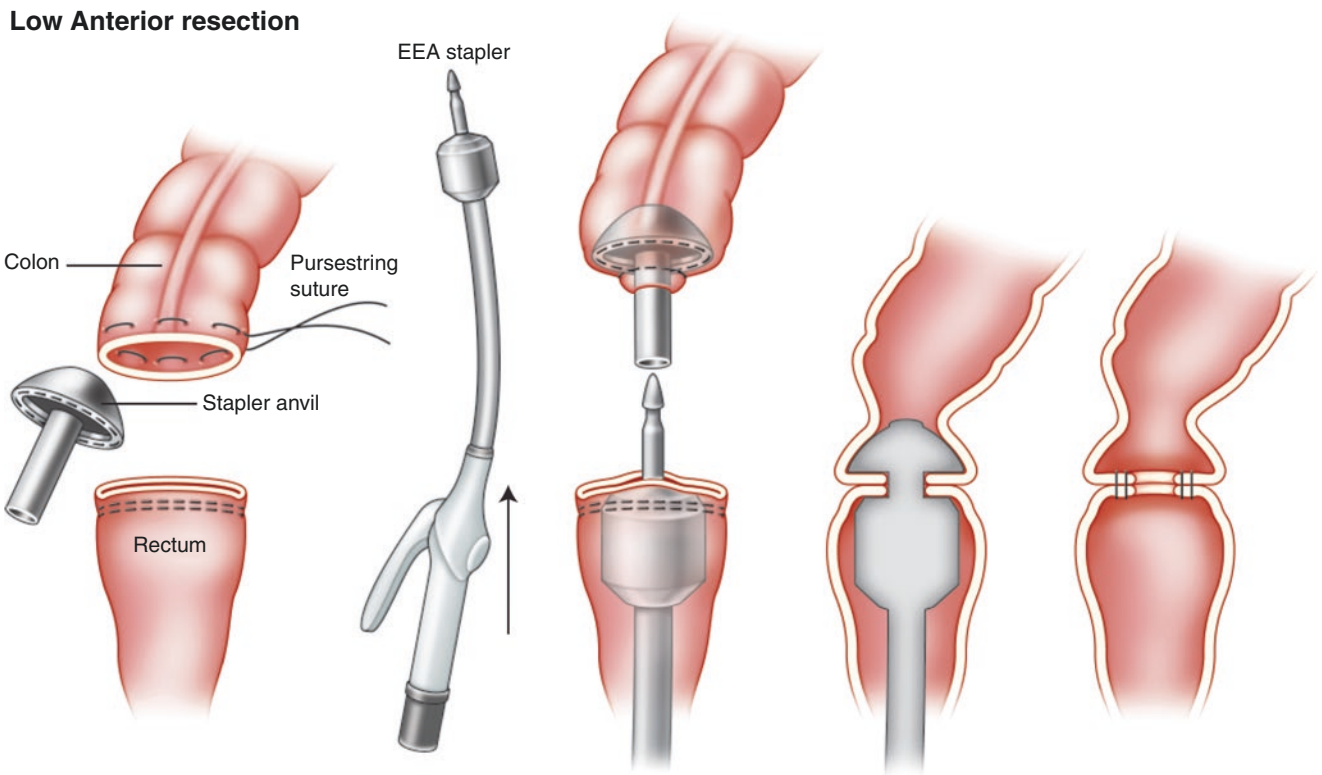

Fig. 9.35 Stapled colorectal anastomosis following a low anterior resection, the EEA stapler is used to construct an end-to-end anastomosis. (Reused with permission from Hunt SR, Silviera ML. Anastomostic construction. Steele et al. [94]. Copyright © 2016 Springer Nature)

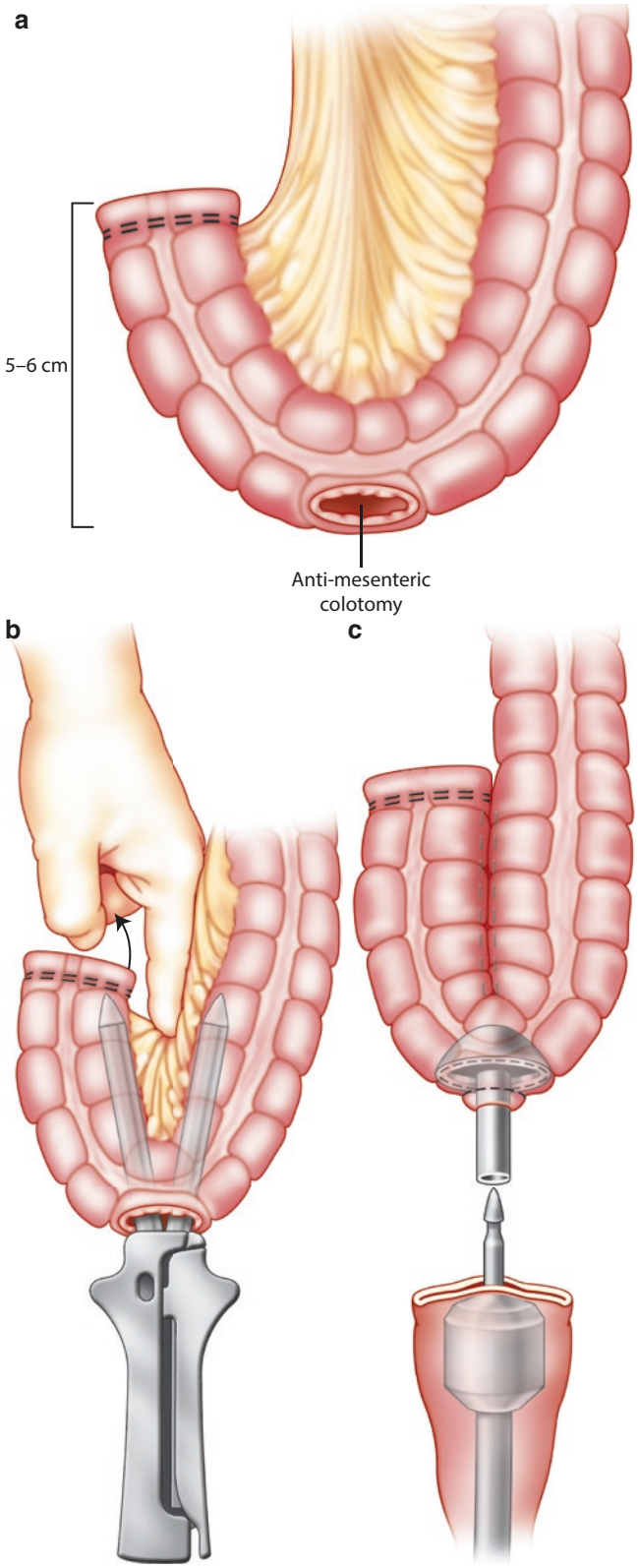

Fig. 9.36 Colonic J-pouch. (**a**) 5–6 cm colonic J-pouch is formed, and a colotomy is made on the antimesenteric portion of the bowel wall. (**b**) The pouch is formed using a linear stapler with 1–2 loads ensuring the colon mesentery is pulled out of the staple line. (**c**) The colorectal anastomosis is constructed using an EEA stapler. (Reused with permission from Hunt SR, Silviera ML. Anastomostic construction. Steele et al. [94]. Copyright © 2016 Springer Nature)

chase and travel [63, 64]. Both animal and clinical investigations have played a role in clarifying optimal practice [64]. Slieker et al. performed a systematic review exploring the scientific evidence for anastomosis and must be credited for the comprehensive effort to clarify the basis for hand-sutured anastomotic construction [66]. The spectrum of variables was examined: suture material, inverting or everting, layers incorporated and size of tissue purchase, distance traveled, and tension of tying. In addition, the number of layers of anastomosis—single- versus two-layered—is often discussed and debated. At times, the seemingly innumerable variables of hand-sutured anastomosis understandably perplex and intimidate the novice surgeon.

In regard to suture material, several features should be considered. Compared to braided suture, monofilament causes less local trauma as it passes through tissues and is less prone for adherence of bacteria [8, 63, 64]. However, monofilament suture has its detractors. Some argue that it is more expensive. It can be challenging to handle due to "memory" or its tendency to return to its original shape. Finally, in contrast to braided suture, knot tying with monofilament is less forgiving given the tendency for a knot to slip.

Slowly absorbable suture (either polyglycolic acid or polydioxanone sulfate) as opposed to rapidly absorbable suture such as chromic catgut provides adequate tensile strength for an adequate period of time and persists well into the remodeling phase of healing [63, 64]. Permanent suture is not necessary as slowly absorbable suture's durability persists until maximal tensile healing has occurred. Finally, some sutures such as linen or silk cause more local tissue inflammation [63, 64] that can affect phases of healing [5, 6].

Inverting anastomosis was popularized by Lembert and involves the apposition of serosa to serosa that results in the mucosal layer being inverted [7]. Everting anastomoses compared to inverting create larger stomata but are criticized for greater local inflammation and resulting adhesions [65]. Interestingly, bowel transected by a stapler is closed without inversion. Studies generally showed equivalency in leak; therefore, the everted sutured anastomosis generally has been abandoned [9].

In terms of tissue purchase, in addition to Lembert's emphasis on the serosa, Halsted highlighted the importance of the submucosal layer in intestinal suturing [9]. He showed that this layer offered the greatest collagen content and the highest degree of inherent tensile strength compared to the other layers. Suture material provides the tensile strength for an anastomosis during the lag or inflammatory phase when collagenolysis prevails. On the other hand, mucosa does not provide any intrinsic strength. Optimal size of recommended purchase varies and may not be well-founded. A range from 3 to 4 mm has been offered and one should take into consideration the caliber of the bowel lumen and thickness of tissues [1, 9]. There remain multiple types of suture techniques involving the type of bite. A

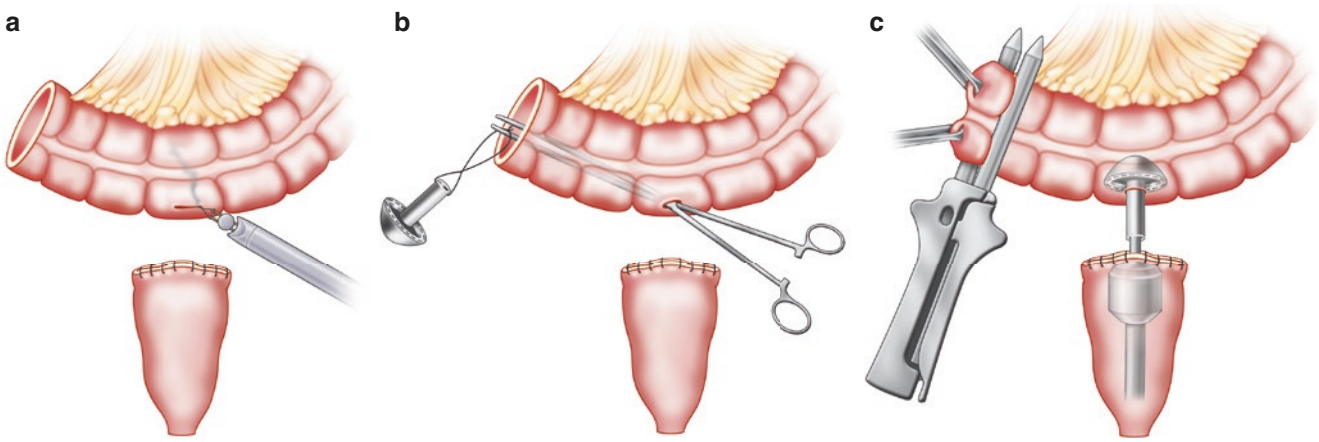

Fig. 9.37 Side-to-end coloanal anastomosis. (**a**) Colotomy is made proximal to the open end of the colon. (**b**) The EEA anvil is passed through this opening. (**c**) The colonic opening is closed using a linear stapler, and the anastomosis is performed using an EEA stapler. (Reused with permission from Hunt and Silviera [95]. Copyright © 2016 Springer Nature)

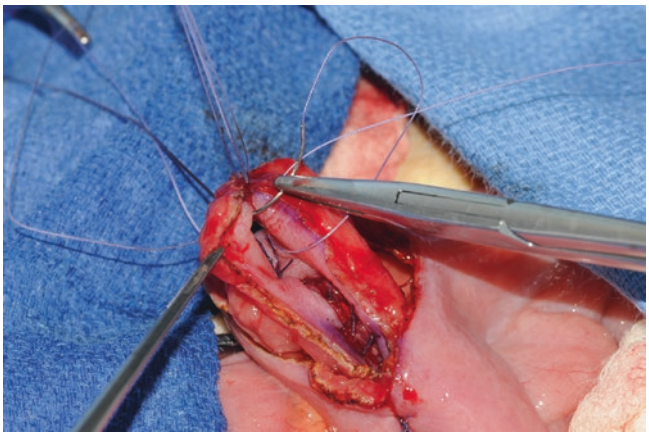

Fig. 9.38 Simple interrupted suture—3 mm bite serosa, submucosa with small purchase of mucosa (back wall of Kono-S anastomosis). (Photo courtesy of HDV)

simple suture encompassing all layers is most commonly practiced with strong emphasis on serosal and submucosal purchase that inverts the mucosa (Fig. 9.38).

The degree of tension placed on sutures during tying should account for tissue swelling and edema that will occur in the early phase of healing. Too much tension leads to ischemia, necrosis, and potential loss of tensile strength. Halsted instructed that one should avoid tying so tightly that tissues appeared "anemic" or strangled. Tying should feel secure with no visible gaping or separation, but with an approximation that will accommodate the ensuing edema.

Sutured anastomosis can be performed using interrupted or continuous suturing technique. Continuous suturing is faster. No difference in outcome can be identified comparing the two techniques [66].

Czerny modified Lembert's technique by adding an inner layer approximating the mucosa (Fig. 9.39). This continues to be a very popular approach to hand-sutured anastomosis. The posterior first rows are interrupted Lembert sutures. The bowel is opened and the inner layer is approximated in continuous fashion full thickness bites posteriorly. The anterior portion of this closure is often performed with the Connell stitch. Finally, the second layer anteriorly is completed using interrupted Lembert sutures. However, the two-layered method takes longer than single layer [67]. In addition, critics point out that two layers result in aperture stenosis relative to one layer, and studies have revealed greater degrees of ischemia and necrosis [66]. Finally, two-layer anastomoses require greater operative time and are therefore felt to be inferior to single-layered in most instances [67]. A Cochrane Database Review revealed that single-layer was equivalent to two-layer technique in terms of anastomotic leak, perioperative complications, mortality, and hospital stay [68]. A recent small, randomized prospective study confirmed these findings [69]. A randomized prospective multicenter trial in Germany unfortunately suffered from slow recruitment and failed to accrue the intended cohort. Thus, the group could not produce conclusive evidence to resolve the debate, but its publication certainly points to the profession's continued interest in establishing a best practice [70].

Hand-sewn anastomosis continues to be an important method and an essential skill for anastomotic construction. In many ways, this technique is the most versatile of method, as it can be performed for a variety of anatomic segments and creates the spectrum of configuration types. Although there are differing opinions regarding suture material and other variables, the reality is that hand-suturing technique must be relied upon in the most challenging situations or anastomosis types. When stapler instruments fail, hand-sewn anastomosis techniques should be the fail-safe technique as a contingency. Following mucosectomy or intersphincteric resection for low rectal cancer, hand-

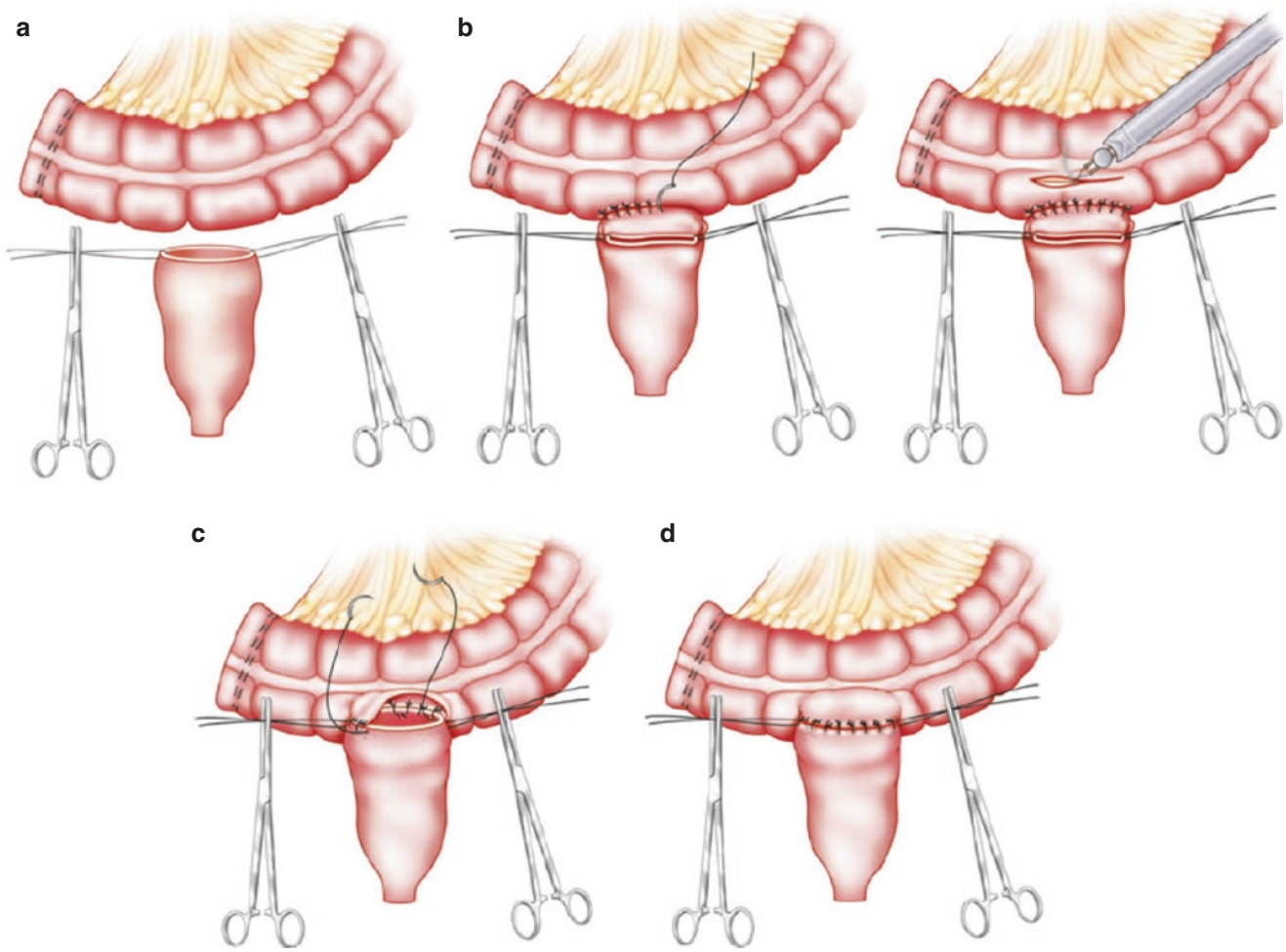

Fig. 9.39 Hand-sewn colorectal anastomosis. (**a**) The distal end of the colon is closed, and stay sutures are placed on the rectum. (**b**) A posterior layer of sutures are placed (left) and a colotomy is made (right) to match the size of the opening on the rectal stump. (**c**) The anastomosis is constructed using two continuous running sutures. (**d**) The anterior suture line is oversewn with interrupted sutures. (Reused with permission from Hunt and Silviera [95]. Copyright © 2016 Springer Nature)

sewn anal anastomosis is generally the relied upon method to achieve the most technically challenging of colorectal anastomoses—the anastomosis within the anal canal (Fig. 9.40). While there continues to be a spectrum of practice regarding suture material and specific technique, hand-sewn anastomosis remains a critically important skill that requires constant practice and focused dedication to attain mastery.

Stapled Anastomosis

Surgical staplers are now a mainstay of modern surgical practice and a major enterprise for medical industry, with sales projected to be four billion dollars in the United States by 2022 [71]. While hand-sutured anastomosis represented the first technique for anastomotic construction, it was initially fraught with high morbidity and mortality [1]. Multiple scientific and technical advances occurred that enabled evolution of safe hand-sewn anastomoses. Surgeons recognized the challenges in precision and reproducibility of the hand-sutured technique [7]. Mechanical methods for anastomotic construction were pursued to address this issue. Introduced in 1917 by Hultl, the original tissue stapler design proved heavy and unwieldy. However, this first iteration established fundamental design concepts including the importance of tissue compression, creation of B-shaped staples, and the presence of two overlapping rows of staples that secure an airtight seal while possessing gaps that ensure perfusion (Fig. 9.41). Remarkably, modern day staplers continue to depend on these essential concepts, and staple shape remains a measure of accurate stapler performance [72]. Surgical staplers revolutionized anastomotic construction, and Hultl's modest design represented a major paradigm shift in operative technique.

Modern stapling technology comes in three distinct types: linear or transverse noncutting, linear cutting, and circular

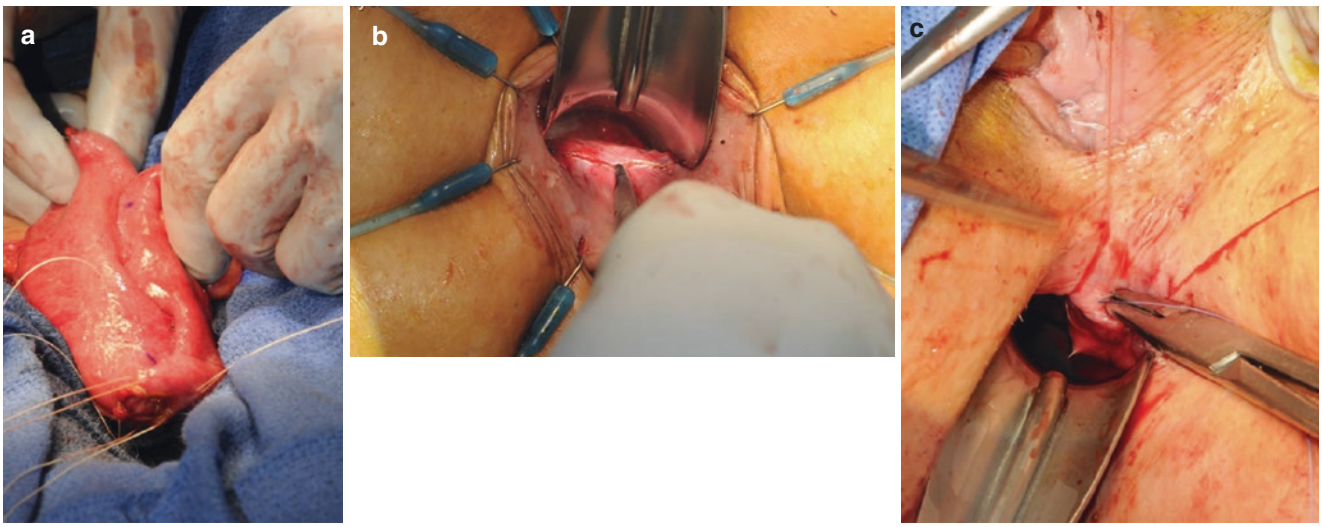

Fig. 9.40 Ileal J-pouch anal anastomosis after mucosal proctectomy. (**a**): Ileal J pouch; (**b**): Mucosal proctectomy for familial polyposis; (**c**): Hand-sewn anal anastomosis. (Photos courtesy of HDV)

cutting models. Various manufacturers and unique characteristics may differentiate staplers. Each stapler type has been used for anastomotic construction. The linear noncutting and transverse staplers are primarily used for bowel resection or closure of a defect or lumen. Linear cutting staplers and circular staplers are the types usually employed for anastomosis. Just as staplers often require some element of suturing, anastomotic construction often requires using a combination of different stapler types. Understanding specific design characteristics therefore must be appreciated. Stapled anastomosis can be undertaken for both open and minimally invasive platforms, though important technical variations are required to perform anastomotic construction.

The titanium staple is permanent and incites the lowest levels of tissue reaction and inflammation compared to other suture material [64, 73]. When shaped properly, staples provide greater levels of tensile strength than suturing.

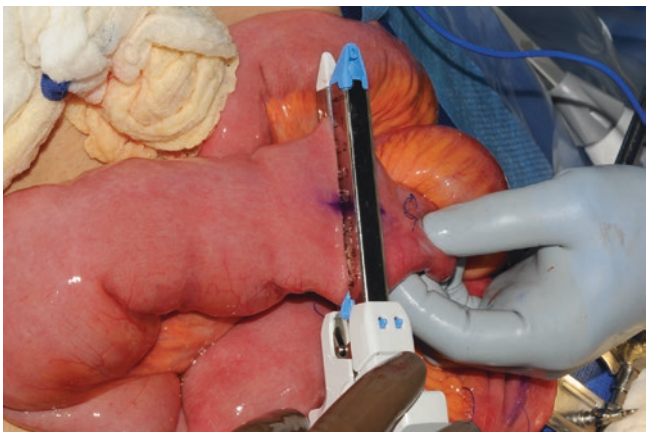

Fig. 9.41 Bowel transection in preparation for Kono-S anastomosis. (Photo courtesy of HDV)

Types of Tissue Staplers

Linear noncutting staplers (Fig. 9.42) place two overlapping staggered rows of staples to produce airtight compression with an array that allows perfusion. Following stapling, the tissue must then be divided manually. A variation of the transverse stapler is the Contour® (Ethicon), a curve-shaped stapler head designed for pelvic transection of the rectum, which provides three staple lines with knife cutting to leave one row on the specimen side of the resected rectum. This closes the specimen to prevent contamination.

Cutting staplers, either linear or circular, also provide the same staggered overlapping staple lines and then are cut between rows of staples with an internal knife leaving staples on both sides of the cut. These staplers are utilized for the actual construction of intestinal anastomosis. Linear cutting staplers vary in length, staple height, and number of rows of staples created. Generally, linear cutting staplers enable creation of side-to-side bowel anastomosis. Staplers have been modified specifically for laparoscopic and now robotic surgery by placing the end effector at the tip of a thin shaft that traverses access ports into the peritoneal cavity. In addition, linear cutting staplers provide an increased number of rows (from four to six), leaving three rows on either side of the cut. Circular staplers differ in diameter. Based on stapler manufacturer,

the device can be chosen based on staple height or the device can be closed to a point that corresponds to the desired staple height. One can perform anastomoses in a variety of configurations though its greatest contribution to anastomotic construction has been performing end-to-end low pelvic anastomoses.

Compression and Tissue Stapling

Compression between the stapler head and anvil causes tissue thinning as water is forced out of intracellular and extracellular spaces. Initial resistance of tissue to load compression ultimately results in stress relaxation of tissues [72]. Proper staple formation occurs as a result of adequate compression

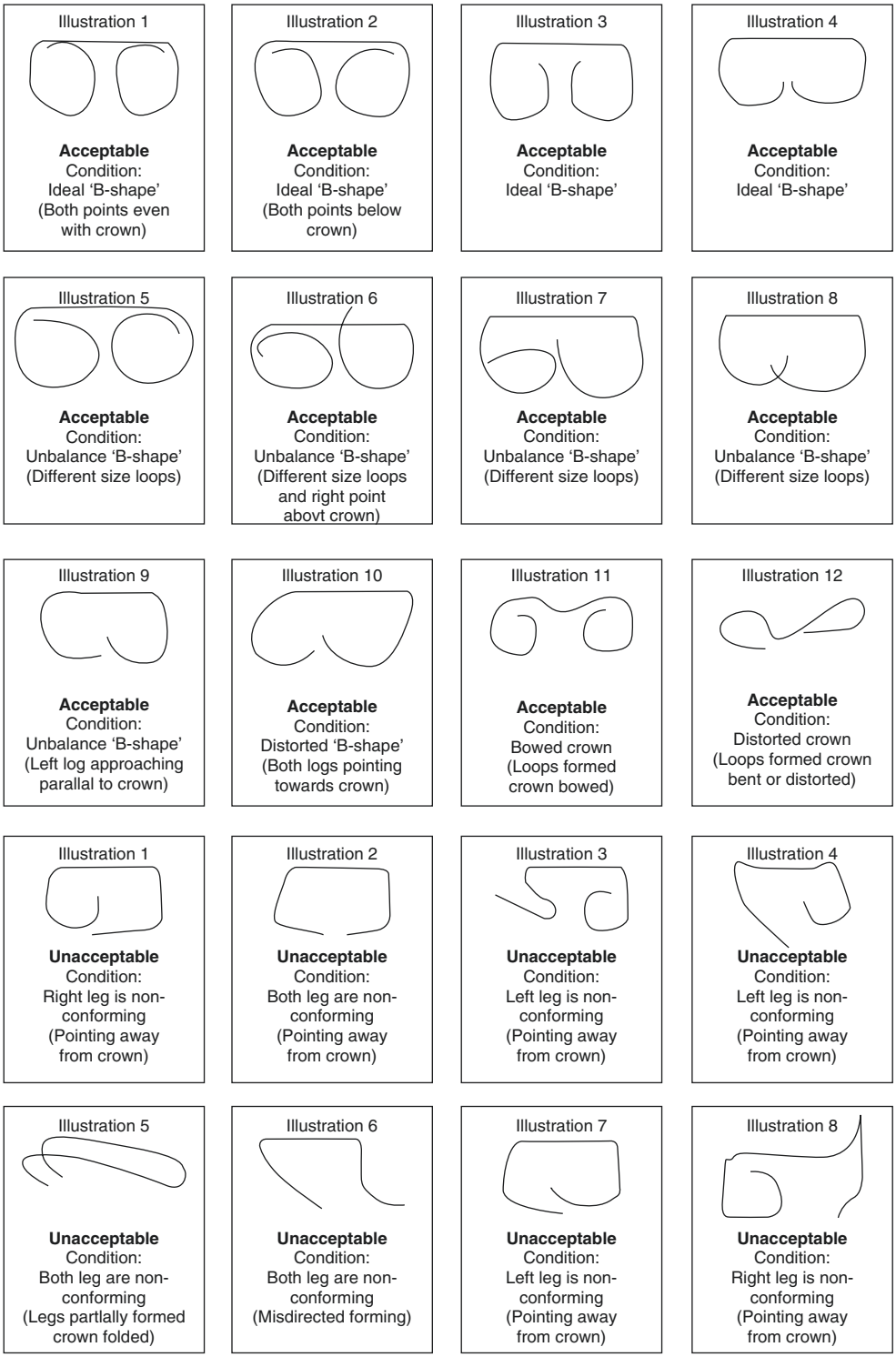

Fig. 9.42 Acceptable and unacceptable staple forms produced after firing of staples into tissue to create an anastomosis. **Note:** Presence of unacceptable forms can compromise integrity and strength of the staple line resulting in an increased rate of leaks and bleeding. (Reprinted from *Am J Surg*. Akiyoshi et al. [96]. Copyright © 2011 Elsevier)

and tissue thinning. Excessive compression can result in tissue tearing and loss of tissue purchase by staples [73] (Baker photo of staple line dehiscence). Approximation of the anastomosis is maintained by proper staple formation and tensile strength of the metal. Compression develops by different mechanisms. Linear and circular staplers provide load to tissues by parallel closure of the stapler head to the anvil. Minimally invasive linear cutting staplers use a cantilever mechanism. The latter may explain differences in compression created near the apex of the stapler as opposed to the distal tip, and accordingly, staple formation can be affected [74].

One of the initial decisions by surgeons regarding linear stapler use is the staple height specific for the organ and anticipated thickness. Staple height can be varied with taller staples with thicker diameters used for increasing thickness of tissue (Fig. 9.43). General recommendations regarding staple height are suggested for various intestinal segments. Inappropriately short staple height relative to tissue thickness can result in tearing, with evidence of this ranging from visible serosal laceration to complete staple line failure [72, 74, 75].

Nakayama et al. examined linear cutting staplers and the role of pre-compression on staple formation in a porcine model utilizing gastric tissue. Several important observations are worthy of mention from this seminal work. First, pre-compression improved staple formation, and there was a correlation between longer duration of compression and more consistent staple form. Second, there was obvious mismatch of staple height where the blue cartridge was used on the thickest bowel (pylorus). Poor staple form occurred irrespective of pre-compression, and thus gross mismatch could not be overcome by varying actual stapler execution. While it can be difficult to precisely know tissue thickness and to what degree pathologic conditions may alter typical wall thickness, slight inaccuracies of staple choice may be addressed by purposefully prolonged tissue precompression prior to staple firing. Third, the tip of the stapler formed staples less consistent than the base. Thus, the area furthest from the action point where precompression develops may experience some decremental level of load on the tissue. Again, increasing precompression time was found to also improve staple formation at the tip. Finally, inspection of the staple line formation comparing the two sides—proximal and distal side ("specimen-side" and "patient-side")—revealed that the staple formation was reliable between the two sides. This suggests that in the clinical setting, following staple firing and complete transection, reviewing the specimen side of the staple line of transection one can infer the status of the staple line left in vivo [74].

Rectal transection in open surgery can typically be accomplished with a single firing of a 30-45 mm transverse staple. Multiple applications of the linear cutting stapler are frequently necessary for rectal transection in laparoscopic or robotic surgery. This appears to be a risk factor for anastomotic leak. Poorly formed staples at the tip of the linear staple line represent a potential hazard. This "migratory" staple can result in stapler malfunction and jamming [72]. Prior to subsequent stapler firings, the in vivo and specimen side staple lines are inspected. If present, the "migratory" staple should be removed.

Another feature unique to laparoscopic linear cutting staplers is the interval firing stroke mechanism. Unlike linear cutters designed for open use, multiple strokes complete the staple line for each cartridge. Compression can be influenced by the speed of stroke firing [75]. In addition to a period of precompression time, interstroke waiting also may impact reliable staple formation [76]. Motorized powerized firing mechanisms perform this aspect of stapling on newer versions of linear staplers. Davinci Sureform linear cutting stapler® (Intuitive) can alter the stroke firing sequence as a result of its tissue thickness sensor, and mid-stroke the mechanism can pause allowing more compression to occur prior to completion. The Signia Stapling System® (Medtronic) similarly assesses compression characteristics of the tissue and alters stroke firing. Future studies will be required to see if these features will improve rates of staple formation, especially at the distal end of staple lines in particular. What is clear is that manufacturers are appropriately focusing efforts on these challenging issues of tissue thickness, compression, and firing stroke mechanism to improve staple formation.

Circular staplers revolutionized stapling to the mid-to-low rectum following low anterior resection, but can be

Color	Rows	Tissue type	Open staple height	Closed staple height
Grey	6	Mesentery	2.0 mm	0.75 mm
White	6	Vascular	2.5 mm	1.0 mm
Blue	6	Standard	3.5 mm	1.5 mm
Gold	6	Standard/thick	3.8 mm	1.8 mm
Green	6	Thick	4.1 mm	2.0 mm

Fig. 9.43 Dimensions of commonly available staple cartridges that are used to accommodate different tissue thicknesses for appropriate tissue management. (Reused with permission from [83]. Copyright © 2014 Dove Press)

employed for end-to-side or side-to-end anastomoses for both pelvic and abdominal anastomosis construction. Interestingly, the circular stapler creates compression differently than the linear cutter in that it staples and cuts upon one single firing. Anastomotic donuts of excised tissue produce the final lumen of the bowel approximation. The mucosa is inverted and two or three rows (depending on manufacturer) of staggered staples are inserted.

Nakayama investigated double stapling and found that the circular stapler produced reliable B- shaped staples irrespective of precompression time or degree of closure of instrument [76]. The authors comment that this most likely is due to the parallel closure mechanism by which compression occurs. Inspection of anastomotic donuts for the presence of all layers as well as intact rings is recommended to assess staple line integrity. Air leak testing is a necessary adjunct for pelvic anastomosis [77]. Videoendoscopy allows for visual inspection as well as air leak testing.

In summary, strategies for safe use of staplers (depending on brand and model) includes assessing tissue thickness and estimating appropriate cartridge load and staple height. Consider waiting longer than the recommended 15 seconds and perhaps as long as 1 minute prior to firing the stapler. Similarly, pausing in between strokes may allow for additional compression and more reliable staple formation. If sequential stapler fires are required to completely transect the entirety of the bowel, look carefully at the staples at the tip for a possible aberrantly formed, loose "crotch" staple that should be removed prior to stapling. After transection, inspection of the specimen side of the staple line can be assessing for staple line integrity, staple formation, and evidence of serosal tearing to alert to possible threatened anastomotic construction. An additional investigation following rectal transection and prior to double stapling is to perform endoscopy with air leak testing [77–79]. While it remains to be seen if the suggestions will translate into better outcomes, consideration for safe practice seems reasonable.

While favored for their consistent and reproducible construction, stapled anastomoses may leak. This holds true even in the case of ileocolic anastomosis, considered to be one of the lower risk anastomoses. In recent large European comparative studies, stapled anastomotic construction has been identified as a factor for leak [80–82]. Errors have been identified during technical performance and these potentially affect patient outcomes [72, 83, 84]. It is important to point out that stapler end effector takes place housed within an instrument, which in the case of laparoscopic or robotic platforms, is separate and at a distance from the surgeon. This is inherently a danger point in anastomotic construction. Automation and physical separation reduce the ability of surgeons to be involved in the actual staple insertion, and the technology impacts our ability to inspect the granular details of an anastomosis. This lack of access to the staple line may diminish surgeon vigilance. Therefore, stapled anastomotic construction requires detailed understanding of the instrument–tissue interaction, and similar to hand-sutured technique, execution of a stapled anastomosis requires focused attention to detail [83].

Compression Ring Anastomosis

This technique is not commonly performed in North America and is currently not performed by either author. However, we remain aware of its use in other centers around the world. Interestingly, some form of compression anastomosis method has been available since the early history of surgical anastomosis construction. First introduced in the nineteenth century by Denans and later refined and popularized by the Murphy Button, this mechanical instrumentation to achieve anastomosis has undergone multiple evolutions and innovations. The idea rests on a sutureless rejoining of the two ends of bowel with a ring left in vivo that acts to physically compress the circumference of the layers of one end of the bowel wall to the other. Ischemia and necrosis occur slowly over time during which the physiology of healing results in regaining intrinsic tensile strength and bowel integrity. The initial integrity of the anastomosis is based upon the purchase of the tissue by the device's circumferential purchase and the compression exerted. The device that can be either metallic or biodegradable eventually passes transanally.

There is no foreign body retained within the wall itself, and the theoretic benefit is less inflammation due to a reduction in the lag or inflammatory phase of healing. Experimental studies in a porcine model demonstrate initial bursting pressures exceeding stapled anastomoses [85]. Histopathology studies have revealed diminished numbers of inflammatory cells as well as less scar formation compared to stapled anastomosis [86]. Interestingly, fewer adhesions were also noted to the anastomosis [86]. The ring, which can be comprised of absorbable or permanent materials, will then be passed per anus with the resumption of fecal flow.

A recent meta-analysis examined compression compared to conventional (hand-sewn and stapled) colorectal anastomosis. Ten RCT's included nearly 2000 patients in the analysis. There were no significant differences in anastomotic leak, stricture formation, or mortality. There was a shorter time to return of bowel function in the compression group but there was no difference in terms of length of hospital stay. No significant difference was seen in post-operative morbidity except for a higher rate of bowel obstruction in the compression group, OR – 1.87. The authors concluded that there was no significant advantage of compression anastomosis over conventional [87].

In summary, compression ring method continues to be a technology available for anastomotic construction and may offer potential benefits from a healing model perspective.

The Conundrum of Best Practice and Continuing Challenge

Clarifying the best practice for anastomotic construction represents one of the most compelling areas of interest. Staplers, though more costly than suture materials, generally offset this difference by being faster. Most identify anastomotic leak as the critical parameter given the tremendous morbidity and increased mortality. In addition, leaks represent a tremendous financial burden due to increased consumption of health-care resources as well as the loss of productivity for those suffering from leak.

Comparison studies looking at hand-sewn versus stapled anastomoses generally do not show any clear-cut difference. A Cochrane Database Review has examined this topic most recently in 2012. The review included nine randomized controlled trials (1233 patients, 622 with stapled, and 611 with the hand-sewn technique) comparing the safety and effectiveness of stapled versus hand-sewn colorectal anastomosis surgery. Meta-analysis was performed. Outcome measures were mortality, anastomotic dehiscence, narrowing (stricture), hemorrhage, need for reoperation, wound infection, anastomosis duration (time taken to perform the anastomosis), and hospital stay. No significant statistical differences were found except that stricture was more frequent with stapling ($P < 0.05$), and the time taken to perform the anastomosis was longer with hand-sewn techniques [88].

Interestingly, looking specifically at ileocolic anastomosis, a prior Cochrane Database Review suggested superiority of the stapled technique over hand-sewn. This systematic review found seven randomized controlled trials with a total of 1125 participants (441 stapled, 684 hand-sewn) comparing these two methods. The leak rate for stapled anastomosis was 2.5%, significantly lower than hand-sewn, 6%. For the sub-group of 825 patients with cancer in four studies, stapled had fewer leaks compared with hand-sewn, being 1.3% and 6.7% respectively. Of note, in 264 noncancer (including patients with Crohn's disease) patients in three studies, there were no differences for the reported outcomes. Overall, there was no significant difference in the other outcomes of stricture, anastomotic bleeding, time of anastomosis, reoperation, mortality, intra-abdominal abscess, wound infection, and length of stay [89].

However, since this review several reports continue to examine this topic of technical differences. The HASTA trial examined ileostomy closure, comparing hand-sewn to stapled anastomosis [90]. This multicenter prospective randomized controlled trial compared 337 randomized patients undergoing closure of loop ileostomy after low anterior resection for rectal cancer in 27 centers. The primary endpoint was the rate of bowel obstruction within 30 days after ileostomy closure. Rate of anastomotic leakage was not different (stapler: 3.0%, hand suture: 1.8%, $P = 0.48$). The overall rate of postoperative ileus after ileostomy closure was 13.4%. Seventeen of 165 (10.3%) patients in the stapler group and 27 of 163 (16.6%) in the hand suture group developed bowel obstruction within 30 days postoperatively [odds ratio (OR) = 1.72; 95% confidence interval (CI): 0.89–3.31 = 0.10]. Operative times were shorter in stapled group.

Several large European studies assessed outcomes of right colectomy including anastomotic leak. Data from the German Society for General and Visceral Surgery registry from 2010 to 2017 were analyzed [91]. A total of 4062 patients who had undergone open right hemicolectomy for colonic cancer were analyzed. All patients had an ileocolic anastomosis, 2742 hand-sewn and 1320 stapled. Baseline characteristics were similar. No significant differences were identified in anastomotic leakage—stapled 3.9% versus hand-sewn 3.0%. No difference was seen in postoperative ileus, reoperation rate, surgical-site infection, LOS, or death. The stapled group had a significantly shorter duration.

A Danish nationwide database examined 1414 patients undergoing right hemicolectomy for adenocarcinoma with primary anastomosis between October 2014 and December 2015 [82]. There were 391 (28%) in the stapled group and 1023 (72%) in the hand-sewn group. Forty-five patients (3.2%) developed anastomotic leak; 21 of 391 (5.4%) and 24 of 1023 (2.4%) in the stapled and hand-sewn groups, respectively ($P = 0.004$). This difference was confirmed in multivariable analysis (adjusted OR: 2.91; 95% CI, 1.53–5.53; $P < 0.001$) and after propensity score matching (OR: 2.41; 95% CI, 1.24–4.67; $P = 0.009$). Thirty-day mortality was 15.6% (7/45) and 2.1% (29/1369) in patients with and without anastomotic leak ($P < 0.001$).

Finally, a multicenter international European cooperative study recently published findings examining right colectomy [92]. This study reports the morbidity and mortality rates for right-sided colon cancer and identifies predictors for unfavorable short-term outcome after right hemicolectomy. This included all patients undergoing elective or emergency right hemicolectomy or ileocecal resection over a 2-month period in early 2015. Predictors for anastomotic leak and 30-day postoperative morbidity and mortality were assessed using multivariable mixed-effect logistic regression models after variables selection with the Lasso method. Of the 2515 included patients, an anastomosis was performed in 97.2% ($n = 2444$): hand-sewn in 38.5% ($n = 940$) and stapled in 61.5% ($n = 1504$) cases. The overall anastomotic leak rate was 7.4% (180/2444), 30-day morbidity was 38.0% ($n = 956$), and mortality was 2.6% ($n = 66$). Patients with anastomotic leak had a significantly increased mortality rate (10.6% vs. 1.6% no-leak patients; $P > 0.001$). At multivariable analysis, the following variables were associated with

anastomotic leak: longer duration of surgery (OR = 1.007 per min; $P = 0.0037$), open approach (OR = 1.9; $P = 0.0037$), and stapled anastomosis (OR = 1.5; $P = 0.041$).

Ileocolic anastomosis is generally considered a straightforward operation with relatively simple anastomotic construction options. These reports highlight the continued issue of anastomotic leak and the absence of differences in outcomes based on technique. Tension and the need for mobilization are far less an issue compared to left-sided resection. Despite our perception of technologic improvement in stapling devices and their broad use, anastomotic construction and unanticipated outcomes continue even with our best efforts. Hand-sewn anastomosis continues to provide arguable equivalent results when compared to stapling techniques. Anastomotic construction continues to be a compelling and challenging topic for study in an effort to improve our understanding of best practice in surgical technique. The hope is that we can reduce the role of the surgeon's performance as a factor in undesired outcomes. The heterogeneity of this endeavor requires a vast array of operative techniques and methods. The reality is that some operations, including the most challenging ones we undertake, require a hand-sewn technique. Surgeons must possess and master a broad skillset that enables judicious adaptation and execution of the various techniques appropriate for each unique operation. Most importantly, we do so firmly intent and focused on adhering to the fundamental principles defining safe anastomotic construction: precise, tension-free, and secure approximation of well-perfused, healthy bowel.

References

1. Dietz UA, Debus E-S. Intestinal anastomoses prior to 1882; a legacy of ingenuity, persistence, and research form a foundation for modern gastrointestinal surgery. World J Surg. 2005;29(3):396–401.
2. McArdle C, McMillan D, Hole D. Impact of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer. British Journal of Surgery: Incorporating European Journal of Surgery and Swiss Surgery. 2005;92(9): 1150–4.
3. García-Granero E, et al. Individual surgeon is an independent risk factor for leak after double-stapled colorectal anastomosis: an institutional analysis of 800 patients. Surgery. 2017;162(5):1006–16.
4. Marinello F, et al. Anastomotic leakage after colon cancer resection: does the individual surgeon matter? Color Dis. 2016;18(6):562–9.
5. Thornton FJ, Barbul A. Healing in the gastrointestinal tract. Surg Clin N Am. 1997;77(3):549–73.
6. Thompson SK, Chang EY, Jobe BA. Clinical review: healing in gastrointestinal anastomoses, part I. Microsurgery. 2006;26(3):131–6.
7. Senn N. Enterorrhaphy; its history, technique and present status. JAMA. 1893;21:215–35.
8. Hardy KJ. A view of the development of intestinal suture. Part II. Principles and techniques. Aust N Z J Surg. 1990;60(5):377–84.
9. Giles D, Talbot E. Suturing, stapling, and tissue adhesion. In: Shackelford's surgery of the alimentary tract, vol. 2. Philadelphia: Elsevier; 2019. p. 1005–13.
10. Gershuni VM, Friedman ES. The microbiome-host interaction as a potential driver of anastomotic leak. Curr Gastroenterol Rep. 2019;21(1):4.
11. Shogan BD, et al. Collagen degradation and MMP9 activation by Enterococcus faecalis contribute to intestinal anastomotic leak. Sci Transl Med. 2015;7(286):286ra68.
12. van der Stappen JW, et al. Collagenolytic activity in experimental intestinal anastomoses. Differences between small and large bowel and evidence for the presence of collagenase. Int J Color Dis. 1992;7(2):95–101.
13. Keighley MR. Atlas of colorectal surgery. London: Churchill Livingstone; 1996.
14. Shikata J-I, Shida T. Effects of tension on local blood flow in experimental intestinal anastomoses. J Surg Res. 1986;40(2):105–11.
15. Smith L, Friend WG, Medwell SJ. The superior mesenteric artery. The critical factor in the pouch pull-through procedure. Dis Colon Rectum. 1984;27(11):741–4.
16. Thirlby RC. Optimizing results and techniques of mesenteric lengthening in ileal pouch-anal anastomosis. Am J Surg. 1995;169(5):499–502.
17. Chu DI, et al. Strategy for the difficult-to-reach ileal pouch-anal anastomosis: technical steps of an in vivo application of a mesenteric-lengthening technique. Tech Coloproctol. 2015;19(11):705–9.
18. İsmail E, et al. Comparison of mesenteric lengthening techniques in IPAA: an anatomic and angiographic study on fresh cadavers. Dis Colon Rectum. 2018;61(8):979–87.
19. Burnstein MJ, et al. Technique of mesenteric lengthening in ileal reservoir-anal anastomosis. Dis Colon Rectum. 1987;30(11):863–6.
20. Girard E, et al. Level of inferior mesenteric artery ligation in low rectal cancer surgery: high tie preferred over low tie. Tech Coloproctol. 2019;23(3):267–71.
21. Bonnet S, et al. High tie versus low tie vascular ligation of the inferior mesenteric artery in colorectal cancer surgery: impact on the gain in colon length and implications on the feasibility of anastomoses. Dis Colon Rectum. 2012;55(5):515–21.
22. Brennan DJ, et al. Routine mobilization of the splenic flexure is not necessary during anterior resection for rectal cancer. Dis Colon Rectum. 2007;50(3):302–7; discussion 307
23. Ludwig KA, Kosinski L. Is splenic flexure mobilization necessary in laparoscopic anterior resection? Another view. Dis Colon Rectum. 2012;55(11):1198–200.
24. Kream J, et al. Achieving low anastomotic leak rates utilizing clinical perfusion assessment. Surgery. 2016;160(4):960–7.
25. Manceau G, Karoui M. Remedial surgery following failed colorectal or coloanal anastomosis. In: Modern management of cancer of the rectum. London: Springer; 2015. p. 435–45.
26. Toupet A. Intermediate colectomy with transmesenteric angulosigmoid anastomosis. La Presse medicale. 1961;69:2693.
27. Hays LV, Davis DR. A technic for restoring intestinal continuity after left hemicolectomy for cancer of the distal colon and rectum. Am J Surg. 1976;131(3):390–1.
28. Rombeau JL, Collins JP, Turnbull RB. Left-sided colectomy with retroileal colorectal anastomosis. Arch Surg. 1978;113(8):1004–5.
29. Le TH, Gathright JB. Reconstitution of intestinal continuity after extended left colectomy. Dis Colon Rectum. 1993;36(2):197–8.
30. Blank JJ, et al. Retroileal anastomosis in hand-assisted laparoscopic left colectomy: experience at a single institution. Surg Endosc. 2019;34:1–6.
31. Chen YYC, et al. Colorectal anastomosis after laparoscopic extended left colectomy: techniques and outcome. Color Dis. 2020;22:1189.
32. Dunlavy P, Allan L, Raman S. Totally laparoscopic retroileal transverse colon to rectal anastomosis following extended left colectomy. Dis Colon Rectum. 2017;60(11):1224.
33. Jouvin I, Pocard M, Najah H. Deloyers procedure. J Visc Surg. 2018;155(6):493–501.

34. Kontovounisios C, et al. Modified right colon inversion technique as a salvage procedure for colorectal or coloanal anastomosis. Color Dis. 2014;16(12):971–5.
35. Manceau G, et al. Right colon to rectal anastomosis (Deloyers procedure) as a salvage technique for low colorectal or coloanal anastomosis: postoperative and long-term outcomes. Dis Colon Rectum. 2012;55(3):363–8.
36. Sciuto A, et al. Laparoscopic Deloyers procedure for tension-free anastomosis after extended left colectomy: technique and results. Tech Coloproctol. 2016;20(12):865–9.
37. Hasegawa H, et al. Impact of intraoperative indocyanine green fluorescence angiography on anastomotic leakage after laparoscopic sphincter-sparing surgery for malignant rectal tumors. Int J Color Dis. 2020;35(3):471–80.
38. Shen R, Zhang Y, Wang T. Indocyanine green fluorescence angiography and the incidence of anastomotic leak after colorectal resection for colorectal cancer: a meta-analysis. Dis Colon Rectum. 2018;61(10):1228–34.
39. Kawada K, et al. Evaluation of intestinal perfusion by ICG fluorescence imaging in laparoscopic colorectal surgery with DST anastomosis. Surg Endosc. 2017;31(3):1061–9.
40. Chang YK, et al. The impact of indocyanine-green fluorescence angiogram on colorectal resection. Surgeon. 2019;17(5):270–6.
41. Jafari MD, et al. Perfusion assessment in laparoscopic left-sided/anterior resection (PILLAR II): a multi-institutional study. J Am Coll Surg. 2015;220(1):82–92.e1.
42. Blanco-Colino R, Espin-Basany E. Intraoperative use of ICG fluorescence imaging to reduce the risk of anastomotic leakage in colorectal surgery: a systematic review and meta-analysis. Tech Coloproctol. 2018;22(1):15–23.
43. Kono T, et al. A new antimesenteric functional end-to-end handsewn anastomosis: surgical prevention of anastomotic recurrence in Crohn's disease. Dis Colon Rectum. 2011;54(5):586–92.
44. Kono T, et al. Kono-S anastomosis for surgical prophylaxis of anastomotic recurrence in Crohn's disease: an international multicenter study. J Gastrointest Surg. 2016;20(4):783–90.
45. Shimada N, et al. Surgical recurrence at anastomotic site after bowel resection in Crohn's disease: comparison of Kono-S and end-to-end anastomosis. J Gastrointest Surg. 2019;23(2):312–9.
46. Binda GA, et al. Surgical treatment of a colon neoplasm of the splenic flexure: a multicentric study of short-term outcomes. Color Dis. 2020;22(2):146–53.
47. Manceau G, et al. Elective surgery for tumours of the splenic flexure: a French inter-group (AFC, SFCD, FRENCH, GRECCAR) survey. Tech Coloproctol. 2020;24(2):191–8.
48. Hida J-I, et al. Comparison of long-term functional results of colonic J-pouch and straight anastomosis after low anterior resection for rectal cancer: a five-year follow-up. Dis Colon Rectum. 2004;47(10):1578–85.
49. Fazio VW, et al. A randomized multicenter trial to compare long-term functional outcome, quality of life, and complications of surgical procedures for low rectal cancers. Ann Surg. 2007;246(3):481–8; discussion 488–90
50. Hallböök O, et al. Randomized comparison of straight and colonic J pouch anastomosis after low anterior resection. Ann Surg. 1996;224(1):58–65.
51. Heriot AG, et al. Meta-analysis of colonic reservoirs versus straight coloanal anastomosis after anterior resection. Br J Surg. 2006;93(1):19–32.
52. Dehni N, et al. Long-term functional outcome after low anterior resection: comparison of low colorectal anastomosis and colonic J-pouch-anal anastomosis. Dis Colon Rectum. 1998;41(7):817–22; discussion 822–3
53. Ho YH, Seow-Choen F, Tan M. Colonic J-pouch function at six months versus straight coloanal anastomosis at two years: randomized controlled trial. World J Surg. 2001;25(7):876–81.
54. Joo JS, et al. Long-term functional evaluation of straight coloanal anastomosis and colonic J-pouch: is the functional superiority of colonic J-pouch sustained? Dis Colon Rectum. 1998;41(6):740–6.
55. Harris G, Lavery I, Fazio V. Function of a colonic J pouch continues to improve with time. Br J Surg. 2001;88(12):1623–7.
56. Dinnewitzer A, et al. Cumulative incidence of permanent stoma after sphincter preserving low anterior resection of mid and low rectal cancer. Dis Colon Rectum. 2013;56(10):1134–42.
57. Lindgren R, et al. What is the risk for a permanent stoma after low anterior resection of the rectum for cancer? A six-year follow-up of a multicenter trial. Dis Colon Rectum. 2011;54(1):41–7.
58. Brown S, et al. Morbidity following coloanal anastomosis: a comparison of colonic J-pouch vs straight anastomosis. Dis Colon Rectum. 2018;61(2):156–61.
59. Wexner SD, Alabaz O. Anastomotic integrity and function: role of the colonic J-pouch. Semin Surg Oncol. 1998;15(2):91–100.
60. Hüttner FJ, et al. Meta-analysis of reconstruction techniques after low anterior resection for rectal cancer. Br J Surg. 2015;102(7):735–45.
61. Machado M, et al. Similar outcome after colonic pouch and side-to-end anastomosis in low anterior resection for rectal cancer: a prospective randomized trial. Ann Surg. 2003;238(2):214.
62. Parc Y, et al. Better function with a colonic J-pouch or a side-to-end anastomosis?: a randomized controlled trial to compare the complications, functional outcome, and quality of life in patients with low rectal cancer after a J-pouch or a side-to-end anastomosis. Ann Surg. 2019;269(5):815–26.
63. Ballantyne GH. The experimental basis of intestinal suturing. Effect of surgical technique, inflammation, and infection on enteric wound healing. Dis Colon Rectum. 1984;27(1):61–71.
64. Koruda MJ, Rolandelli RH. Experimental studies on the healing of colonic anastomoses. J Surg Res. 1990;48(5):504–15.
65. Hardy KJ. A view of the development of intestinal suture. Part I. From legend to practice. Aust N Z J Surg. 1990;60(4):299–304.
66. Slieker JC, et al. Systematic review of the technique of colorectal anastomosis. JAMA Surg. 2013;148(2):190–201.
67. Burch JM, et al. Single-layer continuous versus two-layer interrupted intestinal anastomosis: a prospective randomized trial. Ann Surg. 2000;231(6):832–7.
68. Sajid MS, Siddiqui MR, Baig MK. Single layer versus double layer suture anastomosis of the gastrointestinal tract. Cochrane Database Syst Rev. 2012;(1):Cd005477.
69. Kar S, et al. Single layered versus double layered intestinal anastomosis: a randomized controlled trial. J Clin Diagn Res. 2017;11(6):Pc01–pc04.
70. Herrle F, et al. Single-layer continuous versus double-layer continuous suture in colonic anastomoses-a randomized multicentre trial (ANATECH trial). J Gastrointest Surg. 2016;20(2):421–30.
71. Gaidry AD, et al. The history of surgical staplers: a combination of Hungarian, Russian, and American innovation. Am Surg. 2019;85(6):563–6.
72. Baker RS, et al. The science of stapling and leaks. Obes Surg. 2004;14(10):1290–8.
73. Trimpi HD, et al. Advances in intestinal anastomosis: experimental study and an analysis of 984 patients. Dis Colon Rectum. 1977;20(2):107–17.
74. Nakayama S, et al. The importance of precompression time for secure stapling with a linear stapler. Surg Endosc. 2011;25(7):2382–6.
75. Matsuzawa F, et al. Serosal laceration during firing of powered linear stapler is a predictor of staple malformation. Surg Innov. 2017;24(6):590–7.
76. Nakayama S, et al. Obtaining secure stapling of a double stapling anastomosis. J Surg Res. 2015;193(2):652–7.

77. Kamal T, et al. Should anastomotic assessment with flexible sigmoidoscopy be routine following laparoscopic restorative left colorectal resection? Color Dis. 2015;17(2):160–4.
78. Kwon S, et al. Surgical care and outcomes assessment program (SCOAP) collaborative. Routine leak testing in colorectal surgery in the surgical care and outcomes assessment program. Arch Surg. 2012;147(4):345–51.
79. Wu Z, et al. Is the intraoperative air leak test effective in the prevention of colorectal anastomotic leakage? A systematic review and meta-analysis. Int J Color Dis. 2016;31(8):1409–17.
80. Naumann DN, et al. Stapled versus handsewn intestinal anastomosis in emergency laparotomy: a systemic review and meta-analysis. Surgery. 2015;157(4):609–18.
81. Group, E.S.o.C.C, et al. Relationship between method of anastomosis and anastomotic failure after right hemicolectomy and ileocaecal resection: an international snapshot audit. Colorectal Dis. 2017;19(8):e296–311.
82. Nordholm-Carstensen A, Schnack Rasmussen M, Krarup PM. Increased leak rates following stapled versus handsewn ileocolic anastomosis in patients with right-sided colon cancer: a Nationwide Cohort Study. Dis Colon Rectum. 2019;62(5):542–8.
83. Chekan E, Whelan RL. Surgical stapling device-tissue interactions: what surgeons need to know to improve patient outcomes. Med Devices (Auckl). 2014;7:305–18.
84. Offodile AC 2nd, et al. High incidence of technical errors involving the EEA circular stapler: a single institution experience. J Am Coll Surg. 2010;210(3):331–5.
85. Stewart D, et al. Validation of the NITI Endoluminal Compression Anastomosis Ring (EndoCAR) device and comparison to the traditional circular stapled colorectal anastomosis in a porcine model. Surg Innov. 2007;14(4):252–60.
86. Berho M, et al. Histopathologic advantages of compression ring anastomosis healing as compared with stapled anastomosis in a porcine model: a blinded comparative study. Dis Colon Rectum. 2014;57(4):506–13.
87. Slesser A, et al. Compression versus hand-sewn and stapled anastomosis in colorectal surgery: a systematic review and meta-analysis of randomized controlled trials. Tech Coloproctol. 2016;20(10):667–76.
88. Neutzling CB, et al. Stapled versus handsewn methods for colorectal anastomosis surgery. Cochrane Database Syst Rev. 2012;(2):Cd003144.
89. Choy PYG, et al. Stapled versus handsewn methods for ileocolic anastomoses. Cochrane Database Syst Rev. 2011;(9)
90. Löffler T, et al. HAnd suture versus STApling for closure of loop ileostomy (HASTA trial): results of a multicenter randomized trial (DRKS00000040). Ann Surg. 2012;256(5):828–35; discussion 835–6
91. Jurowich C, et al. Effects of anastomotic technique on early postoperative outcome in open right-sided hemicolectomy. BJS Open. 2019;3(2):203–9.
92. Predictors for anastomotic leak, postoperative complications, and mortality after right colectomy for cancer: results from an international snapshot audit. Dis Colon Rectum. 2020;63(5):606–18.
93. Merchea A, Dozois EJ, Wang JK, Larson DW. Anatomic mechanisms for splenic injury during colorectal surgery. Clin Anat. 2012;25:212–7.
94. Steele SR, Hull TL, Read TE, Saclarides TJ, Senagore AJ, Whitlow CB, editors. The ASCRS textbook of colon and rectal surgery. 3rd ed. Cham: Springer Nature; 2016.
95. Hunt SR, Silviera ML. Anastomostic construction. In: Steele SR, Hull TL, Read TE, Saclarides TJ, Senagore AJ, Whitlow CB, editors. The ASCRS textbook of colon and rectal surgery. 3rd ed. Cham: Springer Nature; 2016.
96. Akiyoshi T, Ueno M, Fukunaga Y, et al. Incidence of and risk factors for anastomotic leakage after laparoscopic anterior resection with intracorporeal rectal transection and double-stapling technique anastomosis for rectal cancer. Am J Surg. 2011;202(3):259–64.

Anastomotic Complications

10

Charles M. Friel and Cindy J. Kin

Key Concepts

- Mechanical bowel prep and oral antibiotics prior to colon resection are associated with a lower risk of anastomotic leak.
- A significant proportion of anastomotic leaks present after the immediate postoperative period, especially if there is a history of pelvic radiation.
- Most early anastomotic bleeds are self-limited; late bleeds may be a sign of anastomotic leak.
- Anastomotic stricture after cancer resection should undergo endoscopic biopsy and imaging to rule out recurrent cancer.
- Benign anastomotic strictures may be amenable to endoscopic management, but some will require surgical revision or completion proctectomy with permanent colostomy if the strictured anastomosis is in the pelvis.
- Anastomotic complications often lead to significant detriments to quality of life with regard to pain, defecatory function, sexual function, and urinary function. Discussion of these issues with patients is critical for surgical decision-making.

Anastomotic Leak

The unfortunate reality faced by every surgeon who performs bowel resections is the occurrence of anastomotic leaks. The incidence of anastomotic leak after bowel anastomosis ranges from 2% to 21% and is associated with significant risk of short- and long-term morbidity [1–5]. This complication can be a devastating event that sets off a cascade of other unfortunate events, resulting in significant detriments to quality of life, increased pain, prolonged disability, and sometimes death. Anastomotic leaks are associated with significantly higher healthcare resource utilization and cost, as patients with this complication are more likely to require additional diagnostic tests, procedures or reoperations, hospital days, outpatient care, and readmissions [6, 7]. Perhaps the most frustrating aspect of anastomotic leaks in colorectal surgery is the fact that leaks and their severe consequences still occur despite the adoption of evidence-based perioperative guidelines, efforts to optimize patient risk factors, and adherence to surgical principles. Although important progress has been made toward reducing the risk of anastomotic leak, there is still much work to be done to increase our understanding of the pathophysiology of anastomotic leak, and effective strategies for prevention.

Risk Factors

The site of anastomosis is strongly related to the risk of anastomotic leak. The risk of leak is lower for small bowel and ileocolic anastomoses, and higher for ileorectal and distal colorectal anastomoses [8, 9]. Patient-related risk factors for anastomotic leak are diabetes mellitus, hyperglycemia and high HbA1c, male sex, higher body mass index, tobacco use, inflammatory bowel disease, chronic immunosuppressive medications, radiation enteritis, malnutrition, hypoalbuminemia, and active infection [10–16]. Among patients undergoing rectal cancer resection for cancer, additional risk factors for anastomotic leak include more distal anastomoses, neoadjuvant pelvic radiation therapy, and advanced tumor stage [17–20].

Intraoperative risk factors include the inability to achieve a tension-free anastomosis and poor blood supply to the ends of bowel used for anastomosis, blood loss and blood transfusions, prolonged operating time, and intraoperative contamination [10–16]. Using multiple stapler firings across the rectum, which is commonly done in laparoscopic and robotic approaches, may also be associated with a higher risk for

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anastomotic leak [21–23]. The operating surgeon is another potential risk factor, although little is known about which surgeon characteristics would increase the risk for a surgical complication [24, 25]. Closed-suction drainage is commonly used in low pelvic anastomoses, but whether its routine use reduces the risk of anastomotic leak is still under debate [26–31]. Even when an anastomotic leak occurs, it is rare that the drain placed during the initial operation would effectively control the pelvic sepsis by draining pus or stool. However, as multiple studies have not shown that drains increase the risk for a leak, placing them at the time of surgery may still be helpful in the event of an abscess or leak, as the interventional radiologists may reposition a surgically placed drain into a better location. These drains may also be useful in controlling pelvic hematomas, thus preventing them from causing inflammation and pressure on the anastomosis.

The role of proximal fecal diversion in reducing the risk of anastomotic leak is also unclear. It has been cited as a risk factor for leak, as a protective factor, and as a neutral factor [17, 32, 33]. It certainly decreases the risk of septic complications of a leak, and it may even prevent an anastomotic leak from manifesting any clinical signs [34–36]. Therefore, the risk for reoperation is lower, as is the risk of mortality [19, 37, 38].

There has been considerable debate over whether mechanical bowel preparation and/or oral antibiotics prior to colorectal resection reduces the risk of anastomotic leak, because the studies had revealed a diverse range of outcomes [39–41]. Multiple analyses using the American College of Surgeons National Surgery Quality Improvement Program database over the last several years are consistent with the conclusion that both mechanical bowel preparation and oral antibiotics together are associated with a lower risk of anastomotic leak [42–50].

An emerging body of research suggests that another risk factor for anastomotic leak resides in the gut microbiome [51]. This offers a biologic explanation for why mechanical bowel preparation with oral antibiotics is helpful for reducing anastomotic leak. This is a particularly compelling area of research as it may explain the leaks that occur in patients with no other risk factors, which are often the most frustrating and confusing events for surgeons. Enterococcus faecalis has been demonstrated to degrade collagen and activate tissue matrix metalloproteinase 9 (MMP9) in host intestinal tissue, thus potentially contributing to the pathogenesis of anastomotic leakage. Particular strains of E. faecalis have greater ability to degrade collagen and activate MMP9, and these strains are more likely to be found in leaking anastomoses in rat models [52]. Pseudomonas aeruginosa colonizing intestinal tissues can mutate to increase collagenase activity and destroy tissue more effectively [53]. Standard oral or intravenous antibiotics do not eliminate these organisms. Recent studies have examined the ability of other compounds or diet modifications to reduce the virulence of these organisms and prevent anastomotic leak in animal models [54–56]. This field of investigation continues to rapidly evolve and findings in the near future may dramatically alter our understanding of why anastomotic leaks occur and how to prevent and treat them.

Diagnosis

The diagnosis of anastomotic leak is not always obvious. Aside from extravasation of retrograde contrast enema on computed tomography (CT) scan, which has the highest sensitivity and specificity for anastomotic leak, there is very little consensus on what clinical findings are confirmatory for an anastomotic leak [57–59]. In the immediate postoperative period, clinical signs that raise concern for an anastomotic leak include fever, leukocytosis, increased pain, suspicious drainage from the wound or surgical drain, and prolonged ileus. If the CT is performed within the first 4 days of the operation, findings may be nonspecific as it often takes until the fifth day for infected fluid to develop rim enhancement. While a postoperative CT may demonstrate an obvious leak with free air, extraluminal extravasation of oral or rectal contrast, or a defect in the anastomosis with adjacent free fluid or an abscess, it more frequently demonstrates rim-enhancing fluid collections or specks of free air that are equivocal for a leak.

Leaks are commonly assumed to occur within the first week of the operation during the index hospitalization, but, in reality, up to half of leaks may present after the patient has been discharged, with a significant proportion detected over a month after surgery [8, 60]. Among patients undergoing low anterior resection for rectal cancer, a third of anastomotic leaks become clinically evident over a month after the operation [61]. In the immediate postoperative period, leaks may present with nonspecific symptoms such as ileus or low-grade fever, or with frank peritonitis and sepsis (Fig. 10.1). Late leaks tend to present insidiously with pelvic pain and failure to thrive.

Elevated serum C-reactive protein (CRP) and procalcitonin are biomarkers that serve as early indicators of anastomotic leak after colorectal surgery. These biomarkers are used in some enhanced recovery clinical pathways, as length of hospitalization has shortened significantly and thus may result in patients with leaks that are not yet clinically apparent being discharged. Serum CRP levels less than 172 mg/L on postoperative day 3, 124 mg/L on postoperative day 4, and 144 mg/L on postoperative day 5 all correspond to a negative predictive value of 97% for anastomotic leak [62]. CRP levels are expected to be higher in patients undergoing open colorectal surgery compared to patients undergoing laparoscopic surgery. In patients undergoing open surgery,

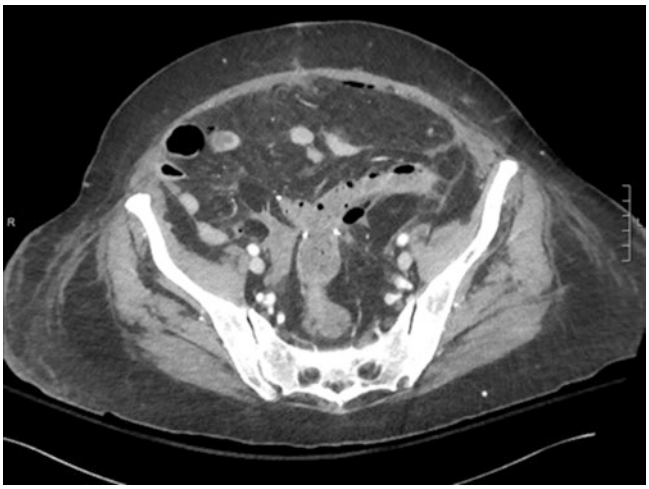

Fig. 10.1 Colorectal anastomotic leak: CT image of a patient who developed anastomotic leak on postoperative day 5 after undergoing sigmoid colectomy for diverticulitis complicated by colovaginal fistula. She required operative intervention for washout and takedown of the anastomosis and creation of an end colostomy

CRP levels over 209 mg/L on postoperative day 3 and 123.5 mg/L on postoperative day 4 are most predictive of leak. In patients undergoing laparoscopic surgery, a CRP level over 146.7 mg/L on postoperative day 2 was most predictive of leak [63]. Serum procalcitonin is also a biomarker studied for its association with anastomotic leak, and can be used in conjunction with CRP. The negative predictive value is 96.9% for a procalcitonin less than 2.7 ng/mL on postoperative day 3, and 98.3% for a procalcitonin less than 2.3 ng/mL on postoperative day 5 [64, 65]. If these biomarkers surpass the cutoff values and the patient appears clinically well, the decision to discharge the patient should be weighed against the higher risk for readmission [66]. A serum CRP value less than 145 mg/L on postoperative day 3 has a 93% negative predictive value for readmission within 30 days of surgery [67].

Management of Anastomotic Leak

In the event of an anastomotic leak, the strategy for managing it depends on several factors: the patient's clinical condition, the timing of the leak, the location of the anastomosis and leak, and whether the leak is contained. On one end of the spectrum, the patient with sepsis with fecal peritonitis has a clear indication for emergent return to the operating room for exploration and washout with source control. The operative decision of whether to take down the anastomosis, or place drains and divert proximally depends on the degree of operative exposure and the location of the anastomosis. If the surgeon cannot safely gain access to the anastomosis due to obliterative adhesions, then the best option is to lay drains in the area of the leak and bring up a proximal stoma to divert the fecal stream. If the surgeon can safely expose the anastomosis, then management largely depends on the location of the anastomosis and the size of the defect. For small bowel and ileocolic anastomoses, resection and re-anastomosis can be performed if the bowel ends are viable and mobile. If the status of the patient or the bowel is marginal, then formation of an end ostomy and mucus fistula, or a divided end-loop stoma is the safest option. For colorectal anastomoses with a significant defect, then the safest option is to take down the anastomosis and bring up an end colostomy. Measures to prevent a dehiscence of the top of the rectal stump, which can lead to chronic pelvic abscesses, include oversewing the rectal stump staple line and placing a rectal tube for decompression. Drains should also be placed over the rectal stump given the high likelihood of a dehiscence. While it may be possible to use a minimally invasive approach to reoperate on patients who have recently undergone a minimally invasive operation, it is quite likely that a laparotomy will be required to perform an adequate washout and gain source control. The surgeon must maintain objectivity in what can be a trying time for all parties, and remain steadfast in doing the safest operation for the patient.

On the other end of the spectrum, the patient with a contained leak and a small abscess <3 cm may successfully undergo non-operative management with broad-spectrum antibiotics. Larger abscesses may require percutaneous drainage in addition to broad-spectrum antibiotics. Fecal diversion may or may not be necessary, depending on the severity of the leak. For colorectal or coloanal anastomotic leaks, drain placement may be performed transrectally through the anastomotic defect and into the extraluminal abscess cavity, and depending on the distance of the leak from the anus, can be performed either by the surgeon or by our colleagues in interventional radiology. Non-operative treatment of leaks may be successful in allowing maintenance of the primary anastomosis in half of patients with anastomotic leaks [68]. If the patient remains stable and the leak is well controlled, then closure of the anastomotic defect and collapse of the associated abscess cavity may occur without the need for a major anastomotic revision. If the leak is not well controlled with drainage and fecal diversion then the patient may need to undergo resection of the anastomosis. If possible, it is ideal to wait at least 3 months to reoperate to allow for resolution of inflammatory adhesions that would make reoperation more treacherous. Waiting even longer will often result in healing of the anastomosis without the need for operative intervention [69]. For colorectal anastomoses that fail to resolve with drainage, resection of the anastomosis with redo colorectal or coloanal anastomosis may be possible. However, completion protectomy with permanent end colostomy may be necessary or preferable to maximize quality of life.

If the anastomosis is distal enough, in select cases a leak may be repaired transanally using an endorectal advancement flap, dermal advancement flap, or primary suture repair [70, 71]. Some groups have described the use of transanal endoscopic platforms such as Transanal Minimally Invasive Surgery (TAMIS) or Transanal Endoscopic MicroSurgery (TEMS) to directly repair anastomotic leaks [72, 73]. Depending on the degree of pelvic or intra-peritoneal contamination, transanal repair may be combined with laparoscopic washout. Creation of a diverting loop ileostomy should also be strongly considered if one of these techniques is used. These transanal techniques are often not feasible given how fibrotic the tissues tend to be around the site of a leak, so completion proctectomy or proctectomy with coloanal anastomosis may be the only options.

Chronic presacral sinus tracts result from anastomotic leaks in the pelvis that do not heal and are a source of ongoing inflammation (Fig. 10.2). Patients may suffer from symptoms including pelvic pain, fevers, rectal discharge, and tenesmus. These tracts typically occur if there is a leak from the posterior aspect of a colorectal anastomosis. Among patients undergoing low anterior resection for rectal cancer after neoadjuvant chemoradiation therapy, presacral sinus tracts may occur in 9.5% and thus represent a significant clinical dilemma [61]. There are several strategies for treatment of these tracts. One option is fecal diversion in combination with a septotomy, in which the bowel wall between the lumen and the sinus tract is divided, effectively unroofing the sinus tract and including the underlying cavity as part of the lumen. This can be done via a direct transanal approach if the anastomosis is distal enough [74]. The transanal endoscopic techniques can be used to access and divide the septum overlying more proximal sinus tracts. This procedure may need to be performed several times over several weeks to months to get the tract to heal in fully [75]. Fibrin glue injection into these sinus tracts has been described and can be done directly via a transanal approach if the opening is distal enough, or endoscopically if it is more proximal [76, 77]. Depending on their level of experience, interventional radiologists may be able to place a transrectal drain through the anastomotic defect into a presacral sinus tract or abscess, and when the tract is small enough, they can inject fibrin glue as they remove the drain to obliterate the space and prevent reaccumulation of an abscess (Fig. 10.3**).** These techniques are often not successful in eliminating the sinus tract and it may be necessary to proceed to resection of the anastomosis, debridement of the cavity, and either re-anastomosis or completion proctectomy [78].

Newer endoscopic techniques for addressing anastomotic leaks have emerged and early reports have demonstrated

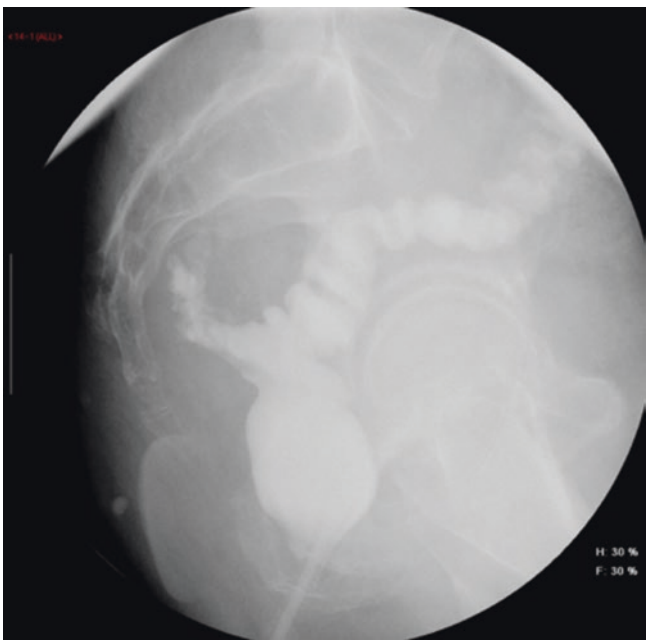

Fig. 10.2 Colorectal anastomotic leak: Fluoroscopic image of a patient who developed a leak 9 days after low anterior resection

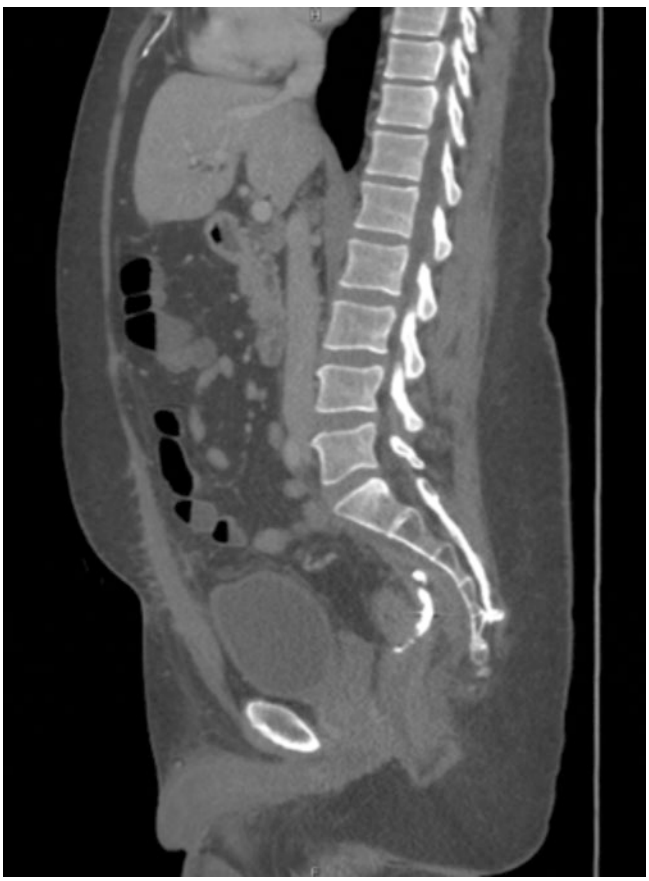

Fig. 10.3 Presacral sinus tract: CT image of a patient who developed a chronic presacral sinus abscess after a colorectal anastomotic leak. A transanal drain was placed through the anastomotic defect and into the presacral abscess. When the cavity had become essentially a sinus tract, fibrin glue was injected into the tract as the drain was removed to fill the tract and prevent reaccumulation

promising results. These include endoscopic vacuum sponge placement, intraluminal covered stents, and over-the-scope clips. Endoscopic vacuum-assisted closure of presacral abscess cavities caused by chronic anastomotic leaks has been shown to be effective in healing the majority of patients [79, 80]. The endoluminal vacuum sponge system is generally managed on an outpatient basis and changed every 2–3 days. It is unclear whether it results in faster healing as it takes weeks to months for complete resolution. It may prevent the formation of a presacral sinus tract and is generally well-tolerated and safe [81–84]. Fecal diversion is commonly part of the strategy, but not in all cases that have been effectively treated. Timely diagnosis and treatment increases the likelihood of success, as patients who start primary endoluminal vacuum therapy within 15 days of diagnosis have a higher chance of success compared to those who undergo salvage therapy with this technique more than 15 days after diagnosis of the leak [85, 86]. Endoscopic placement of covered intraluminal stents has been used to treat colorectal anastomotic leaks with some success in small series [87, 88]. Endoscopic closure of colorectal anastomotic leak using an over-the-scope clip has also been described [89]. Data on the success of this strategy are sparse so the likelihood of successful healing is not known [90, 91]. It should be used only in select cases that would be most amenable to this, and in cases in which the intra-abdominal sepsis has been well controlled. As more surgeons and gastroenterologists report on their experience with these advanced endoscopic techniques, we will gain a better understanding of the indications and limitations of these strategies.

Outcomes After Anastomotic Leak

The risk of perioperative mortality increases in the presence of an anastomotic leak, and ranges from 3% to 14% [9, 11, 92]. For patients with rectal cancer, anastomotic leaks are associated with decreased overall 5-year survival (44–53% versus 64%) and cancer-specific 5-year survival (42% vs 67%) [20, 93, 94]. In some series, patients with anastomotic leaks after colorectal cancer resections were found to have increased local and systemic recurrence rates while in others, there was no difference between those who had anastomotic leaks and those who did not [94–100]. The worse oncologic outcomes have traditionally been attributed to the delay in adjuvant chemotherapy due to the septic complications of a leak. However, there are other potential mechanisms for increased recurrence in patients who suffer a postoperative infection. Postoperative infection has an effect on the cytokines present in the peritoneal fluid and peripheral blood of patients in such an inflammatory state which may increase the ability of residual tumor cells to migrate and invade, and thus potentially allow them to contribute to recurrences [101, 102]. Anastomotic leak and intra-abdominal abscess is also associated with upregulation of genes that encode for cytokines that promote tumorigenesis and angiogenesis, further contributing to this understanding of the pathophysiology of increased recurrence after postoperative infection [103].

The risk of a permanent ostomy after an anastomotic leak depends on the location of the anastomosis – the more distal the leaking anastomosis is, the higher the risk of a permanent ostomy. Functional outcomes and quality of life are also worse after anastomotic leak, particularly one that occurs in a pelvic anastomosis [104, 105]. Colorectal anastomotic leaks are associated with more bowel dysfunction including more frequent bowel movements, poorer continence, and increased pad use [106]. It is likely that the pelvic fibrosis from the chronic inflammation induced by a leak reduces the compliance of the rectum, thus contributing to these symptoms. The potential impact of anastomotic leakage on defecatory dysfunction is underestimated, as many patients who would have had such symptoms opt for an end colostomy [107]. Sexual and urinary functions are also adversely affected and symptoms often go unreported [108]. It is important, therefore, for surgeons to be cognizant of these potential sequelae and be proactive about asking patients about their symptoms rather than passively wait for patients to bring them up. Referral to specialists in urology and gynecology may be helpful for symptomatic management.

Anastomotic Fistula

Anastomotic fistula can be due to either anastomotic leak or a technical error. Symptoms that present in the immediate postoperative period are generally attributable to an intraoperative technical complication. These most commonly occur in pelvis, if the anterior rectal wall has not been adequately mobilized from the posterior vaginal wall, allowing the posterior vaginal wall to be incorporated into the circular stapler fire and creating a stapled fistula between the bowel and the vagina. It is also possible for the ureters or urethra to be inadvertently incorporated into an anastomosis if the rectal stump has not been properly mobilized from the surrounding structures. These fistulas will certainly require reoperation with fecal diversion and reconstruction of normal anatomy. In these situations, it is highly likely that a permanent colostomy will be the result, because usually the rectal stump is rather short and the pelvic dissection was difficult during the initial operation. A coloanal anastomosis is likely to be required if restoration of intestinal continuity is to be attempted.

The more likely etiology of anastomotic fistula is an anastomotic leak that fails to heal. These can occur from a leak from any location along the GI tract. Intra-abdominal leaks from the small bowel or colon may result in an enterocutaneous fistula. High-output fistulas and persistent low-output fistulas require

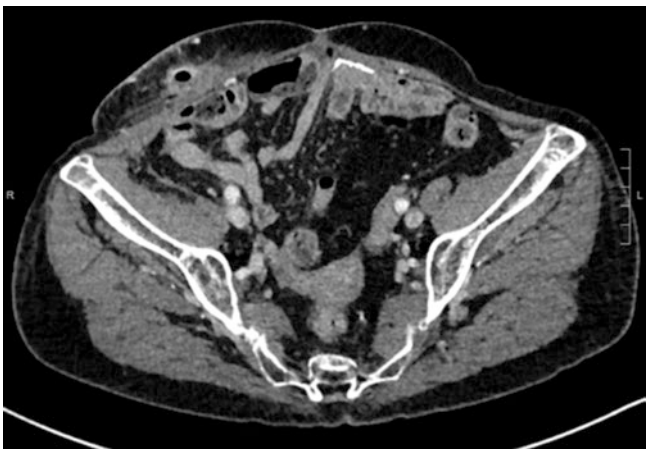

Fig. 10.4 Fistula from ileocolic anastomosis: CT image of a patient who underwent right colectomy complicated by a leak, which subsequently developed into a persistent low-output fistula tract through the abdominal wall. Treatment consisted of resection of the anastomosis and creation of a new ileocolic anastomosis

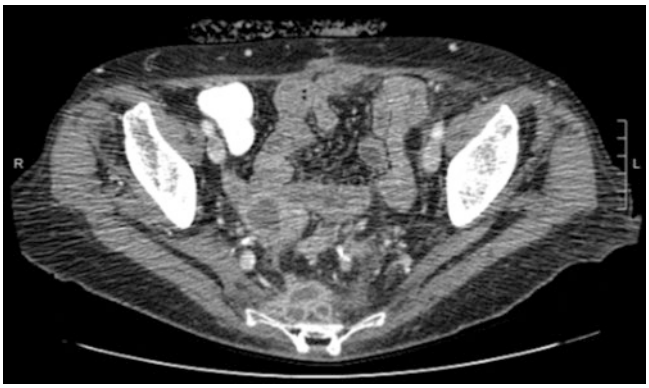

Fig. 10.5 Pelvic abscess and colovaginal fistula: CT image of a patient who underwent sigmoid colectomy for diverticulitis complicated by anastomotic leak. The leak caused pelvic abscesses that necessitated through the vaginal cuff, thus resulting in a colovaginal fistula

reoperation with resection of the leaking anastomosis and construction of a new anastomosis (Fig. 10.4). Judicious timing of reoperation is critical for avoidance of a hostile surgical field that will lead to more injuries and fistulas.

Colorectal anastomotic leaks in the pelvis may also fistulize to the skin of the anterior abdominal wall, or inferiorly to the skin of the buttock. These fistulas can result from a persistent tract of a transgluteal drain initially placed for abscess drainage. Pelvic leaks can also result in fistulas to the vagina, usually if the patient has had a prior hysterectomy, and rarely via the fallopian tube. Reoperation is generally necessary to address these complications, although some may heal with fecal diversion. Patients who undergo sigmoid resection for diverticulitis that was complicated by a colovaginal or colovesical fistula are at risk for recurrence of those fistulas if a colorectal anastomotic leak occurs, since either the vagina or the bladder has a fresh suture line that will be a vulnerable site through which an abscess will necessitate (Fig. 10.5). Placement of an omental flap in the pelvis to form a physical barrier between a fresh bowel anastomosis and other suture lines in the pelvis may decrease the risk of a recurrent fistula.

A rare and potentially very morbid sequela of anastomotic leak is a fistula to the epidural space causing an epidural abscess. This can occur as a complication of a chronic colorectal anastomotic leak and may present initially with nonspecific symptoms such as weight loss, low-grade fever, and malaise. Source control and systemic antibiotics should be the first steps in management. This may involve washout of the pelvic sepsis and fecal diversion or takedown of the anastomosis. Epidural decompression and debridement may also be necessary [109, 110].

Blind Loop Syndrome

Blind loop syndrome (or blind pouch syndrome) is an occasional complication of side-to-side antiperistaltic anastomoses. The blind sac of an antiperistaltic side-to-side bowel anastomosis may dilate over time. In most patients this does not cause any symptoms, but in some, it can be the cause of complications such as small intestinal bacterial overgrowth (SIBO), pseudo-obstruction, volvulus, ulcers, bleeding, and even perforations. These complications usually occur years after the operation. With dilation leading to SIBO or pseudo-obstruction, it is often the case that patients have months to years of vague abdominal symptoms such as bloating, nausea, weight loss, poor appetite, and abdominal discomfort [111, 112]. These symptoms are inconsistently related to dietary intake or eating habits. They may undergo multiple diagnostic studies that are largely unrevealing, as the dilation of the anastomosis is considered to be within normal limits, and the anastomosis is widely patent (Fig. 10.6a, b). Anastomotic ulcers rarely occur and may cause gastrointestinal bleeding or perforation (Fig. 10.7) [113, 114]. Capsule endoscopy or double balloon enteroscopy may be helpful in making the diagnosis. The treatment for any of these complications is resection of the anastomosis with an end-to-end anastomosis. The potential for these rare complications with side-to-side anastomoses should not dissuade surgeons from using this anastomotic technique routinely. However, this syndrome should be considered if patients with a prior side-to-side anastomosis present with these symptoms, and if surgical resection is indicated, an end-to-end anastomosis should be performed to prevent recurrence of the problem.

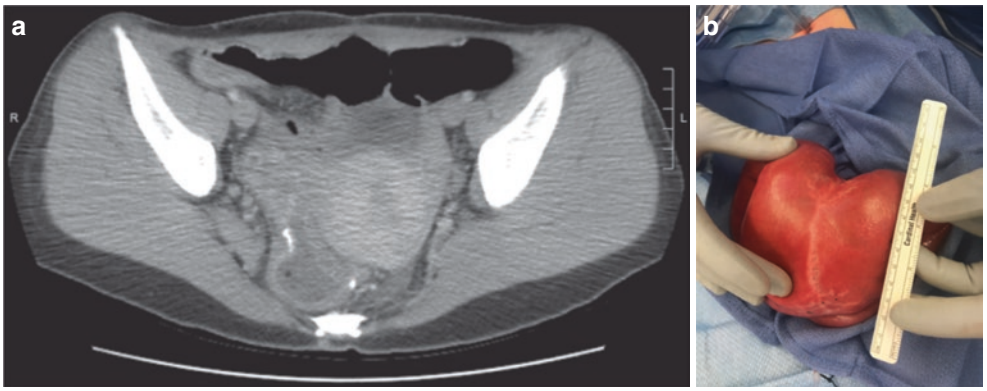

Fig. 10.6 (**a**) Dilated side-to-side stapled anastomosis: CT image of a patient who underwent total proctocolectomy with J-pouch and had a side-to-side anastomosis at the ileostomy takedown site. She had symptoms of intermittent obstruction causing weight loss and chronic abdominal discomfort. (**b**) Dilated anastomosis that appeared atonic and causing intermittent partial obstruction. After resection with end-to-end handsewn anastomosis, symptoms resolved

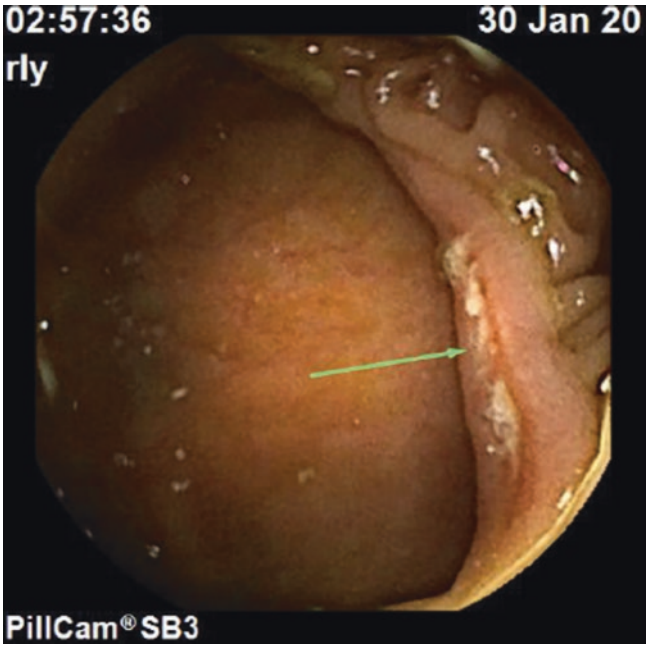

Fig. 10.7 Anastomotic ulcer: Capsule endoscopy diagnosed an anastomotic ulcer in a side-to-side jejunal anastomosis that was created 10 years prior, caused acute gastrointestinal bleeding that spontaneously resolved

Anastomotic Bleeding

While adequate blood supply is critical to the healing of a colonic anastomosis [115], careful hemostasis must be obtained to limit the possibility of postoperative anastomotic bleeding. The true incidence of anastomotic bleeding is difficult to know and depends on the definition of a "bleed." Undoubtedly all anastomotic suture/staple lines bleed to some extent, which may be clinically apparent when patients pass a small amount of dark blood shortly after a colonic resection. However, in patients with normal coagulation and platelet function, clotting rapidly occurs and the blood loss is minimal. Because most of these bleeding episodes are self-limited and of little clinical significance, the majority of bleeds go unreported.

Anastomotic bleeding has been reported in up to 5% of patients having a colorectal anastomosis [116–119]. In a recent study of 314 patients having colorectal surgery, the overall incidence of anastomotic bleeding, defined as a decrease in hemoglobin of 2.0 mg/dL in the setting of hematochezia, was 2.3% [118]. The timing of these bleeds ranged from 1 to 10 days postoperatively with a mean of 6 days. Of the 7 patients who had an intraluminal bleed only 4 required a blood transfusion and of these only one needed an additional intervention. Malik et al. reported on a series of 777 patients having a colorectal resection. In this series, while the total number of anastomotic bleeds was not reported, only 0.8% experienced bleeding that required an intervention. In this series the majority of the major bleeding episodes occurred within the first 24 hours with delayed bleeds being unusual [117]. In a similar series from Martinez-Serrano et al., only 0.5% of the 1389 colon resections had a significant anastomotic bleed requiring blood transfusions. These authors used endoscopy to confirm the diagnosis, but without performing any intervention. Only one patient required an anastomotic revision. Similar to the previous study, the bleeds most commonly occurred within the first 24 hours of surgery [120]. These series suggest that most bleeds will stop on their own with supportive care. Transfusion may be necessary but endoscopic or surgical intervention is rarely needed. Furthermore, while there are some delayed bleeds [121], most significant bleeding is detected within the first 24–48 hours from surgery [122]. When there is delayed bleeding anastomotic breakdown should also be considered and endoscopy or imaging should be performed to evaluate anastomotic integrity (Fig. 10.8a, b) [123].

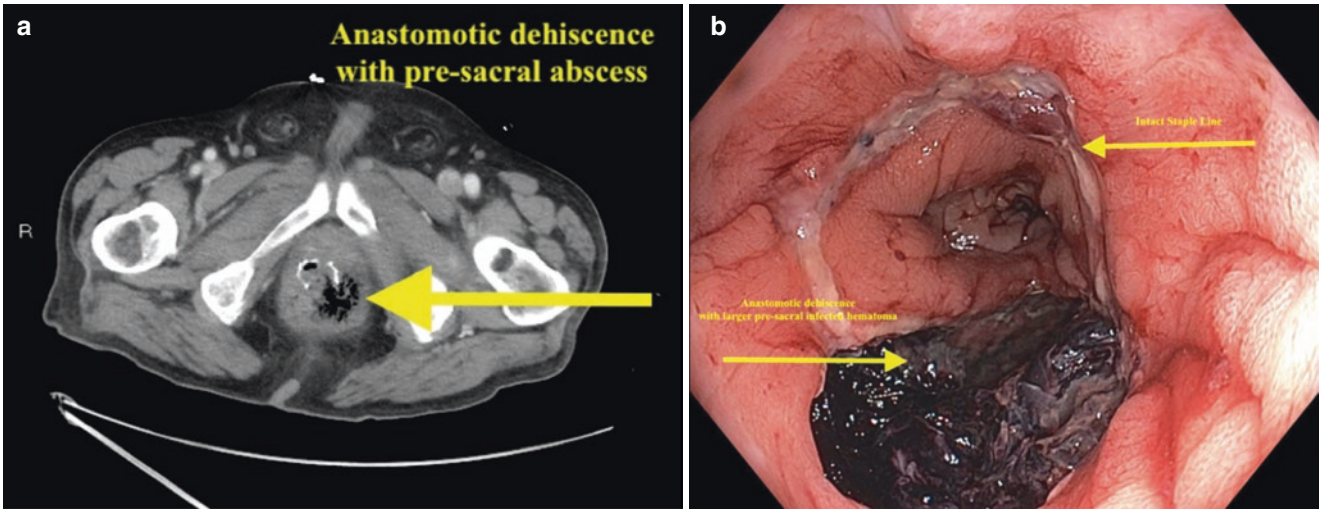

Fig. 10.8 (**a**) CT scan of patient presenting with an anastomotic bleed on POD 9 showing a pelvic abscess and anastomotic dehiscence. (**b**) Endoscopic exam confirming anastomotic dehiscence with pelvic hematoma

The clinical presentation for most anastomotic bleeds is similar to other etiologies of lower gastrointestinal bleeding. Depending on the level of the anastomosis bleeding can be either bright red blood (left-sided anastomosis) or darker clots (right-sided anastomosis) without abdominal pain. The quantity ranges significantly from a small amount to massive bleeding [117, 118]. Patient's vital signs can also range from completely normal to hemodynamic shock. Because of this variability in presentation all bleeding must be respected and mandates, at a minimum, close observation. If bleeding is persistent then monitoring serial hematocrits and coagulation parameters is important for making decisions about clinical management.

The management of an anastomotic bleed is also similar to other patients with a lower gastrointestinal bleed. The major difference between a postoperative gastrointestinal bleed and a spontaneous one is the initial workup. The etiology in the postoperative setting is rarely a diagnostic dilemma and therefore diagnostic studies, such as tagged red blood cell scans and CT angiography, are generally unnecessary. Patients are understandably anxious when passing blood, so reassurance from all healthcare providers is critical. This may mandate moving the patient to a monitored setting with close nursing observation and monitoring. All patients should have adequate intravenous access and blood products available. If there are hemodynamic changes, initial resuscitation with isotonic fluids is appropriate. Any coagulopathy should be corrected and all medications that interfere with coagulation, including nonsteroidal anti-inflammatory drugs, should be held. The need for blood transfusions will depend on the patient's hemodynamics and the clinical judgment necessary to decide if the bleeding has stopped or is ongoing. However, in the setting of large blood loss, transfusions are commonly necessary, and the practitioner need not wait for a low hematocrit to initiate a blood transfusion.

If the bleeding persists then endoscopic interventions are preferred [117, 121, 123]. Other options include angiography [124] and surgery, but both are less preferable compared to the less invasive option of endoscopy [122]. The decision to intervene depends on many factors, including the ease of endoscopic access. Left-sided anastomoses are more accessible endoscopically, so the threshold to intervene for left-sided operations is lower. Nevertheless, a right-sided anastomosis can be safely reached with an experienced endoscopist. Air insufflation should be minimized to avoid putting too much stress on the anastomosis, but anastomotic disruption is rare [123–125]. Bowel preparation is often unnecessary, especially for a left-sided anastomosis, but a rapid purge can be done if there is too much intraluminal blood to do an effective examination. If a clear bleeding site is identified, endoscopic clipping has been shown to be both safe and effective at stopping the bleeding (Fig. 10.9a, b) [117, 123]. Injection of the bleeding site with epinephrine [123] can also be done, especially when the bleeding is not focal, but this strategy may induce ischemia of the rest of the anastomosis. Electrocautery has also been successfully used but also runs the risk of anastomotic fistula [126]. Despite these potential complications endoscopic interventions appear to be safe with a low chance of secondary morbidity [123].

In the rare case when the bleeding neither stops with supportive case nor can be controlled endoscopically, the options for intervention are limited to angiography and surgery. While angiography, either with a vasopressin infusion [127] or embolization, has been successfully used to treat an anastomotic bleed, it does run the very real risk of compromising the blood supply to the anastomosis which can result in subsequent anastomotic breakdown. Therefore, angiography should be used selectively [117]. Surgery may be the better option if the anastomosis is readily accessible and there is

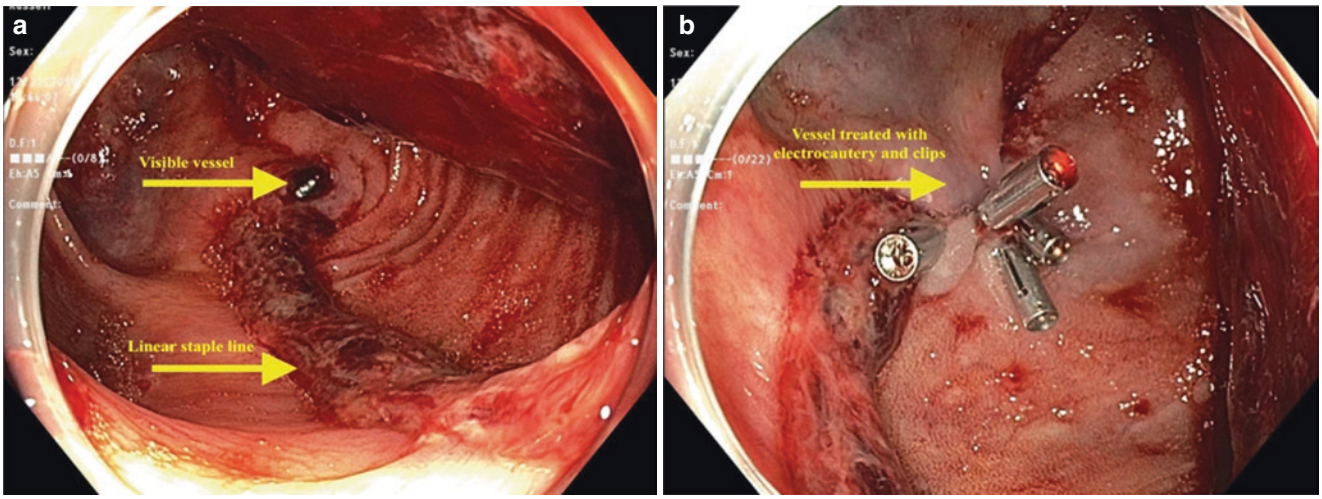

Fig. 10.9 (**a**) Endoscopic evaluation of a functional end-to-end ileocolic anastomosis 48 hours after anastomotic bleed showing staple line and visible vessel. (**b**) Anastomosis after successful use of electrocautery followed by placement of endoscopic clips to stop bleeding

appropriate colonic length for a revision. Anastomotic revision has been shown to stop bleeding in most cases and can be done safely in situations in which the bleeding cannot be otherwise controlled [117].

While there are options to treat anastomotic bleeding, prevention is always preferable to treatment. Proper healing of an anastomosis is dependent upon good blood supply, so seeing pulsatile blood flow when constructing an anastomosis should be comforting. Nevertheless, active examination and controlling this bleeding is important. Unfortunately, all anastomotic techniques are susceptible to bleeding. The Cochrane collaborative noted a slight, but statistically insignificant, difference between a handsewn and stapled anastomosis (3.1% vs. 5.4%) [116, 128] and therefore did not favor one technique over another. Regardless of the technique a well-constructed anastomosis should avoid incorporating the associated mesentery, so the antimesenteric border (Fig. 10.10) should be used for a functional end-to-end anastomosis and the mesentery cleared for an end-to-end anastomosis [118]. However, even when the mesentery is clearly free, bleeding from the staple/suture line is often noted. Therefore, for a functional end-to-end anastomosis direct visualization of the inside of the anastomosis should be done prior to closing the transverse opening. If pulsatile bleeding is present, treatment with cautery should be avoided. Instead, a well-placed figure of eight suture can control the bleeding and then be used to evert the anastomosis, so the entire staple line can be examined (Fig. 10.11). For left-sided anastomoses, endoscopic examination allows one to check for intraluminal bleeding while testing the integrity of the anastomosis [119, 129, 130]. If bleeding is noted, either a clip can be applied or a stitch can be directly placed from the outside of the bowel lumen, using the colonoscope to guide stitch placement [119, 130].

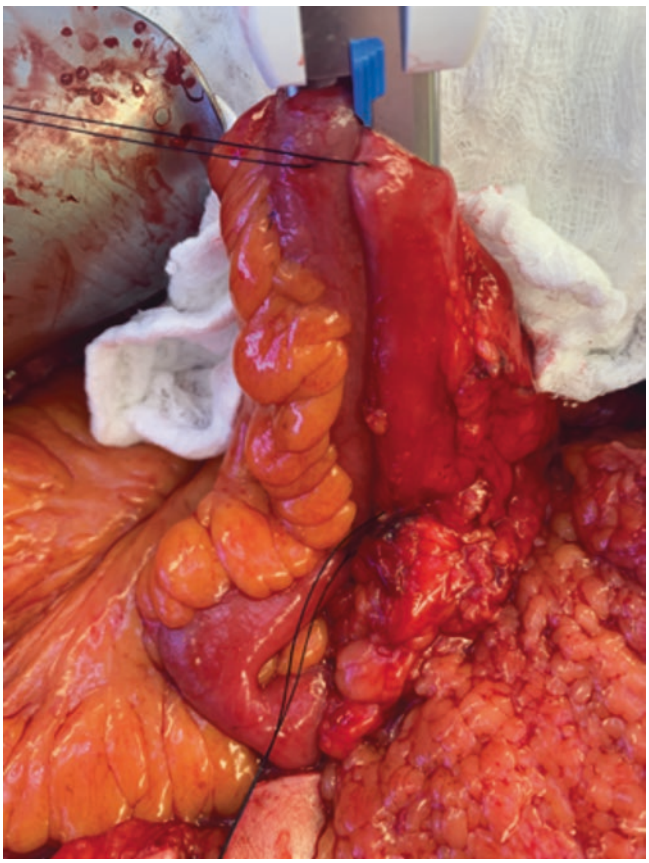

Fig. 10.10 Proper construction of functional end-to-end ileocolic anastomosis using the antimesenteric borders for staple line

In summary, while the true incidence of anastomotic bleeding is not known, clinically significant bleeding is uncommon. Most will stop with supportive care, which may include blood transfusions. For bleeding that persists, endoscopic management is the preferred intervention. Anastomotic

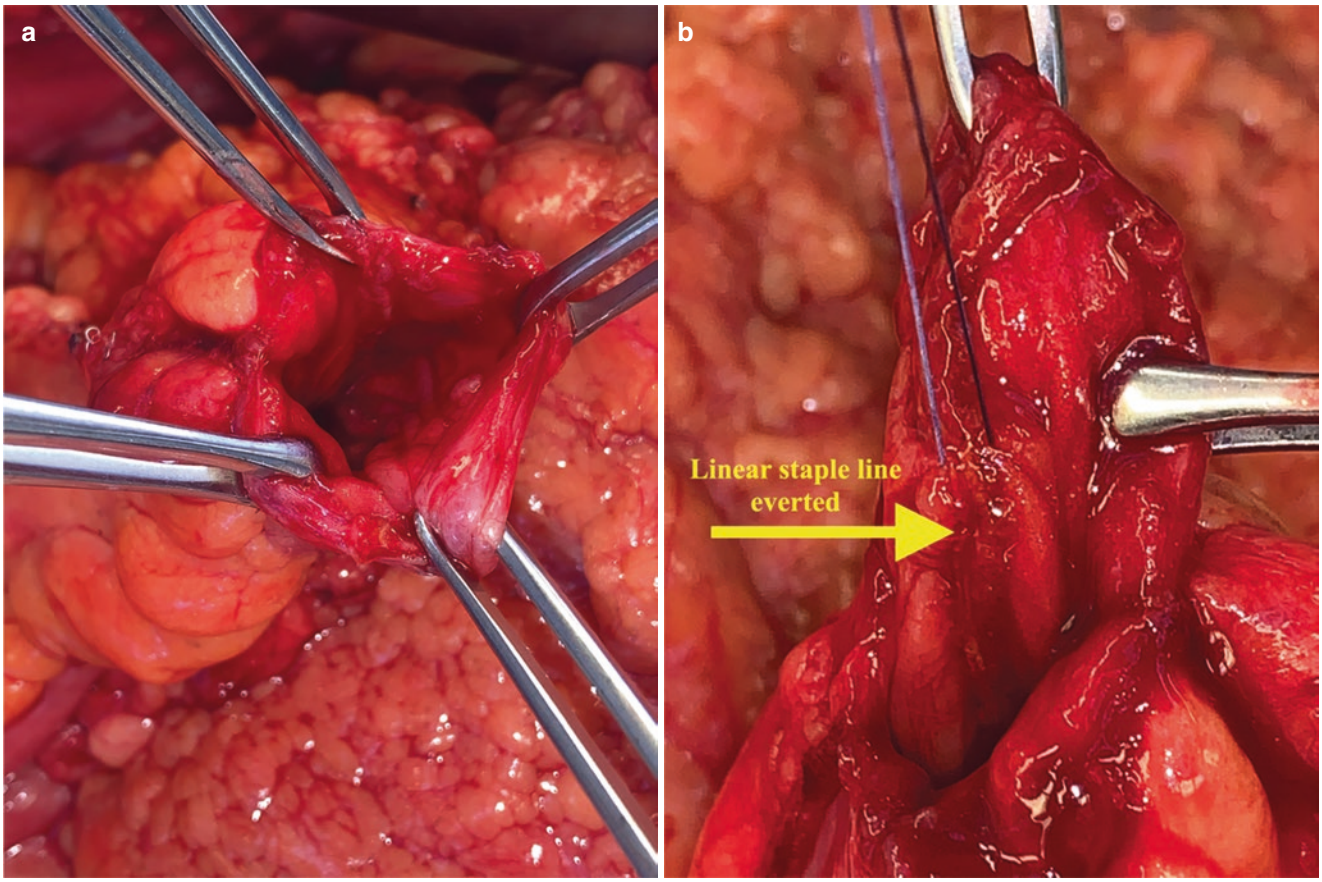

Fig. 10.11 (**a**) Direct examination of staple line prior to closing transverse enterotomy. (**b**) Placement of stitch to evert linear staple line to examine and ligate active pulsatile bleeding

revision is reserved for the rare situation when endoscopic interventions have failed [117].

Anastomotic Stricture

As with anastomotic bleeding the true incidence of anastomotic stricture is not well established, which reflects variability in the definition of a stricture throughout the literature and in clinical practice. It has been estimated to be as high as 30% but this includes clinically insignificant strictures. The most common definition of a stricture is a narrowing of an anastomosis that does not allow passage of either a 12-mm colonoscope or a rigid proctoscope [131–133]. Using this definition, the incidence is likely less than 10% [128, 134, 135]. Many of these patients will develop obstructive symptoms, which can include constipation, cramping, and a decreased caliber of stool [135]. In extreme cases patients may experience overflow diarrhea and incontinence as solid stool cannot pass the stricture. The diagnosis is usually made several months following the initial resection but usually within 12 months if not associated with recurrent disease [134–136]. In addition to impacting patient function, a stricture that cannot be traversed limits the ability to completely evaluate the stricture and to monitor the proximal colon. This is particularly important for patients whose surgery was due to malignant disease since the stricture may represent recurrence and, even if benign, the patient requires ongoing surveillance of the entire colon. What is clear is that the lower the anastomosis the higher the stricture rate, with ileal pouch anal anastomoses and coloanal anastomoses [134, 137] having the highest stricture rates compared with more proximal anastomoses, such as ileocolic anastomoses.

The etiology of an anastomotic stricture is likely multifactorial. A stricture forms when the lumen is compromised by ongoing fibrosis. This can be the result of ischemia, infection, anastomotic leak, radiation and/or recurrent disease [131, 133]. Proximal diversion has also been shown to be a risk factor for a low pelvic anastomosis since no stool is passing through to dilate the anastomosis regularly [135]. In a Cochrane review left-sided end-to-end stapled anastomoses had a higher stricture rate than handsewn anastomoses (8% vs 2%) [128]. However, this may be confounded by the fact that staplers are more often used for low anastomoses, which have a higher risk for ischemia and leak, which can result in stricture. The authors of the review stated that this finding does

not necessarily favor a handsewn approach [138]. For ileocolic resections the Cochrane analysis concluded that the stricture rate of handsewn vs. stapled anastomoses were similarly low [139].

Understanding the exact anatomy of a stricture is important prior to planning an intervention [140]. This can be done endoscopically if the stricture can be traversed with a smaller endoscope or with fluoroscopic imaging if not (Fig. 10.12). It is also important to understand the anastomotic construction since an inexperienced endoscopist may not recognize that with an end-to-side or side-to-side reconstruction the anastomosis may be at 90 degrees to the lumen and misinterpret the "dog ear" as a pinpoint stricture (Fig. 10.13). Once again, when the anatomy is unclear a fluoroscopic examination can be enlightening.

Treatment of an anastomotic stricture depends on the anatomy and the etiology. In the setting of prior malignancy, recurrent disease must be ruled out with biopsies. While many malignant strictures will be clinically evident by the presence of an ulceration and/or a mass, the stricture itself may preclude and adequate evaluation. CEA monitoring and PET CT scans may be helpful under these circumstances. If the suspicion for malignancy remains high even after initial biopsies are negative, repeat biopsies may be necessary [131].

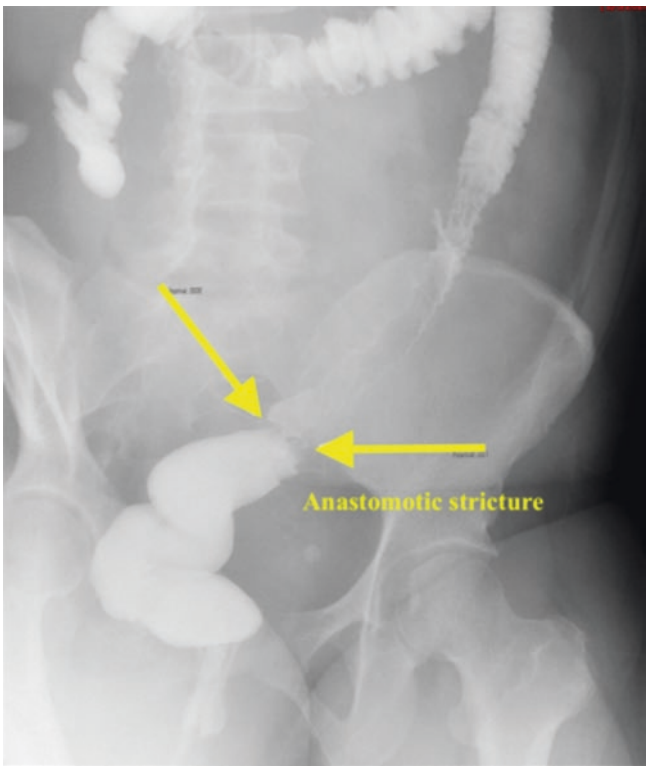

Fig. 10.12 Fluoroscopic image of a stapled end-to-end anastomosis showing a short, tight stricture

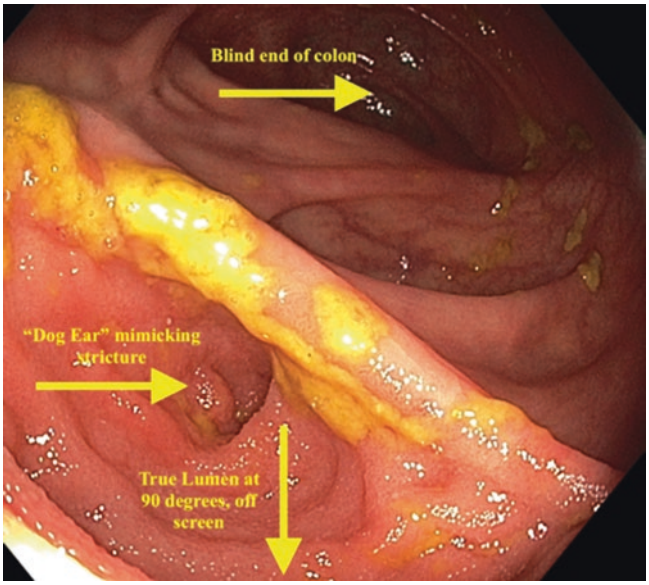

Fig. 10.13 Endoscopic image of functional end-to-end anastomosis demonstrating how the small bowel "dog ear" is easily misinterpreted as an anastomotic stricture

For strictures near the anal canal, such as after a low pelvic anastomosis or an ileal pouch anal anastomosis, dilation can often be accomplished with a digital exam. This is particularly true for patients that have a protective ileostomy who demonstrate a short stricture on a water-soluble contrast enema. For patients with a handsewn coloanal anastomosis, a digital exam prior to reversal is important since a fluoroscopic study may not appreciate the stricture if the tip of the catheter for contrast infusion is placed proximal to the strictured area. Since dilation with a digital exam can be uncomfortable, it is often done under anesthesia (Fig. 10.14). If successful, patients may require intermittent dilation to keep the anastomosis open. Patients can learn to self-dilate with Hegar dilators (Fig. 10.15) if there is a tendency for the stricture to recur. For patients with strictures that are more proximal, mechanical dilation using a bougie has also been successful.

Endoscopic balloon dilation has emerged as the preferred first line treatment for an anastomotic stricture with a success rate ranging from 67% to 100% [141, 142]. Unfortunately, most studies are small and retrospective, and lack details on the specific nature of the anastomotic strictures. Most strictures referred for dilation are probably short (<2 cm), which seems to be the population that is best treated for dilation [133, 141]. Therefore, defining the characteristics of stricture is important prior to intervention. In a series of 94 patients using endoscopic balloon dilatation, Suchan et al. reported an overall success rate of 67%. They noted that the success rate for patients having had an initial benign diagnosis was 88% with few complications. In contrast, in patients having had an initial malignant diagnosis, the success rate was only

59% with many patients experiencing recurrent strictures that needed surgical interventions [131]. In a more recent report, Biraima et al. reported on the long-term success of 76 patients with an anastomotic stricture. They reported a recurrence rate at 1 year, 3 years, and 5 years of 11%, 22%, and 25%, respectively. In 50% of the patients, success was obtained with either one or two dilations. Even in the 25% who eventually recurred most were successfully managed with repeat dilation and only two ultimately required a surgical intervention. Therefore, the secondary success rate was high at 97%, although in the 25% who initially failed, multiple dilations were often necessary. The serious complication rate was low with most being minor bleeding and one perforation, none of whom required a surgical intervention [134]. Of note, the authors did include a significant number of patients with mild stenosis (10–20 mm). When looking at risk factors for recurrence of a stricture following balloon dilation, the authors found that strictures with a luminal diameter < 10 mm, those from a handsewn anastomosis, and those requiring more than two dilations were more likely to recur over time (Fig. 10.16a–c) [134].

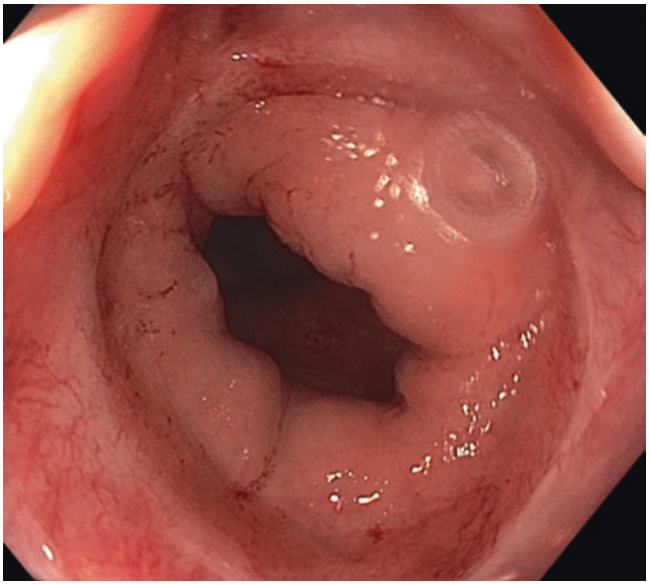

Fig. 10.14 Endoscopic image of handsewn coloanal anastomosis amenable to digital dilation

Fig. 10.15 Hegar dilators

For patients with a significant stricture, endoscopic electrocautery incision (EECI) [143–145], either using cautery or a laser, can initially open up the stricture either as definitive therapy or in conjunction with other therapies, including balloon dilation or steroid injection [146]. Several radial incisions are placed through the fibrotic mucosa along the most resistant portion of the stricture in order to relieve the tension on the stricture (Fig. 10.17) [143–145]. In the previously mentioned series from Suchan et al., 37 of the 68 patients with an initial malignant diagnosis had an incision placed through the stricture using a variety of energy devices. Most were then able to undergo balloon dilation [131]. Endoscopy, TEMS, [147], and TAMIS [148] have all been used to access the stricture and to perform the superficial incisions along the stricture or, in some cases, to fully resect the fibrotic tissue [149]. Using these techniques, success rates of 90–100% have been reported, albeit in small studies with variable long-term follow-up data. [142, 143]. Nevertheless, for short fibrotic strictures that recur following balloon dilation this is a viable alternative to anastomotic revision.

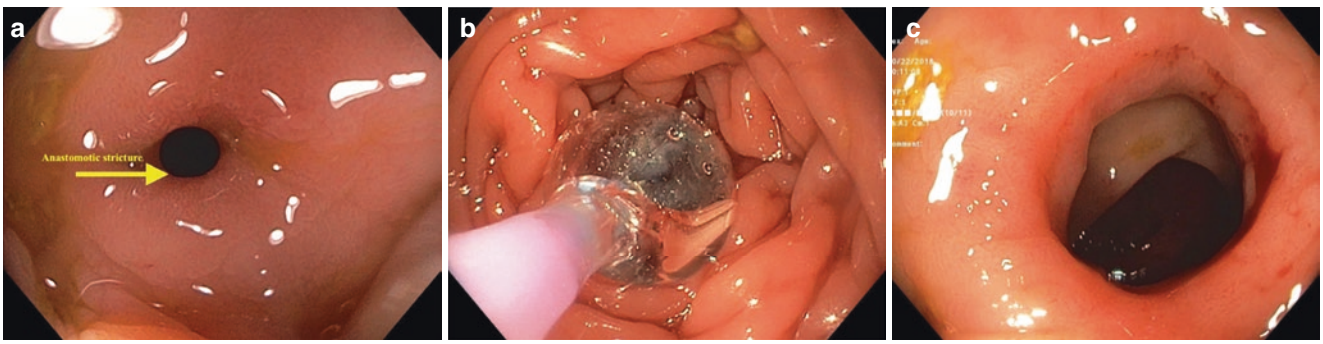

Fig. 10.16 (**a**) Endoscopic view of tight end-to-end stapled anastomosis. (**b**) Balloon dilation. (**c**) Final view after serial dilations showing a wide-open lumen

Self-expanding metal stents (SEMS) have also been used as an adjunct to treat a stricture. In theory, the radial force of the stent will allow persistent pressure on stricture which may reduce recurrence rates [150]. Unfortunately, in this setting the stents frequently migrate and therefore have not been consistently successful. In addition, there have been reports using a circular stapler via a transanal approach to resect the stricture (Fig. 10.18) [151]. However, this technique is only amenable to more mild strictures that would allow the passing of an anvil above the stricture and therefore has not been widely adopted [137]. Finally, both linear staplers [152] and electrocautery [150] have also been used to transanally perform a strictureplasty by resecting a portion of the stricture wall to open the anastomosis. Most data are limited to case reports and small series, so firm conclusions about long-term success are limited.

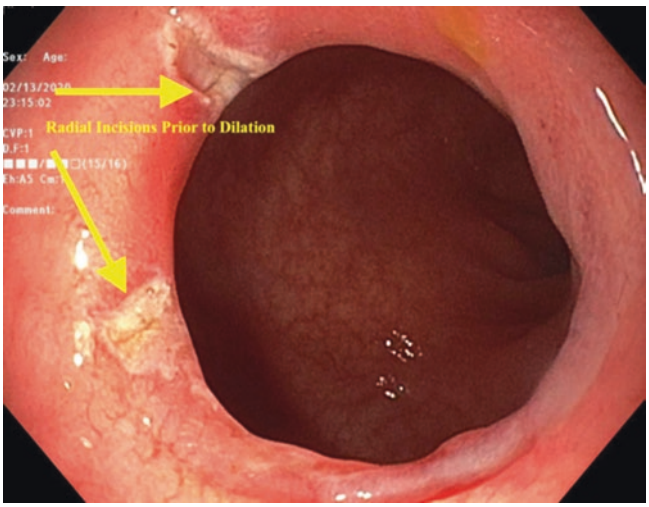

Fig. 10.17 Initial radial incision along the stricture to facilitate a safe and successful balloon dilation

Unfortunately, some anastomotic strictures are not amenable to these noninvasive procedures. Long (> 2 cm), irregular, and angulated strictures either fail interventions or are not anatomically appropriate for these procedures [133]. In these cases, a surgical revision may be the only option [136–142]. Resection and re-anastomosis are very challenging and should not be undertaken without careful consideration. Ureteral stents can help identify the left ureter which is often adherent to the colon and the associated mesentery. The area around the anastomosis will be severely fibrotic and perforation at the anastomosis is common during the resection. The key to a successful anastomosis is to get below the area of fibrosis to soft, pliable colon or rectum [133]. If this is not possible, then a handsewn coloanal anastomosis can be done [136]. Given the complexity of this operation, proximal diversion is reasonable to maximize the chances of long-term success.

Studies looking at re-do pelvic surgery following a failed colorectal anastomosis include a heterogenous group of patients with stenoses, anastomotic fistulas, and even recurrent cancer. Therefore, these studies are not limited to patients with a stricture. Nevertheless, the fibrosis associated with all these processes is significant, so these studies still provide necessary insight into the complexities of these procedures. Despite the challenges presented

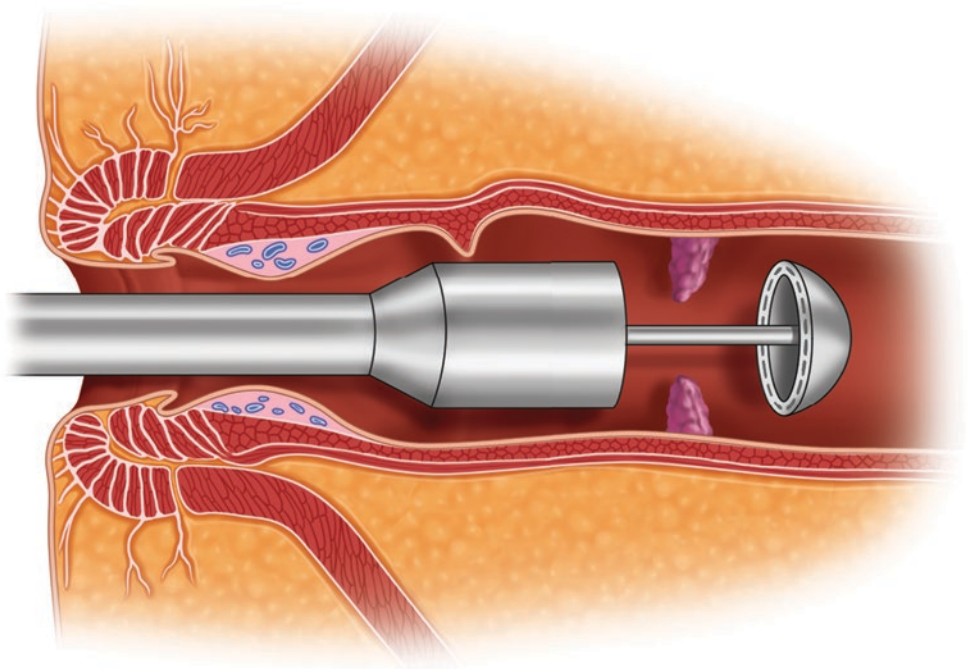

Fig. 10.18 Illustration demonstrating a transanal resection of an anastomotic stricture using an EEA stapler

with these patients, successful revisions have been noted in 57–100% [136] of selected series with a pooled success rate of 79%. When the stricture is located above 11 cm from the anal verge, a new stapled colorectal anastomosis is often feasible. However, if the stricture is less than 11 cm from the verge a handsewn coloanal anastomosis is almost universally constructed [133]. Since pelvic fibrosis is often significant a straight coloanal is most commonly performed, but if there is room in the pelvis a colonic J-pouch remains an option [153]. Both immediate and delayed (Turnbull-Cutait) procedures have been described. Depending on the amount of fibrosis, the entire anastomosis can be resected or alternatively a mucosectomy can be done leaving a rectal muscular tube similar to a Soave procedure [133, 153]. Given the high-risk nature of these anastomoses, proximal diversion is generally the rule [136]. While this success rate is promising, it is important to note that these reports are of highly selected patients and performed by very experienced surgeons in tertiary care facilities. The mean age was relatively young at 58 years, suggesting that older patients may not do well with this approach. Furthermore, while intestinal continuity was achieved in nearly 80%, 17% did have incontinence and nearly 60% had some degree of low anterior resection syndrome [136]. It is critical, therefore, to have frank discussions with patients about functional expectations and to not solely focus on defining success as being "stoma free." Nevertheless, in the fit and highly motivated patient, re-do surgery is certainly a viable option.

Remembering that preserving a high quality of life is of prime importance, it is essential to make the patient aware of all the available options, including a permanent stoma. If a stricture is either not amenable to or fails the previously described non-surgical approaches, or if the patient is not a good surgical risk due to comorbidities or anatomic constraints, a well-functioning colostomy may be the most definitive option that will maintain a high quality of life.

In summary, clinically significant anastomotic strictures will occur in up to 10% of patients following a colorectal resection. Most of these will be left-sided and within the rectum. Fortunately, many strictures are simple and can often be treated with dilation either using a balloon or manually. While often successful, repeat procedures are not uncommon. For those that fail simple dilation, a step-up approach to include incision of the stricture followed by dilation or a transanal strictureplasty may be an option [137]. Revision of the anastomosis is a daunting undertaking, but in the properly selected patients it can be successful. For those patients who are not successfully treated by any of these means, a properly constructed colostomy can restore a high quality of life and should be considered a viable option under these difficult conditions.

References

1. Enker WE, Merchant N, Cohen AM, et al. Safety and efficacy of low anterior resection for rectal cancer: 681 consecutive cases from a specialty service. Ann Surg. 1999;230(4):544–52; discussion 552–544.
2. Law WL, Chu KW. Anterior resection for rectal cancer with mesorectal excision: a prospective evaluation of 622 patients. Ann Surg. 2004;240(2):260–8.
3. Paun BC, Cassie S, MacLean AR, Dixon E, Buie WD. Postoperative complications following surgery for rectal cancer. Ann Surg. 2010;251(5):807–18.
4. Sánchez-Guillén L, Frasson M, García-Granero Á, et al. Risk factors for leak, complications and mortality after ileocolic anastomosis: comparison of two anastomotic techniques. Ann R Coll Surg Engl. 2019;101(8):571–8.
5. Midura EF, Hanseman D, Davis BR, et al. Risk factors and consequences of anastomotic leak after colectomy: a national analysis. Dis Colon Rectum. 2015;58(3):333–8.
6. Hammond J, Lim S, Wan Y, Gao X, Patkar A. The burden of gastrointestinal anastomotic leaks: an evaluation of clinical and economic outcomes. J Gastrointest Surg. 2014;18(6):1176–85.
7. Ashraf SQ, Burns EM, Jani A, et al. The economic impact of anastomotic leakage after anterior resections in English NHS hospitals: are we adequately remunerating them? Color Dis. 2013;15(4):e190–8.
8. Hyman N, Manchester TL, Osler T, Burns B, Cataldo PA. Anastomotic leaks after intestinal anastomosis: it's later than you think. Ann Surg. 2007;245(2):254–8.
9. Ruggiero R, Sparavigna L, Docimo G, et al. Post-operative peritonitis due to anastomotic dehiscence after colonic resection. Multicentric experience, retrospective analysis of risk factors and review of the literature. Ann Ital Chir. 2011;82(5):369–75.
10. van Rooijen SJ, Huisman D, Stuijvenberg M, et al. Intraoperative modifiable risk factors of colorectal anastomotic leakage: why surgeons and anesthesiologists should act together. Int J Surg. 2016;36(Pt A):183–200.
11. Lipska MA, Bissett IP, Parry BR, Merrie AE. Anastomotic leakage after lower gastrointestinal anastomosis: men are at a higher risk. ANZ J Surg. 2006;76(7):579–85.
12. Platell C, Barwood N, Dorfmann G, Makin G. The incidence of anastomotic leaks in patients undergoing colorectal surgery. Color Dis. 2007;9(1):71–9.
13. Vignali A, Fazio VW, Lavery IC, et al. Factors associated with the occurrence of leaks in stapled rectal anastomoses: a review of 1,014 patients. J Am Coll Surg. 1997;185(2):105–13.
14. Law WI, Chu KW, Ho JW, Chan CW. Risk factors for anastomotic leakage after low anterior resection with total mesorectal excision. Am J Surg. 2000;179(2):92–6.
15. Sparreboom CL, van Groningen JT, Lingsma HF, et al. Different risk factors for early and late colorectal anastomotic leakage in a nationwide audit. Dis Colon Rectum. 2018;61(11):1258–66.
16. Nikolian VC, Kamdar NS, Regenbogen SE, et al. Anastomotic leak after colorectal resection: a population-based study of risk factors and hospital variation. Surgery. 2017;161(6):1619–27.
17. Matthiessen P, Hallböök O, Andersson M, Rutegård J, Sjödahl R. Risk factors for anastomotic leakage after anterior resection of the rectum. Color Dis. 2004;6(6):462–9.
18. Konishi T, Watanabe T, Kishimoto J, Nagawa H. Elective colon and rectal surgery differ in risk factors for wound infection: results of prospective surveillance. Ann Surg. 2006;244(5):758–63.
19. Park JS, Choi GS, Kim SH, et al. Multicenter analysis of risk factors for anastomotic leakage after laparoscopic rectal cancer excision: the Korean laparoscopic colorectal surgery study group. Ann Surg. 2013;257(4):665–71.

20. Vu L, Penter C, Platell C. Long-term significance of an anastomotic leak in patients undergoing an ultra-low anterior resection for rectal cancer. ANZ J Surg. 2019;89(10):1291–5.
21. Braunschmid T, Hartig N, Baumann L, Dauser B, Herbst F. Influence of multiple stapler firings used for rectal division on colorectal anastomotic leak rate. Surg Endosc. 2017;31(12):5318–26.
22. Otsuka K, Kimura T, Matsuo T, et al. Laparoscopic low anterior resection with two planned stapler fires. JSLS. 2019;23(1):e2018.00112.
23. Kim JC, Lee JL, Kim CW, Lim SB, Alsaleem HA, Park SH. Mechanotechnical faults and particular issues of anastomotic complications following robot-assisted anterior resection in 968 rectal cancer patients. J Surg Oncol. 2019;120(8):1436–45.
24. Group ESoCC. The impact of stapling technique and surgeon specialism on anastomotic failure after right-sided colorectal resection: an international multicentre, prospective audit. Colorectal Dis. 2018;20(11):1028–40.
25. García-Granero E, Navarro F, Cerdán Santacruz C, et al. Individual surgeon is an independent risk factor for leak after double-stapled colorectal anastomosis: an institutional analysis of 800 patients. Surgery. 2017;162(5):1006–16.
26. Yeh CY, Changchien CR, Wang JY, et al. Pelvic drainage and other risk factors for leakage after elective anterior resection in rectal cancer patients: a prospective study of 978 patients. Ann Surg. 2005;241(1):9–13.
27. Zhang HY, Zhao CL, Xie J, et al. To drain or not to drain in colorectal anastomosis: a meta-analysis. Int J Color Dis. 2016;31(5):951–60.
28. Menahem B, Vallois A, Alves A, Lubrano J. Prophylactic pelvic drainage after rectal resection with extraperitoneal anastomosis: is it worthwhile? A meta-analysis of randomized controlled trials. Int J Color Dis. 2017;32(11):1531–8.
29. Cavaliere D, Popivanov G, Cassini D, et al. Is a drain necessary after anterior resection of the rectum? A systematic review and meta-analysis. Int J Color Dis. 2019;34(6):973–81.
30. Rondelli F, Bugiantella W, Vedovati MC, et al. To drain or not to drain extraperitoneal colorectal anastomosis? A systematic review and meta-analysis. Color Dis. 2014;16(2):O35–42.
31. Guerra F, Giuliani G, Coletta D, et al. A meta-analysis of randomized controlled trials on the use of suction drains following rectal surgery. Dig Surg. 2018;35(6):482–90.
32. Kang CY, Halabi WJ, Chaudhry OO, et al. Risk factors for anastomotic leakage after anterior resection for rectal cancer. JAMA Surg. 2013;148(1):65–71.
33. Konishi T, Watanabe T, Kishimoto J, Nagawa H. Risk factors for anastomotic leakage after surgery for colorectal cancer: results of prospective surveillance. J Am Coll Surg. 2006;202(3):439–44.
34. Hüser N, Michalski CW, Erkan M, et al. Systematic review and meta-analysis of the role of defunctioning stoma in low rectal cancer surgery. Ann Surg. 2008;248(1):52–60.
35. Montedori A, Cirocchi R, Farinella E, Sciannameo F, Abraha I. Covering ileo- or colostomy in anterior resection for rectal carcinoma. Cochrane Database Syst Rev. 2010;(5):CD006878.
36. Phan K, Oh L, Ctercteko G, et al. Does a stoma reduce the risk of anastomotic leak and need for re-operation following low anterior resection for rectal cancer: systematic review and meta-analysis of randomized controlled trials. J Gastrointest Oncol. 2019;10(2):179–87.
37. Peeters KC, Tollenaar RA, Marijnen CA, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg. 2005;92(2):211–6.
38. Gastinger I, Marusch F, Steinert R, et al. Protective defunctioning stoma in low anterior resection for rectal carcinoma. Br J Surg. 2005;92(9):1137–42.
39. Cannon JA, Altom LK, Deierhoi RJ, et al. Preoperative oral antibiotics reduce surgical site infection following elective colorectal resections. Dis Colon Rectum. 2012;55(11):1160–6.
40. Garfinkle R, Abou-Khalil J, Morin N, et al. Is there a role for oral antibiotic preparation alone before colorectal surgery? ACS-NSQIP analysis by coarsened exact matching. Dis Colon Rectum. 2017;60(7):729–37.
41. Güenaga KF, Matos D, Wille-Jørgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev. 2011;9:CD001544.
42. group ESoCEc. Association of mechanical bowel preparation with oral antibiotics and anastomotic leak following left sided colorectal resection: an international, multi-centre, prospective audit. Colorectal Dis. 2018;20(Suppl 6):15–32.
43. Kiran RP, Murray AC, Chiuzan C, Estrada D, Forde K. Combined preoperative mechanical bowel preparation with oral antibiotics significantly reduces surgical site infection, anastomotic leak, and ileus after colorectal surgery. Ann Surg. 2015;262(3):416–25; discussion 423-415
44. Scarborough JE, Mantyh CR, Sun Z, Migaly J. Combined mechanical and oral antibiotic bowel preparation reduces incisional surgical site infection and anastomotic leak rates after elective colorectal resection: an analysis of colectomy-targeted ACS NSQIP. Ann Surg. 2015;262(2):331–7.
45. Althumairi AA, Canner JK, Gearhart SL, et al. Risk factors for wound complications after abdominoperinal resection: analysis of the ACS NSQIP database. Color Dis. 2016;18:O260.
46. Dolejs SC, Guzman MJ, Fajardo AD, et al. Bowel preparation is associated with reduced morbidity in elderly patients undergoing elective colectomy. J Gastrointest Surg. 2017;21(2):372–9.
47. Morris MS, Graham LA, Chu DI, Cannon JA, Hawn MT. Oral antibiotic bowel preparation significantly reduces surgical site infection rates and readmission rates in elective colorectal surgery. Ann Surg. 2015;261(6):1034–40.
48. Klinger AL, Green H, Monlezun DJ, et al. The role of bowel preparation in colorectal surgery: results of the 2012-2015 ACS-NSQIP data. Ann Surg. 2019;269(4):671–7.
49. Vo E, Massarweh NN, Chai CY, et al. Association of the addition of oral antibiotics to mechanical bowel preparation for left colon and rectal cancer resections with reduction of surgical site infections. JAMA Surg. 2018;153(2):114–21.
50. Koller SE, Bauer KW, Egleston BL, et al. Comparative effectiveness and risks of bowel preparation before elective colorectal surgery. Ann Surg. 2018;267(4):734–42.
51. Gaines S, Shao C, Hyman N, Alverdy JC. Gut microbiome influences on anastomotic leak and recurrence rates following colorectal cancer surgery. Br J Surg. 2018;105(2):e131–41.
52. Shogan BD, Belogortseva N, Luong PM, et al. Collagen degradation and MMP9 activation by Enterococcus faecalis contribute to intestinal anastomotic leak. Sci Transl Med. 2015;7(286):286ra268.
53. Olivas AD, Shogan BD, Valuckaite V, et al. Intestinal tissues induce an SNP mutation in Pseudomonas aeruginosa that enhances its virulence: possible role in anastomotic leak. PLoS One. 2012;7(8):e44326.
54. Hyoju SK, Adriaansens C, Wienholts K, et al. Low-fat/high-fibre diet prehabilitation improves anastomotic healing via the microbiome: an experimental model. Br J Surg. 2019;107:743.
55. Wiegerinck M, Hyoju SK, Mao J, et al. Novel de novo synthesized phosphate carrier compound ABA-PEG20k-Pi20 suppresses collagenase production in Enterococcus faecalis and prevents colonic anastomotic leak in an experimental model. Br J Surg. 2018;105(10):1368–76.
56. Hyoju SK, Klabbers RE, Aaron M, et al. Oral polyphosphate suppresses bacterial collagenase production and prevents anastomotic

leak due to Serratia marcescens and Pseudomonas aeruginosa. Ann Surg. 2018;267(6):1112–8.
57. van Rooijen SJ, Jongen AC, Wu ZQ, et al. Definition of colorectal anastomotic leakage: a consensus survey among Dutch and Chinese colorectal surgeons. World J Gastroenterol. 2017;23(33):6172–80.
58. Huiberts AA, Dijksman LM, Boer SA, Krul EJ, Peringa J, Donkervoort SC. Contrast medium at the site of the anastomosis is crucial in detecting anastomotic leakage with CT imaging after colorectal surgery. Int J Color Dis. 2015;30(6):843–8.
59. Kauv P, Benadjaoud S, Curis E, Boulay-Coletta I, Loriau J, Zins M. Anastomotic leakage after colorectal surgery: diagnostic accuracy of CT. Eur Radiol. 2015;25(12):3543–51.
60. Leahy J, Schoetz D, Marcello P, et al. What is the risk of clinical anastomotic leak in the diverted colorectal anastomosis? J Gastrointest Surg. 2014;18:1812.
61. Borstlap WAA, Westerduin E, Aukema TS, Bemelman WA, Tanis PJ, Group DSR. Anastomotic leakage and chronic presacral sinus formation after low anterior resection: results from a large cross-sectional study. Ann Surg. 2017;266(5):870–7.
62. Singh PP, Zeng IS, Srinivasa S, Lemanu DP, Connolly AB, Hill AG. Systematic review and meta-analysis of use of serum C-reactive protein levels to predict anastomotic leak after colorectal surgery. Br J Surg. 2014;101(4):339–46.
63. Waterland P, Ng J, Jones A, et al. Using CRP to predict anastomotic leakage after open and laparoscopic colorectal surgery: is there a difference? Int J Color Dis. 2016;31(4):861–8.
64. Giaccaglia V, Salvi PF, Antonelli MS, et al. Procalcitonin reveals early dehiscence in colorectal surgery: the PREDICS study. Ann Surg. 2016;263(5):967–72.
65. Garcia-Granero A, Frasson M, Flor-Lorente B, et al. Procalcitonin and C-reactive protein as early predictors of anastomotic leak in colorectal surgery: a prospective observational study. Dis Colon Rectum. 2013;56(4):475–83.
66. Benoit O, Faron M, Margot N, et al. C-reactive protein values after colorectal resection: can we discharge a patient with a C-reactive protein value >100? A retrospective cohort study. Dis Colon Rectum. 2019;62(1):88–96.
67. Pantel HJ, Jasak LJ, Ricciardi R, et al. Should they stay or should they go? The utility of C-reactive protein in predicting readmission and anastomotic leak after colorectal resection. Dis Colon Rectum. 2019;62(2):241–7.
68. Challine A, Lefèvre JH, Creavin B, et al. Can a local drainage salvage a failed colorectal or coloanal anastomosis? A prospective cohort of 54 patients. Dis Colon Rectum. 2020;63(1):93–100.
69. Hedrick TL, Sawyer RG, Foley EF, Friel CM. Anastomotic leak and the loop ileostomy: friend or foe? Dis Colon Rectum. 2006;49(8):1167–76.
70. Blumetti J, Chaudhry V, Prasad L, Abcarian H. Delayed transanal repair of persistent coloanal anastomotic leak in diverted patients after resection for rectal cancer. Color Dis. 2012;14(10):1238–41.
71. Brunner W, Rossetti A, Vines LC, Kalak N, Bischofberger SA. Anastomotic leakage after laparoscopic single-port sigmoid resection: combined transanal and transabdominal minimal invasive management. Surg Endosc. 2015;29(12):3803–5.
72. Dapri G, Guta D, Grozdev K, et al. Colorectal anastomotic leakage corrected by transanal laparoscopy. Color Dis. 2016;18(6):O210–3.
73. Beunis A, Pauli S, Van Cleemput M. Anastomotic leakage of a colorectal anastomosis treated by transanal endoscopic microsurgery. Acta Chir Belg. 2008;108(4):474–6.
74. Whitlow CB, Opelka FG, Gathright JB, Beck DE. Treatment of colorectal and ileoanal anastomotic sinuses. Dis Colon Rectum. 1997;40(7):760–3.
75. Olavarria OA, Kress RL, Shah SK, Agarwal AK. Novel technique for anastomotic salvage using transanal minimally invasive surgery: a case report. World J Gastrointest Surg. 2019;11(5):271–8.
76. Swain BT, Ellis CN. Fibrin glue treatment of low rectal and pouch-anal anastomotic sinuses. Dis Colon Rectum. 2004;47(2):253–5.
77. López V, Abrisqueta J, Luján J, Serrano A, Parrilla P. Endoscopic treatment with biologic glue of chronic presacral sinus after low anterior resection. Cir Esp. 2015;93(3):197–9.
78. Sloothaak DA, Buskens CJ, Bemelman WA, Tanis PJ. Treatment of chronic presacral sinus after low anterior resection. Color Dis. 2013;15(6):727–32.
79. Strangio G, Zullo A, Ferrara EC, et al. Endo-sponge therapy for management of anastomotic leakages after colorectal surgery: a case series and review of literature. Dig Liver Dis. 2015;47(6):465–9.
80. Gardenbroek TJ, Musters GD, Buskens CJ, et al. Early reconstruction of the leaking ileal pouch-anal anastomosis: a novel solution to an old problem. Color Dis. 2015;17(5):426–32.
81. Milito G, Lisi G, Venditti D, et al. Endoluminal vacuum therapy as treatment for anastomotic colorectal leakage. Surg Technol Int. 2017;30:125–30.
82. van Koperen PJ, van Berge Henegouwen MI, Rosman C, et al. The Dutch multicenter experience of the endo-sponge treatment for anastomotic leakage after colorectal surgery. Surg Endosc. 2009;23(6):1379–83.
83. Riss S, Stift A, Meier M, Haiden E, Grünberger T, Bergmann M. Endo-sponge assisted treatment of anastomotic leakage following colorectal surgery. Color Dis. 2010;12(7 Online):e104–8.
84. von Bernstorff W, Glitsch A, Schreiber A, Partecke LI, Heidecke CD. ETVARD (endoscopic transanal vacuum-assisted rectal drainage) leads to complete but delayed closure of extraperitoneal rectal anastomotic leakage cavities following neoadjuvant radiochemotherapy. Int J Color Dis. 2009;24(7):819–25.
85. Borstlap WAA, Musters GD, Stassen LPS, et al. Vacuum-assisted early transanal closure of leaking low colorectal anastomoses: the CLEAN study. Surg Endosc. 2018;32(1):315–27.
86. Abdalla S, Cotte E, Epin A, et al. Short-term and long-term outcome of endoluminal vacuum therapy for colorectal or coloanal anastomotic leakage: results of a Nationwide Multicenter Cohort Study From the French GRECCAR Group. Dis Colon Rectum. 2020;63(3):371–80.
87. Cereatti F, Fiocca F, Dumont JL, et al. Fully covered self-expandable metal stent in the treatment of postsurgical colorectal diseases: outcome in 29 patients. Ther Adv Gastroenterol. 2016;9(2):180–8.
88. Cooper CJ, Morales A, Othman MO. Outcomes of the use of fully covered esophageal self-expandable stent in the management of colorectal anastomotic strictures and leaks. Diagn Ther Endosc. 2014;2014:187541.
89. Kobayashi H, Kikuchi A, Okazaki S, et al. Over-the-scope-clipping system for anastomotic leak after colorectal surgery: report of two cases. World J Gastroenterol. 2014;20(24):7984–7.
90. Sulz MC, Bertolini R, Frei R, Semadeni GM, Borovicka J, Meyenberger C. Multipurpose use of the over-the-scope-clip system ("Bear claw") in the gastrointestinal tract: Swiss experience in a tertiary center. World J Gastroenterol. 2014;20(43):16287–92.
91. Wedi E, Gonzalez S, Menke D, Kruse E, Matthes K, Hochberger J. One hundred and one over-the-scope-clip applications for severe gastrointestinal bleeding, leaks and fistulas. World J Gastroenterol. 2016;22(5):1844–53.
92. Stafford C, Francone TD, Marcello PW, Roberts PL, Ricciardi R. Is diversion with ileostomy non-inferior to Hartmann resection for left-sided colorectal anastomotic leak? J Gastrointest Surg. 2018;22(3):503–7.

93. McArdle CS, McMillan DC, Hole DJ. Impact of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer. Br J Surg. 2005;92(9):1150–4.
94. Branagan G, Finnis D, Group WCCAW. Prognosis after anastomotic leakage in colorectal surgery. Dis Colon Rectum. 2005;48(5):1021–6.
95. Bell SW, Walker KG, Rickard MJ, et al. Anastomotic leakage after curative anterior resection results in a higher prevalence of local recurrence. Br J Surg. 2003;90(10):1261–6.
96. Law WL, Choi HK, Lee YM, Ho JW, Seto CL. Anastomotic leakage is associated with poor long-term outcome in patients after curative colorectal resection for malignancy. J Gastrointest Surg. 2007;11(1):8–15.
97. Eberhardt JM, Kiran RP, Lavery IC. The impact of anastomotic leak and intra-abdominal abscess on cancer-related outcomes after resection for colorectal cancer: a case control study. Dis Colon Rectum. 2009;52(3):380–6.
98. Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg. 2011;253(5):890–9.
99. Zimmermann MS, Wellner U, Laubert T, et al. Influence of anastomotic leak after elective colorectal cancer resection on survival and local recurrence: a propensity score analysis. Dis Colon Rectum. 2019;62(3):286–93.
100. Wang S, Liu J, Zhao H, Ge S, Wang W. Adverse effects of anastomotic leakage on local recurrence and survival after curative anterior resection for rectal cancer: a systematic review and meta-analysis. World J Surg. 2017;41(1):277–84.
101. Salvans S, Mayol X, Alonso S, et al. Postoperative peritoneal infection enhances migration and invasion capacities of tumor cells in vitro: an insight into the association between anastomotic leak and recurrence after surgery for colorectal cancer. Ann Surg. 2014;260(5):939–43; discussion 943–934.
102. Alonso S, Pascual M, Salvans S, et al. Postoperative intra-abdominal infection and colorectal cancer recurrence: a prospective matched cohort study of inflammatory and angiogenic responses as mechanisms involved in this association. Eur J Surg Oncol. 2015;41(2):208–14.
103. Alonso S, Mayol X, Nonell L, et al. Peripheral blood leucocytes show differential expression of tumour progression-related genes in colorectal cancer patients who have a postoperative intra-abdominal infection: a prospective matched cohort study. Color Dis. 2017;19(5):O115–25.
104. Mongin C, Maggiori L, Agostini J, Ferron M, Panis Y. Does anastomotic leakage impair functional results and quality of life after laparoscopic sphincter-saving total mesorectal excision for rectal cancer? A case-matched study. Int J Color Dis. 2014;29(4):459–67.
105. Nesbakken A, Nygaard K, Lunde OC. Outcome and late functional results after anastomotic leakage following mesorectal excision for rectal cancer. Br J Surg. 2001;88(3):400–4.
106. Ashburn JH, Stocchi L, Kiran RP, Dietz DW, Remzi FH. Consequences of anastomotic leak after restorative proctectomy for cancer: effect on long-term function and quality of life. Dis Colon Rectum. 2013;56(3):275–80.
107. Kverneng Hultberg D, Svensson J, Jutesten H, et al. The impact of anastomotic leakage on long-term function after anterior resection for rectal cancer. Dis Colon Rectum. 2020;65:619.
108. Hain E, Manceau G, Maggiori L, Mongin C, Prost À la DJ, Panis Y. Bowel dysfunction after anastomotic leakage in laparoscopic sphincter-saving operative intervention for rectal cancer: a case-matched study in 46 patients using the low anterior resection score. Surgery. 2017;161(4):1028–39.
109. Gaignard E, Bergeat D, Kieser D, Robin F, Meunier B. Fatal epidural abscess with meningitis: a rare complication of colorectal surgery. Acta Chir Belg. 2019:1–4.
110. Zeitoun J, Menahem B, Fohlen A, Lebreton G, Lubrano J, Alves A. Emergency surgery for epidural abcess secondary to sacral fistula after laparoscopic proctectomy. J Surg Case Rep. 2016;2016(7)
111. Walfish J, Frankel A. Chronic pseudo-obstruction secondary to side-to-side intestinal anastomosis. Arch Surg. 1979;114(9):1075–8.
112. Jackson CC, Bettolli MM, De Carli CF, Bass J, Rubin SZ, Sweeney B. Beware of stapled side-to-side bowel anastomoses in small children. Eur J Pediatr Surg. 2007;17(6):426–7.
113. Valle RD, Zinicola R, Iaria M. Blind loop perforation after side-to-side ileocolonic anastomosis. World J Gastrointest Surg. 2014;6(8):156–9.
114. Kubo K, Suzuoki M, Kimura N, et al. Blind pouch syndrome-associated anastomotic ulcer diagnosed with capsule and double-balloon endoscopy. Intern Med. 2019;58(22):3235–8.
115. Davis B, Rivadeneira DE. Complications of colorectal anastomoses: leaks, strictures, and bleeding. Surg Clin North Am. 2013;93(1):61–87.
116. Lustosa SA, Matos D, Atallah AN, Castro AA. Stapled versus handsewn methods for colorectal anastomosis surgery. Cochrane Database Syst Rev. 2001;(3):CD003144.
117. Malik AH, East JE, Buchanan GN, Kennedy RH. Endoscopic haemostasis of staple-line haemorrhage following colorectal resection. Color Dis. 2008;10(6):616–8.
118. Hebert J, Eltonsy S, Gaudet J, Jose C. Incidence and risk factors for anastomotic bleeding in lower gastrointestinal surgery. BMC Res Notes. 2019;12(1):378.
119. Shamiyeh A, Szabo K, Ulf Wayand W, Zehetner J. Intraoperative endoscopy for the assessment of circular-stapled anastomosis in laparoscopic colon surgery. Surg Laparosc Endosc Percutan Tech. 2012;22(1):65–7.
120. Martinez-Serrano MA, Pares D, Pera M, et al. Management of lower gastrointestinal bleeding after colorectal resection and stapled anastomosis. Tech Coloproctol. 2009;13(1):49–53.
121. Lou Z, Zhang W, Yu E, Meng R, Fu C. Colonoscopy is the first choice for early postoperative rectal anastomotic bleeding. World J Surg Oncol. 2014;12:376.
122. Linn TY, Moran BJ, Cecil TD. Staple line haemorrhage following laparoscopic left-sided colorectal resections may be more common when the inferior mesenteric artery is preserved. Tech Coloproctol. 2008;12(4):289–93.
123. Besson R, Christidis C, Denet C, et al. Management of postoperative bleeding after laparoscopic left colectomy. Int J Color Dis. 2016;31(8):1431–6.
124. Golda T, Zerpa C, Kreisler E, Trenti L, Biondo S. Incidence and management of anastomotic bleeding after ileocolic anastomosis. Color Dis. 2013;15(10):1301–8.
125. Amr MA, Alzghari MJ, Polites SF, et al. Endoscopy in the early postoperative setting after primary gastrointestinal anastomosis. J Gastrointest Surg. 2014;18(11):1911–6.
126. Cirocco WC, Golub RW. Endoscopic treatment of postoperative hemorrhage from a stapled colorectal anastomosis. Am Surg. 1995;61(5):460–3.
127. Atabek U, Pello MJ, Spence RK, Alexander JB, Camishion RC. Arterial vasopressin for control of bleeding from a stapled intestinal anastomosis. Report of two cases. Dis Colon Rectum. 1992;35(12):1180–2.
128. Neutzling CB, Lustosa SA, Proenca IM, da Silva EM, Matos D. Stapled versus handsewn methods for colorectal anastomosis surgery. Cochrane Database Syst Rev. 2012;(2):CD003144.

129. Kamal T, Pai A, Velchuru VR, et al. Should anastomotic assessment with flexible sigmoidoscopy be routine following laparoscopic restorative left colorectal resection? Color Dis. 2015;17(2):160–4.
130. Li VK, Wexner SD, Pulido N, et al. Use of routine intraoperative endoscopy in elective laparoscopic colorectal surgery: can it further avoid anastomotic failure? Surg Endosc. 2009;23(11):2459–65.
131. Suchan KL, Muldner A, Manegold BC. Endoscopic treatment of postoperative colorectal anastomotic strictures. Surg Endosc. 2003;17(7):1110–3.
132. Luchtefeld MA, Milsom JW, Senagore A, Surrell JA, Mazier WP. Colorectal anastomotic stenosis. Results of a survey of the ASCRS membership. Dis Colon Rectum. 1989;32(9):733–6.
133. Schlegel RD, Dehni N, Parc R, Caplin S, Tiret E. Results of reoperations in colorectal anastomotic strictures. Dis Colon Rectum. 2001;44(10):1464–8.
134. Biraima M, Adamina M, Jost R, Breitenstein S, Soll C. Long-term results of endoscopic balloon dilation for treatment of colorectal anastomotic stenosis. Surg Endosc. 2016;30(10):4432–7.
135. Bertocchi E, Barugola G, Benini M, et al. Colorectal anastomotic stenosis: lessons learned after 1643 colorectal resections for deep infiltrating endometriosis. J Minim Invasive Gynecol. 2019;26(1):100–4.
136. Westerduin E, Klaver CEL, van Geloven AAW, Westerterp M, Bemelman WA, Tanis PJ. Outcome after redo surgery for complicated colorectal and coloanal anastomosis: a systematic review. Dis Colon Rectum. 2018;61(8):988–98.
137. Kraenzler A, Maggiori L, Pittet O, Alyami MS, Prost Al DJ, Panis Y. Anastomotic stenosis after coloanal, colorectal and ileoanal anastomosis: what is the best management? Color Dis. 2017;19(2):O90–6.
138. Lustosa SA, Matos D, Atallah AN, Castro AA. Stapled versus handsewn methods for colorectal anastomosis surgery: a systematic review of randomized controlled trials. Sao Paulo Med J. 2002;120(5):132–6.
139. Choy PY, Bissett IP, Docherty JG, Parry BR, Merrie AE. Stapled versus handsewn methods for ileocolic anastomoses. Cochrane Database Syst Rev. 2007;(3):CD004320.
140. Hiranyakas A, Da Silva G, Denoya P, Shawki S, Wexner SD. Colorectal anastomotic stricture: is it associated with inadequate colonic mobilization? Tech Coloproctol. 2013;17(4):371–5.
141. Ragg J, Garimella V, Cast J, Hunter IA, Hartley JE. Balloon dilatation of benign rectal anastomotic strictures – a review. Dig Surg. 2012;29(4):287–91.
142. Garcea G, Sutton CD, Lloyd TD, Jameson J, Scott A, Kelly MJ. Management of benign rectal strictures: a review of present therapeutic procedures. Dis Colon Rectum. 2003;46(11):1451–60.
143. Jain D, Sandhu N, Singhal S. Endoscopic electrocautery incision therapy for benign lower gastrointestinal tract anastomotic strictures. Ann Gastroenterol. 2017;30(5):473–85.
144. Brandimarte G, Tursi A, Gasbarrini G. Endoscopic treatment of benign anastomotic colorectal stenosis with electrocautery. Endoscopy. 2000;32(6):461–3.
145. Bravi I, Ravizza D, Fiori G, et al. Endoscopic electrocautery dilation of benign anastomotic colonic strictures: a single-center experience. Surg Endosc. 2016;30(1):229–32.
146. Lucha PA Jr, Fticsar JE, Francis MJ. The strictured anastomosis: successful treatment by corticosteroid injections–report of three cases and review of the literature. Dis Colon Rectum. 2005;48(4):862–5.
147. Kato K, Saito T, Matsuda M, Imai M, Kasai S, Mito M. Successful treatment of a rectal anastomotic stenosis by transanal endoscopic microsurgery (TEM) using the contact Nd:YAG laser. Surg Endosc. 1997;11(5):485–7.
148. Nepal P, Mori S, Kita Y, et al. Radial incision and cutting method using a transanal approach for treatment of anastomotic strictures following rectal cancer surgery: a case report. World J Surg Oncol. 2019;17(1):48.
149. Baatrup G, Svensen R, Ellensen VS. Benign rectal strictures managed with transanal resection–a novel application for transanal endoscopic microsurgery. Color Dis. 2010;12(2):144–6.
150. Forshaw MJ, Maphosa G, Sankararajah D, Parker MC, Stewart M. Endoscopic alternatives in managing anastomotic strictures of the colon and rectum. Tech Coloproctol. 2006;10(1):21–7.
151. Nissotakis C, Sakorafas GH, Vugiouklakis D, Kostopoulos P, Peros G. Transanal circular stapler technique: a simple and highly effective method for the management of high-grade stenosis of low colorectal anastomoses. Surg Laparosc Endosc Percutan Tech. 2008;18(4):375–8.
152. Pagni S, McLaughlin CM. Simple technique for the treatment of strictured colorectal anastomosis. Dis Colon Rectum. 1995;38(4):433–4.
153. Genser L, Manceau G, Karoui M, et al. Postoperative and long-term outcomes after redo surgery for failed colorectal or coloanal anastomosis: retrospective analysis of 50 patients and review of the literature. Dis Colon Rectum. 2013;56(6):747–55.

Part II

Anorectal Disease

Hemorrhoids

11

Jennifer S. Davids and Timothy J. Ridolfi

Key Concepts

- Hemorrhoids represent a sizeable source of patient morbidity, with a broad array of associated symptoms.
- Knowledge of anorectal and hemorrhoid anatomy is critical to selecting the appropriate treatment.
- Minimizing straining, improving hydration, and increasing fiber intake are the first step for patients with symptomatic hemorrhoids.
- Most office procedures are best suited for symptomatic grade I–III internal hemorrhoids or thrombosed external hemorrhoids.
- One's armamentarium should include a variety of techniques for symptomatic hemorrhoids to optimize outcomes and provide individualized therapy.
- Complications of hemorrhoid surgery include urinary retention, bleeding, infection, stenosis, incontinence, and recurrence.
- Special considerations include pregnant patients, as well as those with Crohn's disease, immunocompromise, or portal hypertension.

Epidemiology

Although hemorrhoids have been described since Biblical times, they continue to mystify most providers and patients [1]. Accordingly, they are one of the most common health conditions searched on the Internet [2, 3]. Hemorrhoidal disease is estimated to affect approximately 4% of the US population [4]. The true incidence of symptomatic hemorrhoids is likely underestimated due to limitations in establishing a clear diagnosis and under-reporting of symptoms to health care providers. Hemorrhoidal disease accounts for over three million outpatient office visits per year, at an estimated cost of over 770 million dollars [5]. Hemorrhoid symptoms affect men and women with equal frequency, with the highest incidence between age 45 and 65 [6]. Symptomatic hemorrhoids are more common in individuals from higher socioeconomic backgrounds and in whites [7].

Anatomy

As anatomic structures, hemorrhoids are part of normal human anatomy. Hemorrhoids are arteriovenous structures that lie in the submucosal layer within the anal canal. Their three primary locations (left lateral, right anterior, right posterior) receive arterial inflow from the terminal branches of the superior hemorrhoidal and middle hemorrhoidal arteries (Fig. 11.1). Venous outflow is from the superior, middle, and inferior hemorrhoidal veins, which drain into the internal pudendal vein and then the inferior vena cava.

Hemorrhoids are classified as either internal or external based on their anatomic relationship to the dentate line. Internal hemorrhoids are proximal to the dentate line, and external hemorrhoids are distal (Fig. 11.2). The term "mixed" hemorrhoids applies to a hemorrhoid complex containing both an internal and external component. Internal hemorrhoids have overlying columnar mucosa, whereas external hemorrhoids have overlying modified squamous epithelium (anoderm).

Internal hemorrhoids are graded based on the degree of prominence and prolapse [8]. The grading system is useful clinically for characterizing the hemorrhoids and selecting appropriate treatments (Fig. 11.2). *Grade I* hemorrhoids are visibly engorged but do not prolapse below the dentate line. *Grade II* hemorrhoids prolapse below the dentate on Valsalva or defecation but spontaneously reduce. *Grade III* hemorrhoids prolapse but require manual reduction. *Grade IV* are prolapsed and not reducible.

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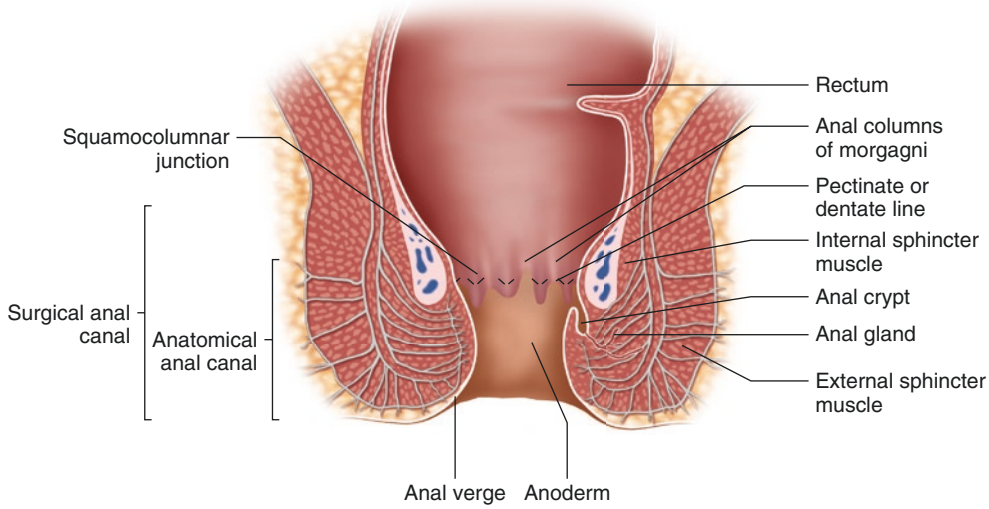

Fig. 11.1 Hemorrhoid anatomy

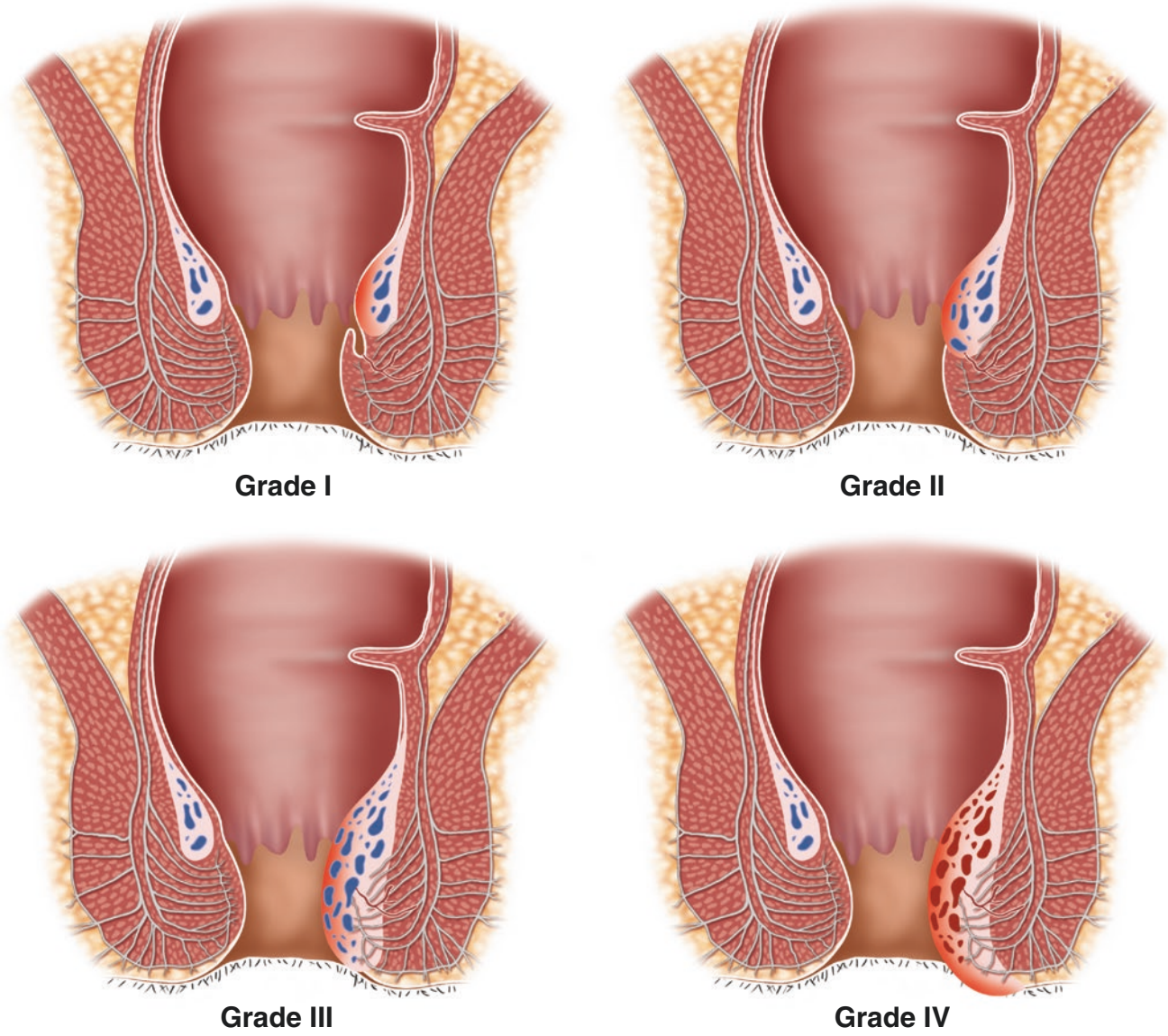

Fig. 11.2 Hemorrhoid classification and grading system

Other clinically important descriptions of hemorrhoids include "strangulated" hemorrhoids, which are grade IV that have become edematous to the point of compromised blood supply, leading to necrosis or gangrene in extreme cases (Fig. 11.3). Thrombosed hemorrhoids are typically external and contain a clot under pressure, causing them to have a rounded, bluish appearance (Fig. 11.4). The distinction between anal "skin tags" and external hemorrhoids is somewhat obscure but is often of great concern to patients. Although anal skin tags are somewhat synonymous with external hemorrhoids, they are typically considered those that are less engorged and bluish in color and are characterized by redundant anoderm. Often a skin tag will develop after a thrombosed hemorrhoid has fully resolved and the clot has absorbed.

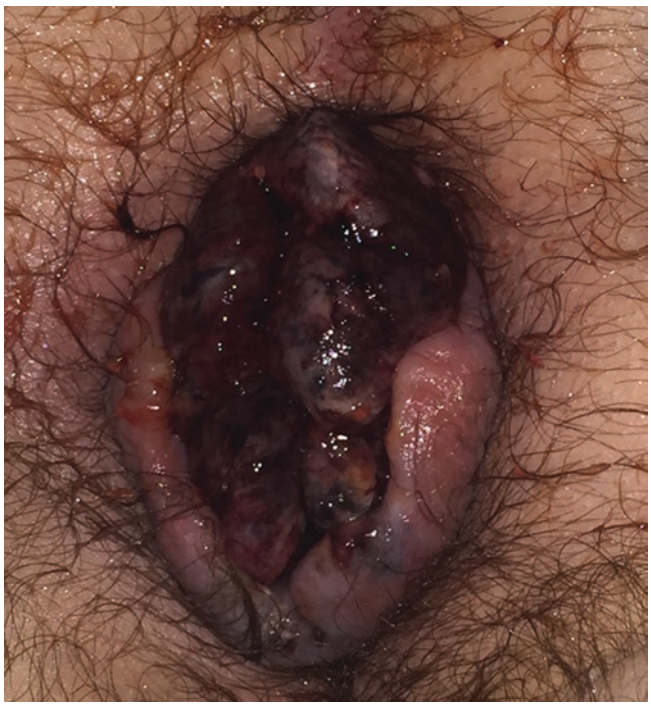

Fig. 11.3 Strangulated, gangrenous hemorrhoids. (Courtesy of Carrie Y. Peterson, MD)

Understanding hemorrhoid innervation and sensation is essential to establish the correct diagnosis and select the appropriate treatment strategy [9]. Internal hemorrhoids have visceral innervation, and thus are sensitive to pressure but not pain or temperature. External hemorrhoids have somatic innervation and are exquisitely sensitive to pain and temperature. Importantly, hemorrhoids contribute to up to 20% of baseline continence, acting as a passive buttress to block seepage of stool, and they also engorge on Valsalva and thus potentiate their effect; this may have important implications on patients' bowel function after hemorrhoid procedures, particularly individuals who have marginal continence [10].

Pathogenesis

Multiple theories exist to explain the development of hemorrhoidal disease in some individuals. Only about 40% of those with enlarged hemorrhoids are symptomatic [11]. Straining

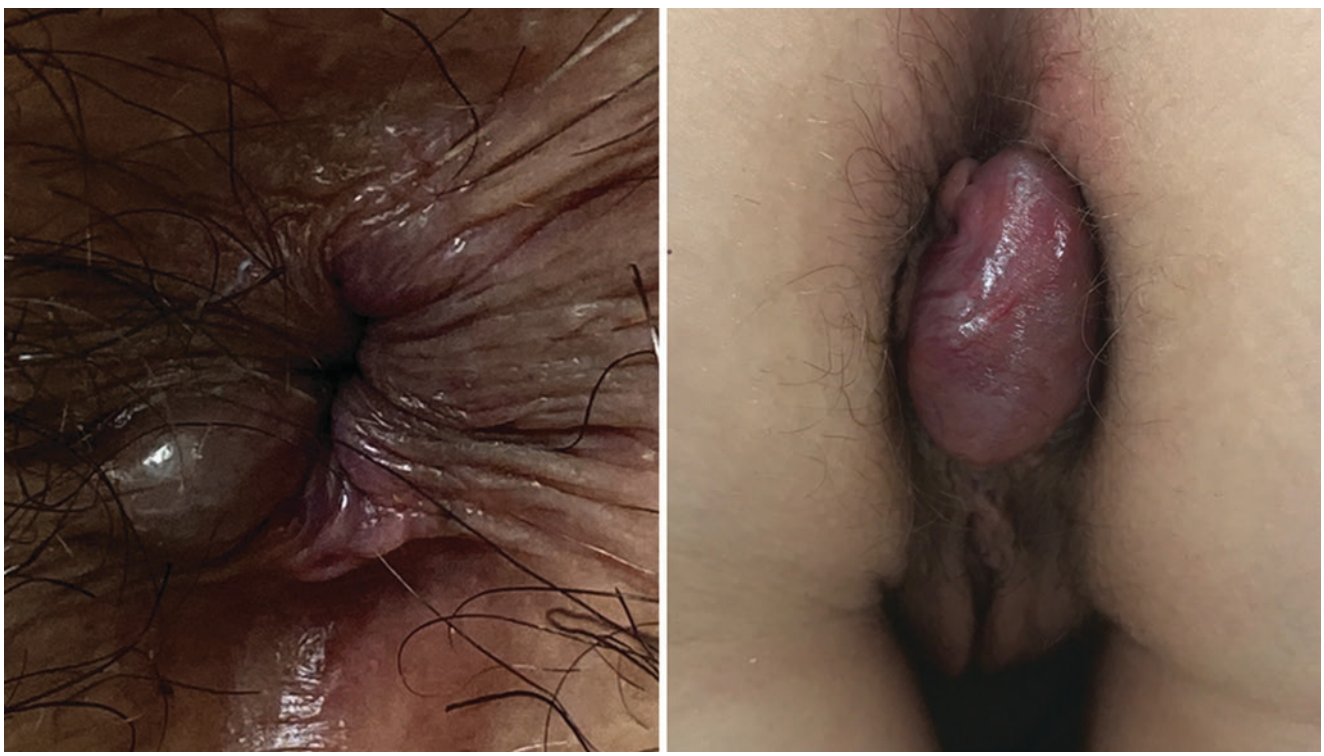

Fig. 11.4 Thrombosed external hemorrhoid

is felt to be a major contributor—most commonly straining with defecation as is typically encountered with constipation, due to either hard stools or pelvic outlet dysfunction. Patients who frequently Valsalva may also be at risk, with common examples being weightlifters or patients with COPD or chronic cough. Compared to a more natural "squatting" position, the typical Western commode requires its users to strain in an unnatural fashion to defecate and may be a contributor to hemorrhoid pathology. Conditions with impaired venous return, including the later stages of pregnancy or pelvic outlet dysfunction, are associated with hemorrhoid engorgement and eventual tissue swelling and laxity. Very little is understood regarding genetic factors contributing to hemorrhoidal disease, although a genome-wide association study (GWAS) found particular mutations associated with the condition [12]. On a tissue level, matrix metalloproteinases, vascular endothelial growth factor (VEGF), and nitric oxide synthase have all been shown to be associated with hemorrhoidal disease [13]. In addition to vessel engorgement, neovascularization may also play an important role [14].

Clinical Presentation

Frequently, anorectal symptoms are incorrectly attributed to hemorrhoids, by both patients and physicians unfamiliar with the associated symptoms and exam findings. A thorough history and physical exam are essential in correctly identifying hemorrhoidal disease and excluding the many other benign and malignant conditions that must be considered.

The most common symptoms associated with internal hemorrhoids are bleeding, pain, and tissue protrusion [15]. Painless bleeding with bowel movements accompanied by intermittent protrusion of tissue from the anal canal are the classic symptoms of enlarged internal hemorrhoids. The bleeding is usually bright red and is commonly described as on the toilet tissue, dripping, or even squirting into the toilet water. The degree of prolapse is also variable and may be intermittent or persistent and spontaneously reduce, require digital manipulation or may not be reducible. Other common symptoms of internal hemorrhoids include rectal pressure, mucus discharge, and soiling of undergarments with stool seepage. Although it can appear significant to patients, bleeding from hemorrhoids is rarely the cause of anemia, although possible with chronic substantial blood loss. Pain is not typically associated with internal hemorrhoids unless they are prolapsed and strangulated, which is not a subtle finding. In fact, the presence of pain should prompt the clinician to question the diagnosis in favor of other perianal processes, such as thrombosed external hemorrhoid, anal fissure, or abscess.

Common symptoms associated with external hemorrhoids include itching, irritation, perianal moisture, and difficulty with hygiene. External hemorrhoids do not cause pain unless thrombosis is present. In this instance, a firm nodule that has a blue or purple tinge is visible and palpable at the anal orifice (Fig. 11.4). These may be nontender or exquisitely painful, and the contained clot can erode through the overlying stretched skin. Spontaneous resolution of thrombosed external hemorrhoids often leaves a skin tag. These may reduce in size over time, but typically do not regress completely, and may be associated with symptoms such as itching and difficulty cleansing the region.

History

The diagnosis of hemorrhoidal disease is almost always a clinical one and should start with a medical history, with great care taken to identify associated symptoms and risk factors. Focus should be on the extent, severity, and duration of symptoms such as bleeding and extent of prolapse, issues of perineal hygiene, and presence or absence of pain. A careful review of fiber intake and bowel habits, including frequency, consistency, and ease of evacuation, should also be performed, as constipation predisposes patients to hemorrhoidal disease. Additionally, acute changes in bowel habits associated with bleeding may signify a more ominous cause, such as inflammatory bowel disease or neoplasm. All patients should be asked about other factors that are related to development of hemorrhoidal disease such as chronic heavy lifting or chronic cough from asthma or chronic obstructive pulmonary disease, or unusual toileting behavior such as withholding or limited access to bathroom facilities. Specific note should be made of anticoagulant use, fecal incontinence symptoms, previous anorectal surgery, obstetric history, and history of radiation to the pelvis, because these may affect management decisions.

Physical examination can be done in the prone or lateral decubitus position. Findings should be noted in anterior–posterior and right–left terms and documented as such. The examination begins with inspection of the gluteal cleft and then, with gentle retraction of the buttocks, inspection of the perianal area and perineum. The skin is inspected for findings such as external hemorrhoids, skin tags, condyloma, skin breakdown, fistulous openings, fissures, erythema, scars, masses, and any gape of the anus at rest. Digital rectal examination should evaluate for other anal pathology and sphincter integrity. Anoscopy should be performed to assess the anatomy [16]. Internal hemorrhoids, located above the dentate line, should be assigned a grade, which will help guide therapy. In addition, an evaluation of the patient while straining on the commode will assist in the diagnosis of hemorrhoid prolapse, as well as exclude full-thickness rectal

prolapse. Laboratory or radiographic studies are not typically required for diagnostic purposes.

Although hemorrhoids are the most common reason for hematochezia, other disease processes, such as colorectal cancer or polyps, inflammatory bowel disease, other colidities, diverticular disease, and angiodysplasia, can also precipitate bleeding [17]. While the majority of patients with hematochezia will not have colorectal cancer, rectal bleeding attributed to hemorrhoids represents the most common missed opportunity to establish a cancer diagnosis [18]. Any patient with age greater than 45, or with a change in bowel habits, anemia, weight loss, or those with a family history of colorectal cancer or suggestive of hereditary nonpolyposis colorectal cancer or Lynch syndrome, should be further examined with colonoscopy [19].

Treatment

Patients generally seek treatment for hemorrhoids once they experience symptoms. Unless patients are presenting in an acute fashion with heavy bleeding, thrombosis, or strangulation, simple non-procedural strategies are the first-line approach. An initial trial of conservative management is typically employed for a period of 6–8 weeks, at which point in-office reassessment is warranted, to determine response to treatment and decide whether further interventions are needed.

Medical Management

Stool Habits

Patients should be encouraged to maintain stooling habits that promote a healthy anal canal by minimizing pressure and strain on the hemorrhoids. Specifically, patients should be educated to avoid sitting on the toilet for prolonged periods of time (discourage reading on the toilet!). The act of defecation should not take more than just a few minutes; if an attempt is unproductive, the patient should get up and try again later when the urge returns. A foot stool will promote a more natural "squatting" position and may help those who endorse straining, or those with a component of pelvic outlet dysfunction constipation [20].

Stool Texture

Critical to alleviating hemorrhoid symptoms is improving the texture of the stool, with the goal of having soft, yet formed stools with adequate bulk [21]. Fiber acts as a "sponge" and prevents stool from becoming overly hard or loose depending on dietary variation or occasional indiscretions. This can be accomplished by supplementing the diet with soluble fiber, with a goal of 25–50 grams daily. Commercially available fiber supplements include psyllium, methylcellulose, and calcium polycarbophil. Even a strict vegetarian or self-declared "healthy eater" is unlikely to achieve this goal with diet alone and thus should be encouraged to add a supplement. Hard stool causes straining and puts pressure on the hemorrhoids, whereas loose stool can be highly irritating, and frequent defecation can cause symptoms to escalate. Fiber works best when water intake is increased to at least 64 ounces, with more being needed for warmer climates or significant physical activity. For some patients, prebiotics and probiotics are an adjunct to maintain colon health and stool texture [22]. Those with severe chronic constipation may require stool softeners or laxatives to correct their stool texture, and those with chronic loose stools despite fiber supplementation may require antidiarrheals; however, these medications should not be first line in most circumstances.

Hygiene

In addition, soaking in the bath tub, or in a sitz bath, is soothing to the hemorrhoids, allows for relaxation of the pelvic floor, can facilitate reduction of tissue prolapse, and decrease edema. Soaks can be performed at 15-minute intervals in warm water for symptomatic relief, without the need for salts or emollients, which may cause irritation.

Topical Therapies

Generally, patients present for in-office evaluation for hemorrhoids because over-the-counter remedies have already failed. There are no quality data to support the use of commercially available topical therapies (creams, wipes) and suppositories; however, if the patient reports a perceived benefit, it is generally acceptable to continue their use, given the overall low side-effect profile of these preparations. Most common topical products contain topical anesthetics such as lidocaine, steroids such as hydrocortisone, and/or pramoxine, which is an anti-inflammatory. Daily use of topicals beyond 7 days may lead to dermatitis and exacerbate symptoms [23, 24]. Formulations containing steroids also should not be used for more than 7 days as they can lead to thinning of the delicate anoderm. Warm or cold packs can also provide symptomatic relief.

Oral Therapies

Non-steroidal anti-inflammatories may help relieve general discomfort and reduce inflammation. Phlebotonics represent a class of oral plant-derived flavonoids and synthetic drugs that were originally intended for chronic venous disease and are currently used for hemorrhoidal disease predominantly in Europe and Asia, as they are not approved by the Federal Drug Administration for use in the United States. Phlebotonics have been shown to decrease hemorrhoid symptoms through multiple effects, including reducing

inflammation and increasing vascular tone [25]. Multiple studies and meta-analyses have demonstrated modest benefits in reducing symptoms of pruritis and bleeding, and also may be used in the post-operative setting [26, 27].

Office-Based Procedures

With appropriate patient selection, office-based procedures for hemorrhoids can be fast, economical, effective, and low risk. The key to achieving consistently good outcomes is careful patient selection and proper understanding of the technical aspects of each procedure. Outcomes are optimized when patients also utilize the conservative strategies mentioned above. It is important to take a thorough history, paying particular note to use of anticoagulants and bleeding disorders.

Internal Hemorrhoids

Multiple techniques exist for safe in-office treatment of symptomatic internal hemorrhoids, including rubber band ligation, infrared photocoagulation/bipolar diathermy, and sclerotherapy. Patients with grade I–II and some grade III hemorrhoids with symptoms of bleeding are ideal candidates for office procedures. Those with large prolapsing grade III hemorrhoids primarily with associated symptoms of tissue prolapse may need a surgical approach, or an attempt at conservative measures to downgrade them before attempting an office procedure. The techniques described below can all be done in either left lateral decubitus or prone position, based on surgeon preference, and involve instrumentation through an anoscope. Patients who cannot tolerate anoscopy in the office are therefore not suitable candidates for these procedures.

Rubber band ligation involves placement of a rubber band on the redundant mucosa of the hemorrhoid column above the dentate line (Fig. 11.5a). The strangulated hemorrhoid tissue captured within the band necroses after 5–7 days, leaving a small ulcer that eventually will scar in. This technique has been a mainstay of office hemorrhoid procedures since the early 1960s [28]. There are several varieties of hemorrhoid banding devices that exist, including the McGown suction ligator, which applies suction (instead of a separate grasper) to bring the tissue into the device, with a trigger to deploy the band (Fig. 11.5b). While it does require purchase of a suction machine, it enables the surgeon to perform the procedure without a hand from an assistant. The device is used through the anoscope to secure the band onto the mucosa of the selected hemorrhoid. While more than one column may be banded safely in a single office visit, studies demonstrate a higher rate of symptoms including pain and urinary retention.

With proper technique, the patients may feel mild rectal pressure during the procedure (which may last up to 1–2 days), but should not experience pain, which is most likely from band placement too distal within the anal canal. While patients on anticoagulation (other than 80 mg aspirin) are conventionally recommended to hold anticoagulation prior to rubber band ligation [29], a recent retrospective case-control study of 82 patients demonstrated no difference in bleeding risk for patients on clopidogrel compared to the control group, 3.75% versus 2.78%, $p = 0.74$ [30]. Risk of bleeding peaks at post-procedure day 5–7, when the tissue necroses and the band falls off, and in rare instances requires operative management. Risk of pelvic sepsis, characterized by fever, urinary retention, swelling, and pain, is rare but can be rapidly progressing and fatal if not immediately recognized.

Energy ablation techniques include infrared photocoagulation and bipolar diathermy. *Infrared photocoagulation (IPC)* causes coagulation and results in vascular sclerosis and fixation of the tissue (Fig. 11.6). Best used for grade I–II hemorrhoids, it uses a tungsten-halogen lamp as an energy source, converting the light to heat with a polymer probe tip. Similar to bipolar diathermy, the probe tip is applied 3–4 times to the apex of the internal hemorrhoid to deliver 0.5–2 second pulses of heat at a 2.5–3 mm depth of penetration. One advantage of this technique is that it can be used on multiple hemorrhoid columns at one time. *Bipolar diathermy* is another similar office technique for grade I–III hemorrhoids that involves the use of 20 watts of pulsed electrocautery at a depth of 2.2 mm focused at the apex of the hemorrhoid, causing tissue coagulation. If applied too distally, these techniques can cause pain and can potentially lead to ulceration or fissure formation.

In terms of outcomes, a prospective randomized trial of 122 patients comparing bipolar diathermy to IPC demonstrated similar outcomes [31]. A small prospective randomized crossover study of 94 patients comparing IPC to rubber band ligation demonstrated less analgesic use and bleeding in the IPC group in the first 24 hours following the procedures, although notably the complication rates in the RBL group were higher than typical [32].

Sclerotherapy is the oldest technique for grade I–III hemorrhoids, having been first described in 1869 [33]. The procedure involves the injection of 1–1.5 mL of a sclerosing agent into the submucosal layer of the base of the engorged hemorrhoid, using a 21-gauge spinal needle (Fig. 11.7). The sclerosant causes fibrosis and fixation of the hemorrhoid. Critical to the technical success of this procedure is avoiding injecting either too superficially, resulting in damage to the mucosa, or too deep, which can cause pain, infection, and abscess. The most common sclerosing agents are hypertonic saline and 5% phenol in oil. One of the advantages of sclero-

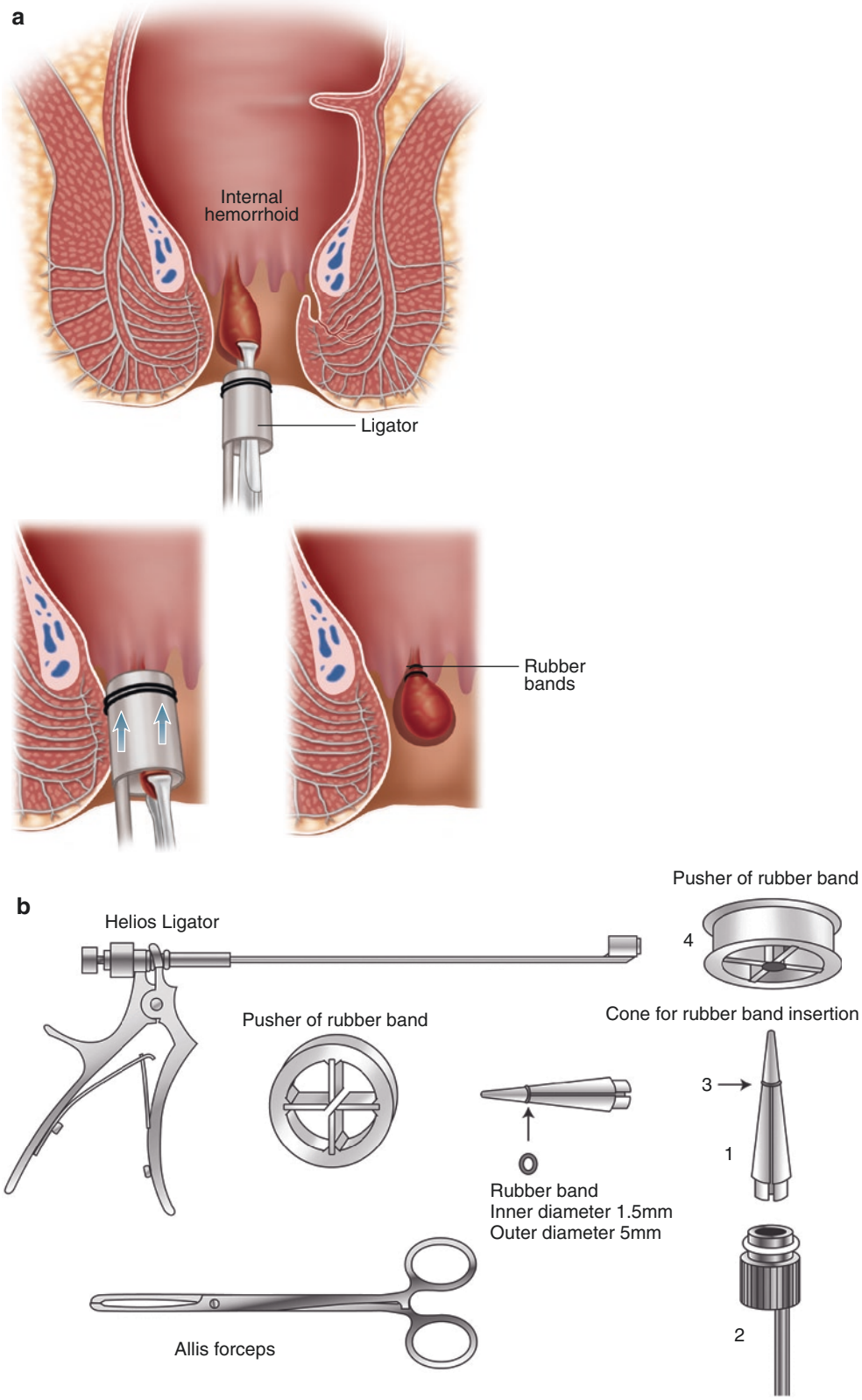

Fig. 11.5 Hemorrhoid banding – (**a**): technique and (**b**): equipment

therapy is that it is safe for patients on anticoagulation. Multiple small trials compare rubber band ligation to sclerotherapy, with differing results but overall favorable outcomes with both, leading one to conclude that they are comparable and at the discretion and preference of the surgeon [34, 35].

Thrombosed Hemorrhoid Excision

Some of the most grateful patients are those who undergo excision of a thrombosed hemorrhoid in the office setting. Optimal timing of the procedure is critical, and thus knowl-

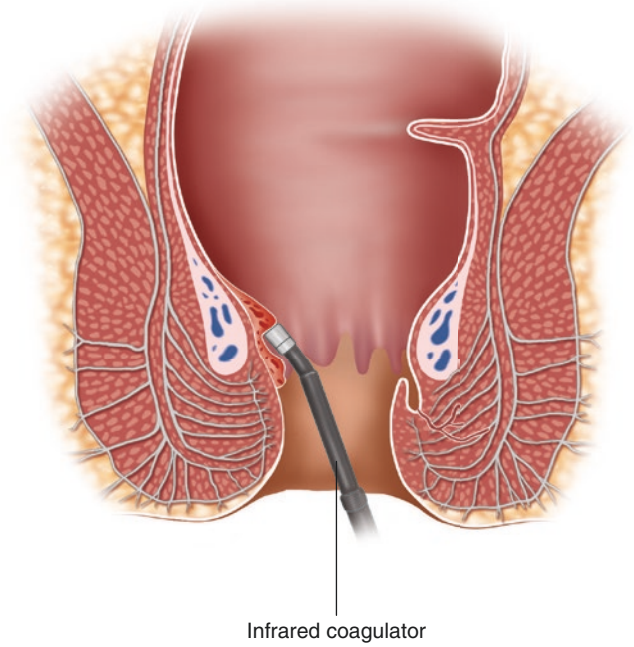

Fig. 11.6 Infrared photocoagulation technique

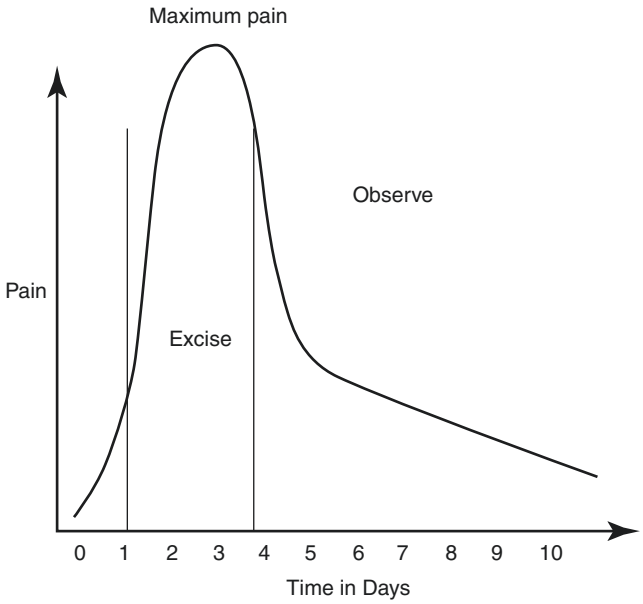

Fig. 11.8 Timing of excision of a thrombosed external hemorrhoid. (With permission from Cintron and Abcarian [101])

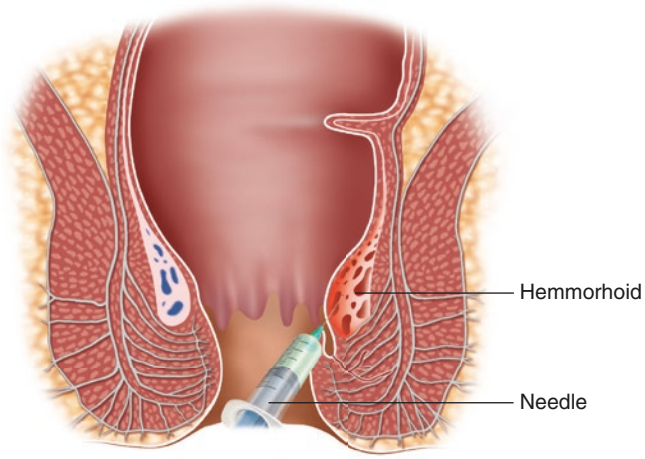

Fig. 11.7 Sclerotherapy technique

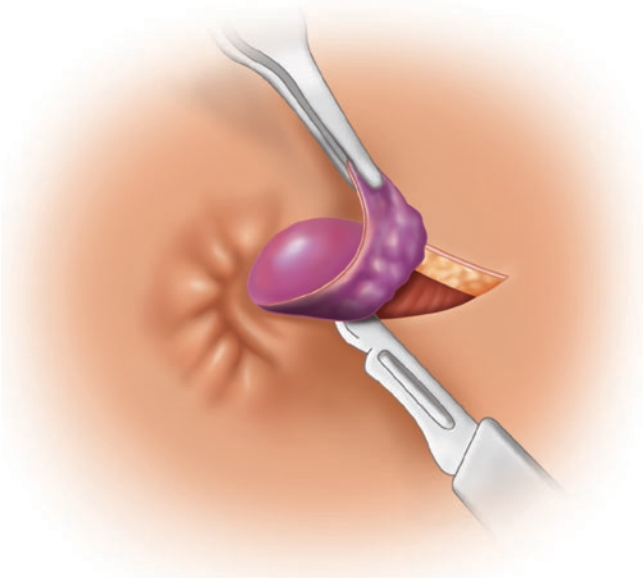

Fig. 11.9 Excision of thrombosed hemorrhoid

edge of the natural history of thrombosed hemorrhoids is important (Fig. 11.8). As most patients should start to experience spontaneous improvement within 72 hours of the onset of symptoms, excision beyond this time point may only serve to increase the intensity and duration of pain. For those not meeting criteria for excision, topical nifedipine has been shown to improve pain scores by decreasing associated sphincter spasm [36]. A small subset of patients will present with persistent pain and a palpable lump for several days to weeks, with no improvement in symptoms, and may also be good candidates for excision. Compared to incision and clot evacuation, excision of the thrombosed hemorrhoid is associated with improved outcomes, specifically decreased rate of recurrence and less pain.

To excise a thrombosed hemorrhoid, the perianal skin is cleansed with a betadine solution and allowed to dry (Fig. 11.9). Local anesthetic (1% lidocaine with or without epinephrine 1:200,000) is injected using a 27-gauge needle into the base of the hemorrhoid. Toothed forceps are used to grasp the most lateral or radial aspect of the hemorrhoid, while a fine Metzenbaum scissor (or an office cautery device) is used to meticulously dissect around the hemorrhoid and

associated clot in an ellipse shape, superficial to the sphincter muscle. Dissection in the proper tissue plane results in minimal blood loss. Care is used to prevent going unnecessarily wide on the anoderm, creating a larger wound than necessary. Pressure is held on the excision site, and silver nitrate can be used for hemostasis.

Operative Management of Hemorrhoids

Operative management of hemorrhoids is usually reserved for those patients who have failed medical management or have recurrent, persistent disease despite medical therapy or office-based procedures. Typically, only 5–10% of patients with hemorrhoid-related complaints require operative hemorrhoidectomy [37]. Additionally, operative approaches are most effective for grade III and IV internal hemorrhoids, those with a large external component, and may be the only realistic option for extensive hemorrhoidal disease or incarcerated, strangulated, or gangrenous hemorrhoids.

Excisional hemorrhoidectomy has excellent results, minimal recurrence rates, few complications and remains the gold standard in the surgical management of hemorrhoids. Excisional hemorrhoidectomies can be classified as being done in a closed (Ferguson technique) or open (Milligan-Morgan technique). Because both excisional techniques are associated with significant postoperative pain, other surgical techniques have been devised with the goal of achieving the excellent results of excisional hemorrhoidectomy while reducing postoperative discomfort. More specifically, these other primary operative management techniques include use of ultrasonic energy devices, stapled hemorrhoidopexy, and transanal hemorrhoid dearterialization.

In all operative interventions, bowel preparation and preoperative antibiotics are not required [29]. A preoperative enema can be given at the surgeon's discretion to clear out the distal rectum of stool. The anesthetic technique can be tailored to the patient and can range from local with sedation to full general anesthetic. Positioning in lithotomy, prone jackknife, or left lateral positioning is per surgeon preference. All operations begin with a thorough visual inspection of the perianal skin, followed by digital rectal exam and anoscopy to determine which hemorrhoid columns require intervention and to rule out other pathology not identified during the office examination.

Excisional Hemorrhoidectomy Closed Technique (Ferguson Technique)

First described by Dr. Lynn Ferguson of the Ferguson Clinic in the early 1950s, the closed hemorrhoidectomy technique remains the most common operation for hemorrhoids in the United States [38, 39]. An elliptical incision is made, starting at the perianal skin and continuing to the anorectal ring, dissecting the hemorrhoid tissue away from the sphincter complex (Fig. 11.10). Dissection can be completed with a scissors, scalpel, or Bovie electrocautery. Dissection is carried out beyond the enlarged internal component at which point the pedicle is suture ligated with absorbable suture and the hemorrhoid tissue amputated. The wound is then closed in a running fashion with the same absorbable suture used to ligate the hemorrhoid pedicle. The suture may be run in locking fashion to improve hemostasis, and small bites of the underlying sphincter complex may be taken to close the dead space. A few millimeters of the anal margin wound may be left open for drainage. One to three columns may be excised using this technique. Care should be taken to preserve bridges of viable skin and mucosa between excision sites to prevent stenosis [40]. Hemorrhoids may be sent as individual specimens, so that any incidental finding on final pathology can be attributed to a specific quadrant, although the likelihood of an incidental findings is only about 1% in the literature [41].

Excisional Hemorrhoidectomy Open Technique (Milligan-Morgan)

The open technique of hemorrhoidectomy is commonly used in the United Kingdom. Perioperative considerations are the same as for the Ferguson technique. The excision is also very similar, however, following suture ligation of the pedicle and amputation of the hemorrhoid bundle the wounds are left open to heal by secondary intent (Fig. 11.11). Again, one to three columns can be excised, with the same caveat regarding preservation of viable bridges of skin and mucosa. Both open and closed techniques are considered appropriate. A recent meta-analysis of 11 RCTs comparing open versus closed hemorrhoidectomy demonstrated that the closed approach was associated with decreased postoperative pain, faster wound healing, and lesser risk of postoperative bleeding. Postoperative complications, hemorrhoid recurrence, and infectious complications were similar [42]. However, multiple individual randomized controlled trials have demonstrated little difference [42–46].

Use of Energy Devices in Excisional Hemorrhoidectomy

Both the open and closed techniques have been modified to include the use of alternative energy sources, such as the bipolar diathermy and ultrasonic shears. A Cochrane review was completed to compare bipolar energy hemorrhoidectomy to standard excisional hemorrhoidectomy [47]. The authors concluded that early postoperative pain was less when the bipolar device was used; however, the difference was no longer noted at day 14. Hemorrhoidectomy completed with a bipolar energy device was also found to be faster. Use of ultrasonic shears seems to produce similar results [48].

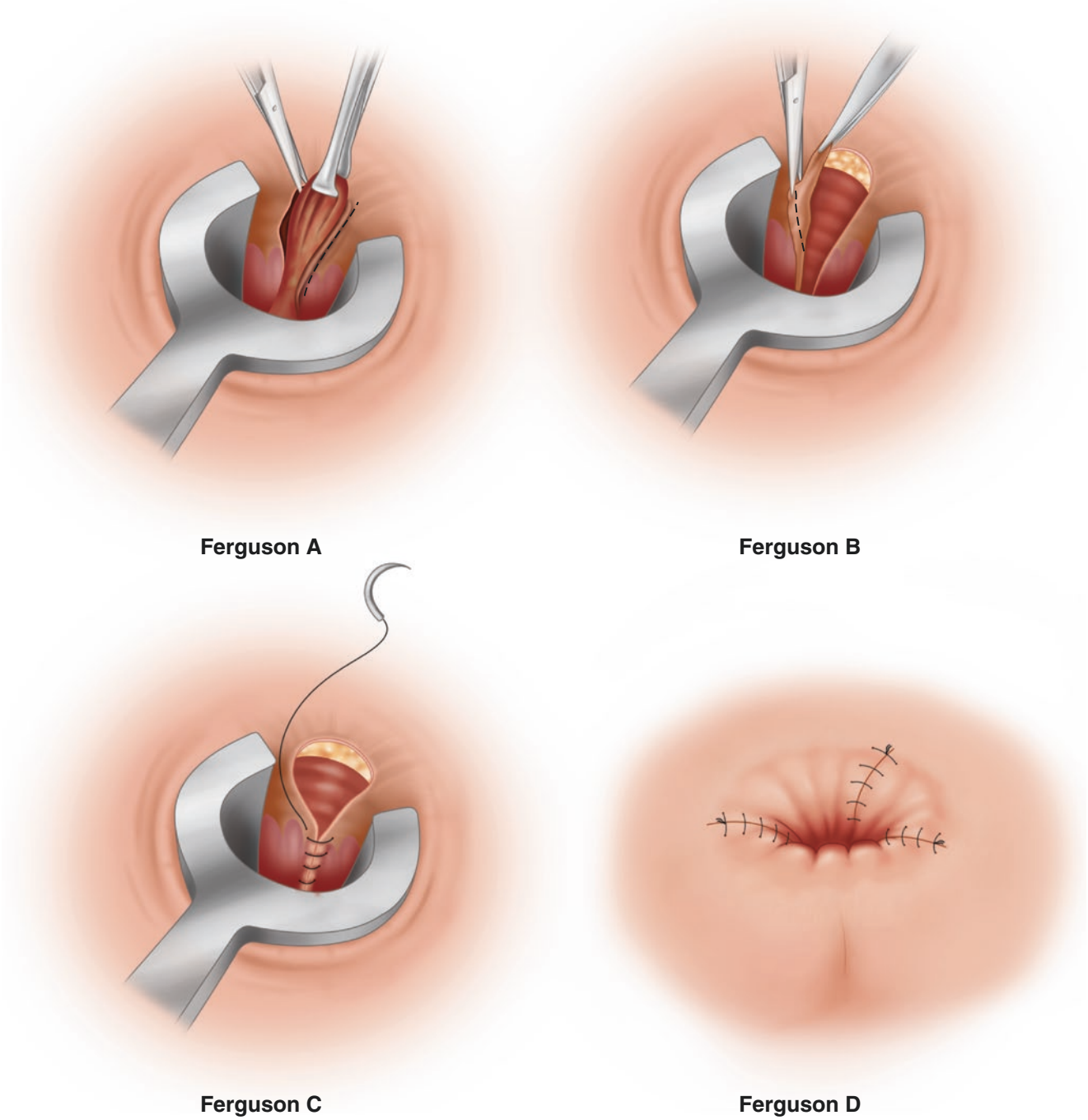

Fig. 11.10 Closed hemorrhoidectomy

When these two devices were evaluated head to head in a randomized controlled trial of patients undergoing closed hemorrhoidectomy, postoperative pain scores were similar, with no differences in clinical outcomes [49]. Other approaches including diathermy and the use of laser technology have not demonstrated improvements in pain and may be associated with higher cost [50–53].

Whitehead Hemorrhoidectomy

The Whitehead hemorrhoidectomy technique, once common in the United Kingdom, involves a circumferential excision of internal hemorrhoidal tissue and redundant anoderm just proximal to the dentate line. This procedure never gained wide acceptance in the United States, in part owing to a high incidence of postoperative complications including anal ste-

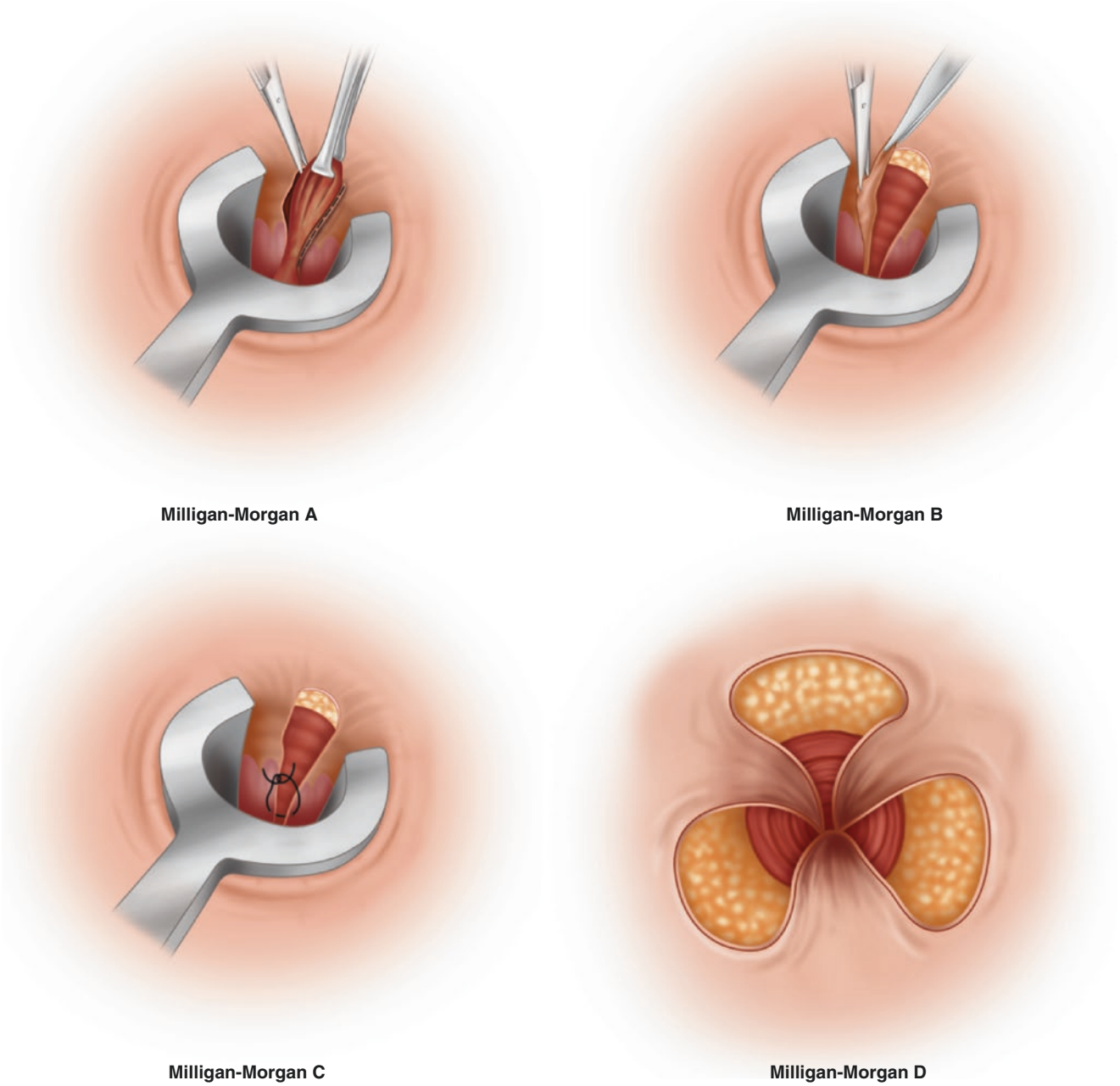

Fig. 11.11 Open hemorrhoidectomy (Milligan-Morgan)

nosis, mucosal ectropion (the "Whitehead deformity"), and disturbed continence (Fig. 11.12). Most centers have abandoned this approach.

Stapled Hemorrhoidopexy

Stapled hemorrhoidopexy, first developed in Italy, uses a circular stapling device to address circumferential internal hemorrhoids and create a mucosa-to-mucosa anastomosis. In doing so, the submucosa proximal to the dentate line is excised, resulting in removal of redundant tissue, a cephalad relocation of the anal cushions and interruption of the feeding arteries (Fig. 11.13). Although effective for internal prolapsing disease, it does not address external hemorrhoids. To perform the procedure, a translucent anoscope, provided with the circular stapler, is introduced transanally. After placing the anoscope, a purse-string suture is placed in a circumferential manner into the submucosa, approximately 2 cm above the dentate line (Fig. 11.14). The head of the stapler is then placed through the anoscope and into the rectum. The purse string is tied down around the shaft of the stapler. The stapler is slowly closed while providing traction on the purse-string. Once closed, the stapler is fired and then

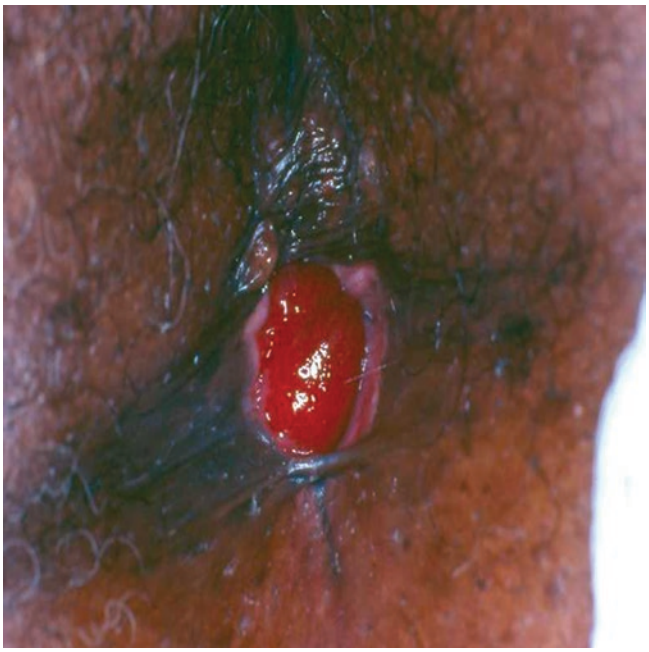

Fig. 11.12 Whitehead deformity

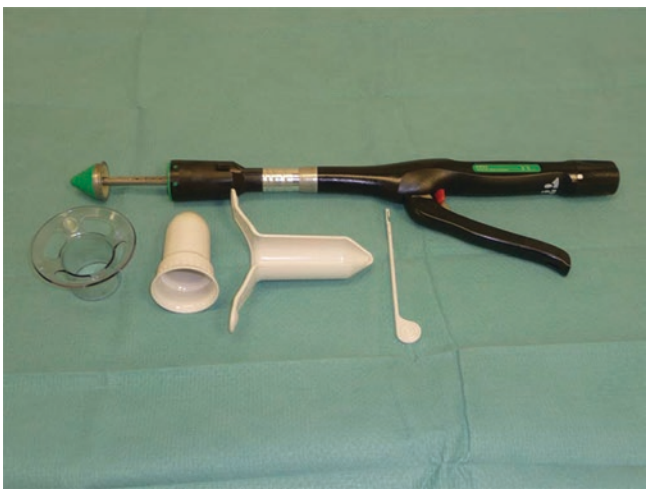

Fig. 11.13 Stapled hemorrhoidectomy. (Reused with permission Wexner and Fleshman [102]. Copyright © 2018 Wolters Kluwer)

removed along with the excised tissue. The staple line is inspected for bleeding and controlled, if present, with suture ligation. In females the vagina should be inspected and palpated prior to firing the instrument to ensure that a vaginal cuff has not been inadvertently included.

Early cohort and smaller nonrandomized trials reported stapled hemorrhoidopexy to be associated with less pain and faster recovery when compared with excisional hemorrhoidectomy. A randomized controlled trial of 777 patients undergoing either stapled hemorrhoidectomy or traditional excisional hemorrhoidectomy demonstrated less pain in the stapled group with similar complication rates. Despite these advantages of the stapled technique, the excisional hemorrhoidectomy group had significantly better quality-of-life scores than the hemorrhoidopexy group. Further, in the stapled hemorrhoidopexy group, 32% of patients reported that their symptoms had recurred compared with only 14% in the excisional hemorrhoidectomy group, and this difference was maintained at 24 months [54]. A Cochrane review of 12 trials including 1097 patients demonstrated similar findings. Additionally, patients undergoing hemorrhoidopexy were more likely to require an additional operative procedure. Lastly, patients undergoing excisional hemorrhoidectomy surgery were more likely than those undergoing stapled hemorrhoidopexy to be asymptomatic following surgery [55].

Stapled hemorrhoidopexy has been associated with several unique complications, including rectovaginal fistula, staple line bleeding, and stricture at the staple line. A systematic review of 784 articles including a total of 14,232 patients found a median complication rate of 16.1%, with five documented mortalities [56]. Between 2000 and 2009, there were 40 published cases in the literature of rectal perforation after stapled hemorrhoidopexy. Thirty-five patients required a laparotomy with fecal diversion, and one patient was successfully treated with low anterior resection. Despite surgical treatment and resuscitation, there were four deaths [57]. The severity of possible complications associated with stapled hemorrhoidopexy have deterred many from its use and reflect the importance of proper training and surgical technique.

Doppler-Guided Hemorrhoidectomy

Originally described by Morinaga in 1995 [58], Doppler-guided/assisted hemorrhoid artery ligation (HAL) uses an anoscope fashioned with a Doppler probe to identify each hemorrhoid artery. The artery is subsequently ligated and, although not initially described, is often followed by a suture mucopexy for patients with symptomatic prolapse. Potential benefits are the lack of tissue excision and less pain.

Patient preparation and setup is identical to any excisional technique. A specialized anoscope with Doppler ultrasound is introduced into the anal canal (Fig. 11.15). The Doppler and anoscope are rotated until a feeding artery is identified (Fig. 11.16). With the aid of a guide to ensure proper depth and location, the artery is suture ligated. The Doppler can be used to confirm loss of signal, indicating ablation of arterial inflow. The process is repeated until the four to six hemorrhoidal arteries have been ligated. Depending on the degree of prolapse, a suture mucopexy may be included using the same stich as the ligation. This is completed by running a continuous suture from the ligation point toward the distal anal canal, just proximal to the dentate line. The free end of the stich is then tied to the tail of the suture, pulling the hemorrhoid column into the proximal anal canal toward the ligation.

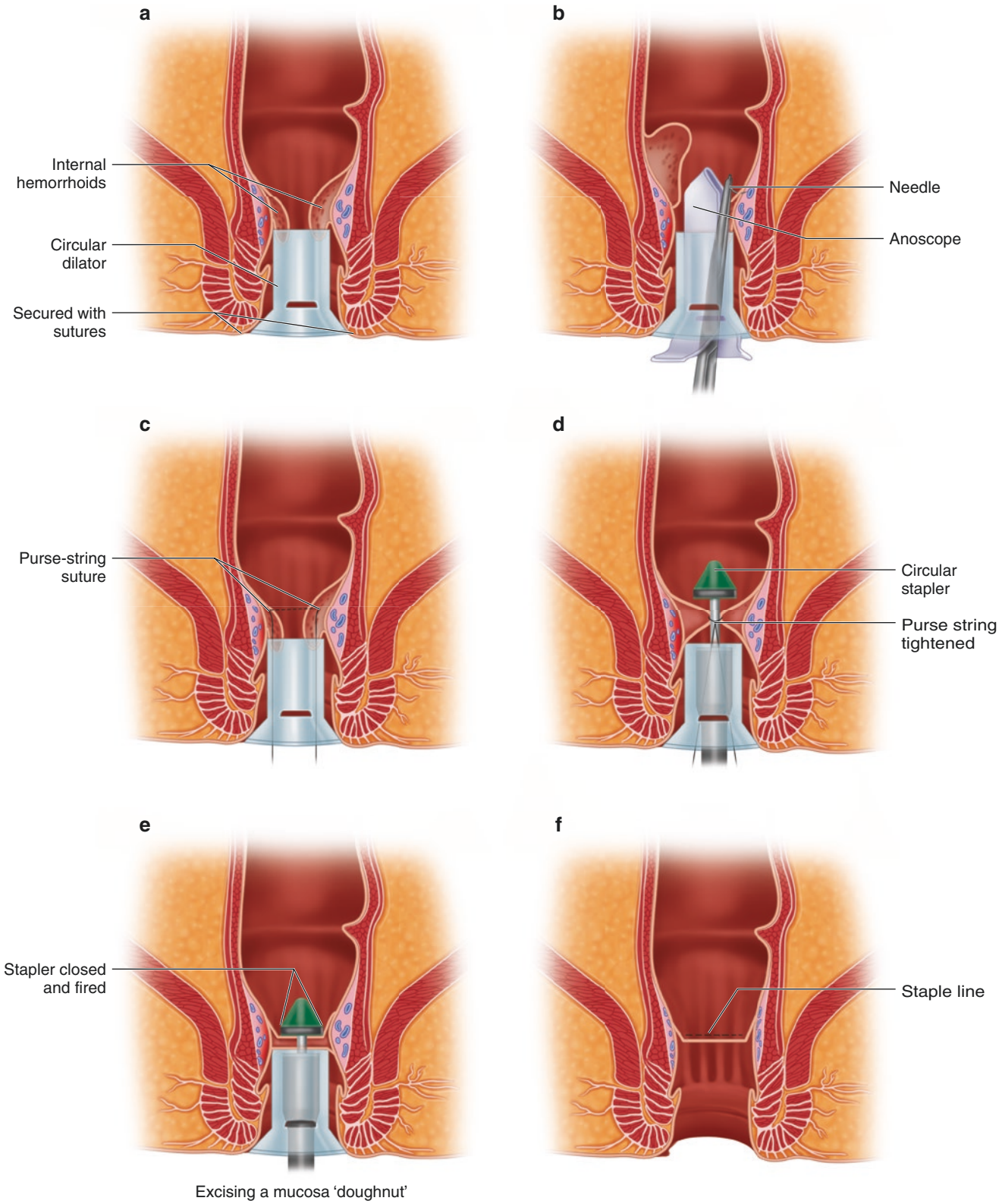

Fig. 11.14 Stapled hemorrhoidectomy technique

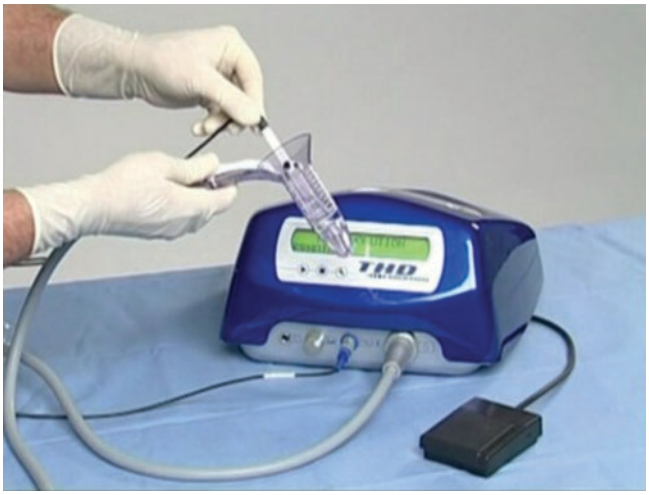

Fig. 11.15 Transanal hemorrhoidal dearterialization device

Prospective studies using HAL have demonstrated favorable short-term results [59]. A systematic review evaluating 28 studies, including 2904 patients with grade I–IV hemorrhoids, demonstrated a pooled recurrence rate of 17.5%, with the highest rates for grade IV hemorrhoids. Overall postoperative complication rates were low, with an overall bleeding rate of 5% and an overall reintervention rate of 6% [60]. In a randomized prospective trial comparing RBL with HAL for the treatment of grade II and III hemorrhoids, recurrence rates, symptom scores, complications, quality-of-life assessment, and continence score were similar. Patients had more pain in the early postoperative period after HAL. HAL was also more expensive and was not found to be cost-effective compared with RBL in terms of incremental cost per quality-adjusted life-year [61]. In respect to long-term outcomes, a recently completed meta-analysis of comparing stapled hemorrhoidectomy to HAL demonstrated a statistically significant difference in recurrence (OR 0.55; 95% CI, 0.340.90 $P = 0.02$) with increased recurrence in the HAL group [62]. A similar meta-analysis demonstrated that recurrence was highest in those with grade IV hemorrhoids [63]. When comparing HAL to excisional hemorrhoidectomy, one meta-analysis, which included 286 patients in the evaluation of recurrence, found no difference [64]. However, the data regarding long-term comparisons between excisional and HAL hemorrhoidectomy are somewhat lacking. In conclusion, HAL demonstrates favorable short-term results but may be associated with increased recurrence, especially in those with grade IV hemorrhoids.

Pain Management and Postoperative Care

Pain management after hemorrhoidectomy starts with adequate patient counseling in the preoperative setting. Setting realistic expectations for the patient can go a long way in terms of allaying their concerns and ensuring they are prepared with enough time to recuperate before planning to return to normal activity. Recovery time is variable and depends on the type of procedure, anticipated extent of surgery, as well as the patient's intrinsic tolerance and if they are on preoperative narcotics. Multimodal pain control is critical to minimize discomfort associated with surgery for hemorrhoids, while limiting narcotics.

For patients under conscious sedation, a pudendal nerve block consisting of a 1:1 mix of 1% lidocaine and 0.25% bupivacaine is most commonly used, for a total volume of 40–60 mL depending on patient weight. The addition of 1:200,000 epinephrine to one of the local analgesics will increase the maximum dose and duration of action. Although from a pharmacokinetic standpoint, the onset of lidocaine is faster than bupivacaine, under 2 minutes versus 5 minutes, and the duration of action is shorter, 1–2 hours versus 2–4 hours, the clinically observed differences between the two drugs have not been shown to be significant, with an overall time to onset between 12 and 29 seconds, with a duration of action between 6 and 7 hours [65].

Use of liposomal bupivacaine either as monotherapy or volume expanded in bupivacaine will result in improved analgesia for the first 72 hours postoperatively. A prospective, randomized, controlled double-blind study of 100 patients undergoing excisional hemorrhoidectomy demonstrated significant increase in time to first opioid use, 19 hours versus 8 hours, $p = 0.005$, with corresponding reduction in pain scores [66]. It is our practice to volume-expand a 20 mL bottle of liposomal bupivacaine with 20 mL of 0.25% bupivacaine and inject this at the onset of the procedure as a pudendal nerve block. Importantly, liposomal bupivacaine cannot be volume-expanded in lidocaine, which will competitively drive the bupivacaine out of the liposomes and lead to toxicity. While the cost of liposomal bupivacaine is far greater than conventional non-liposomal alternatives, there are no studies that have performed a cost analysis for outpatient anorectal surgery, although it has been found to be cost-effective (or at least comparable) in many other types of surgery, in part, due to decreased length of stay, which is not applicable in this setting [67–69].

Given that narcotics are associated with unfortunate side effects (such as constipation) and have been shown to increase risk of long-term addiction and contribute to the "opioid crisis" in the United States, it is best to minimize their use [70]. A pudendal nerve block is essential for postoperative pain control, regardless of whether general endotracheal or monitored anesthesia care is used. A prospective, randomized, double-blind, placebo-controlled trial of 61 patients undergoing anorectal surgery compared the use of preoperative oral acetaminophen and gabapentin and intraoperative intravenous ketamine and dexamethasone to pla-

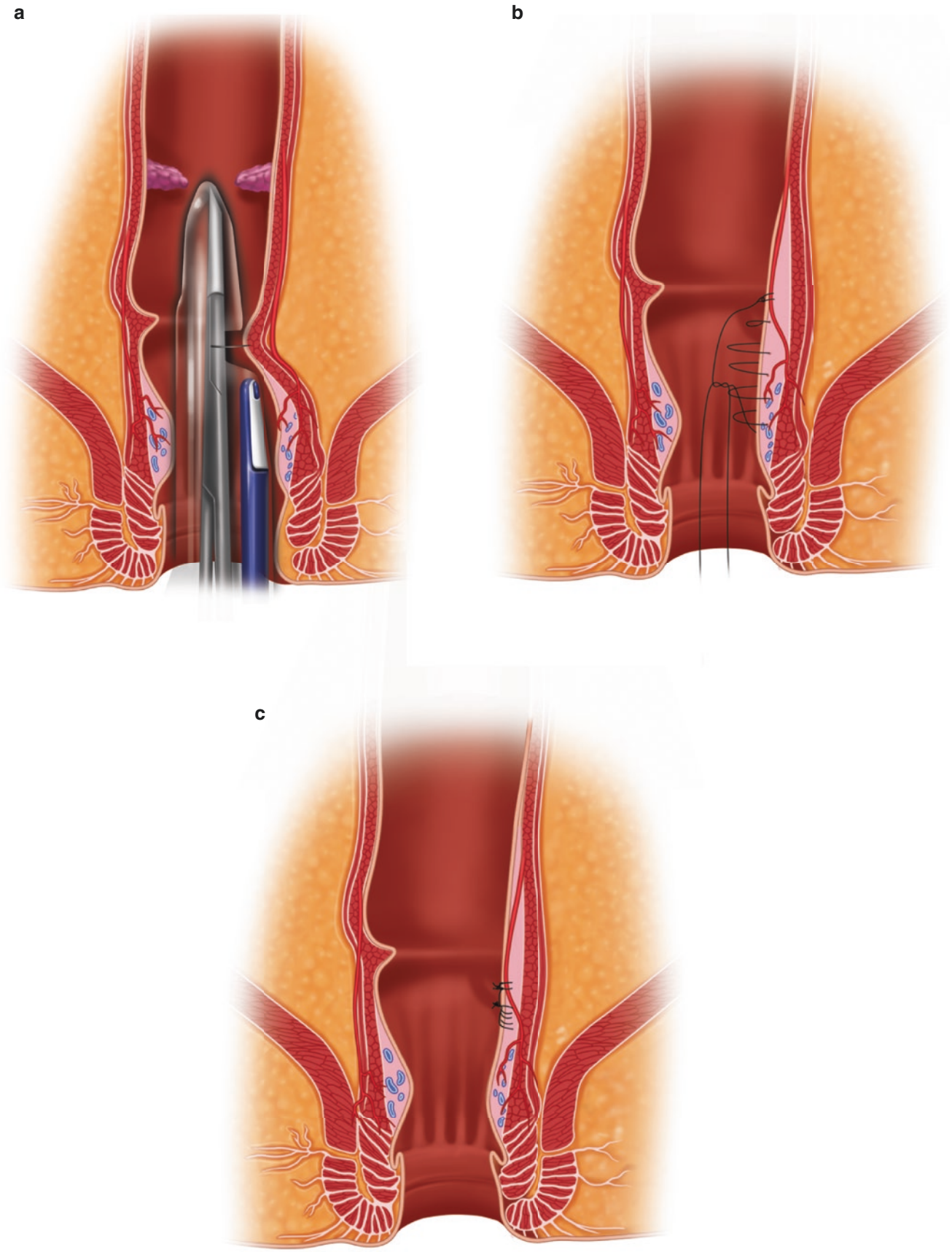

Fig. 11.16 Transanal hemorrhoidal dearterialization

cebo and found significantly decreased self-reported pain scores (50% and 40% decrease) and breakthrough narcotic use (relative risk reduction 76% and 92%) in the post-anesthesia care unit and at 8 hours postoperatively. Unfortunately, as is the case with many such studies, the trial was underpowered to detect a difference in hemorrhoid patients ($n = 17$) [71].

As for oral medications, non-narcotic medications should be used as a mainstay, with narcotic pain medication for breakthrough pain. Recommended effective Motrin dose is 600 mg TID. Acetaminophen can be used either simultaneously or alternating, at doses not to exceed 4 g/day. Diazepam is a very helpful adjunct in reducing sphincter spasm, although this has not been studied formally in the literature. Oral metronidazole has been given in the postoperative setting, although studies are mixed regarding its efficacy in terms of decreasing pain. A 2017 meta-analysis of five randomized controlled trials involving 337 patients found that the metronidazole group had significantly lower pain scores on postoperative days 1 and 4, as well as a significantly faster return to activity; however, when a sensitivity analysis was performed, the largest trial was excluded due to bias, and consequently all the observed findings were no longer statistically significant [72].

No formal guidelines exist to inform clinicians on appropriate prescribing of narcotics after hemorrhoidectomy, although a recent study of over 6200 patients in a claims database determined that a 5- to 10-day prescription is optimal for most patients, noting there was over threefold increased odds of needing a prescription refill in patients with history of opioid use. One of the major limitations of the study was that it could not determine the number of pills or type of narcotic prescribed [73]. A more recent retrospective single-institution study of 77 patients who underwent ambulatory excisional hemorrhoidectomy evaluated postoperative opioid usage to create a prospective prescribing guideline. It was determined that, to meet opioid needs for 80% of patients, the equivalent of 27 pills of 5 mg oxycodone would need to be prescribed postoperatively for home use [74]. Additionally, it is our preferred practice to prescribe narcotics that do not contain acetaminophen, such as oxycodone, to minimize risk of acetaminophen toxicity.

Topicals After Hemorrhoidectomy

Various topical preparations can be considered in the postoperative setting, as data suggest a modest benefit. A prospective, double-blind, randomized controlled trial of 66 patients with grade III–IV hemorrhoids undergoing open hemorrhoidectomy compared use of 5% topical baclofen to placebo and demonstrated a significant reduction in pain and analgesic consumption in the treatment arm at 1 and 2 weeks postop [75]. A 2010 meta-analysis of five randomized controlled trials of 333 patients using topical glyceryl trinitrate (GTN) ointment after hemorrhoidectomy demonstrated significant reduction in pain on postoperative days 3 and 7, but not on day 1. It also demonstrated an odds ratio of 3.57 for wound healing at 3 weeks postop, compared to placebo ($p < 0.0001$), without a statistically significant difference in incidence of headache [76]. A 2019 study of 40 patients found similar results with regard to postoperative pain, but there was a significantly higher rate of headache in the GTN arm [77]. Additionally, studies demonstrate modest benefits of topical lidocaine in the postoperative setting, when combined with diclofenac or nifedipine [78, 79].

Routine Postoperative Care

Following hemorrhoidectomy, in addition to pain control, patients are instructed to avoid constipation. Patients who have corrected their stool texture prior to undergoing surgery will have the best outcomes. Fecal impaction in the postoperative period can be a devastatingly painful complication and is to be avoided with rigorous attention to maintaining a proper bowel regimen. It is essential to educate patients on the constipating side effects of narcotics, and to counteract this with water intake and fiber, stool softeners, laxatives, and other adjuncts such as prune juice and probiotics. Conversely, patients are also encouraged to avoid diarrhea, whether it be due to underlying conditions (which are best optimized prior to surgery) or by overdoing it with laxatives. Frequent loose stools will be painful and irritating and may delay healing. Lastly, Sitz baths and warm or cool packs will also provide relief from pain. Most patients are familiar with these interventions from their time prior to surgery.

Complications of Hemorrhoidectomy

Urinary Retention

Urinary retention is one of the most common complications following hemorrhoidectomy and occurs at a rate of 1–15%. It is also the most common reason for failure of surgical patients to be discharged from an ambulatory setting [80]. The incidence is higher after spinal anesthesia and after HAL procedures. The risk may be mitigated with decreasing volume of intravenous fluids to less than 500 cc and through judicious use of local anesthesia [81].

Postoperative Hemorrhage

Delayed post-hemorrhoidectomy bleeding is a rare but serious complication after hemorrhoidectomy [82]. The incidence of delayed postoperative hemorrhage has been reported to be 0.9–10% [83, 84]. While some minor bleeding is expected following hemorrhoidectomy, patients who describe passage of an entire bowel movement of blood clots are likely to require and exam under anesthesia. The culprit vessel may not always be found, but if it is, it can usually be managed

with an interrupted figure of eight absorbable suture. It is also reasonable to evacuate any residual clot from the rectum and distal sigmoid via rigid proctoscopy to reduce the chances of clouding the postoperative clinical picture with ongoing hematochezia. Some data suggest that delayed bleeding is linked to risk factors such as the surgical procedure, infection, defecation with excessive straining, and number of piles [85, 86]. Interestingly, a study that evaluated 45 patients with delayed bleeding reported that male gender and individual surgeons were independent risk factors [83]. There was no significant difference in the occurrence of hemorrhage between patients who underwent a closed or open hemorrhoidectomy [43] or between conventional hemorrhoidectomy and using a bipolar energy device [87].

Fecal Incontinence

Incontinence to stool following hemorrhoidectomy can occur but is rare and may be multifactorial in nature. There may be undue stretch placed on the anal sphincter at the time of surgery, direct sphincter injury, or loss of the bulk of the hemorrhoid cushions. Proper technique which avoids the sphincter muscles should have no impact on sphincter integrity or function.

Anal Stenosis

Anal stenosis can occur following hemorrhoidectomy if excessive anoderm is removed. It is most commonly encountered following emergency hemorrhoidectomy and is usually secondary to inadequate remaining skin bridges. Treatment can involve bulk laxatives, dilation, and anoplasty (described elsewhere) [88, 89].

Special Patient Populations

Strangulated Hemorrhoids

Strangulated hemorrhoids are internal hemorrhoids that have prolapsed and become incarcerated and irreducible. Edema and thrombosis of the external hemorrhoids often accompany this condition. The incarcerated internal hemorrhoids may be beefy red, or ulcerated and necrotic, depending on the length of time of incarceration. If not necrotic, circumferential injection of local anesthetic and reduction of the strangulated hemorrhoids can be accomplished, followed by bed rest. One small randomized trial published in 1991 compared reduction followed by banding of the internal component and excision of the external thromboses with excisional hemorrhoidectomy; 13.5% of patients treated with reduction and banding went on to require excisional hemorrhoidectomy [90]. Unless the patient has prohibitive operative risk, the best option for strangulated hemorrhoids is expeditious excisional hemorrhoidectomy; in the presence of necrosis, excision is a necessity. Either an open or a closed technique can be used. If tissues are very edematous, or if devitalized tissue is present, one may consider leaving the wounds open to prevent abscess. Postoperative care is as usual after excisional hemorrhoidectomy [91].

Hemorrhoids in Pregnancy

Engorgement of the internal hemorrhoids and edema of the external hemorrhoid are common during pregnancy, possibly related to impaired venous return, constipation, and pressure on the pelvic floor. A single institution prospective study of 94 Dutch women demonstrated a 14.4% prevalence of hemorrhoidal prolapse in the third trimester and a 14.6% prevalence of thrombosis in the postpartum period [92]. Hemorrhoid symptoms almost always resolve after delivery and rarely need urgent intervention. Surgical intervention in pregnancy is reserved for strangulated hemorrhoids, or occasionally a very symptomatic external thrombosis. When necessary, operation should be performed using local anesthesia with the patient positioned in the left lateral decubitus position to avoid compression of the inferior vena cava.

Hemorrhoids, Varices, and Portal Hypertension

Rectal varices and hemorrhoids are distinct and different. Rectal varices in patients with portal hypertension provide collateral circulation for the portal system into the systemic venous circulation. Incidence of hemorrhoid symptoms in patients with portal hypertension is like that of the general population [93]. Although rectal varices are common in patients with portal hypertension, they bleed much less commonly than esophageal varices [94]. In the rare instance of bleeding from rectal varices, portal hypertension should be addressed first, whether it be by medical management of transjugular intrahepatic portosystemic shunt, or by portosystemic shunts, or even by liver transplant. Direct control methods such as sclerotherapy and suture ligation will have a higher rate of success if the portal system is decompressed and should be reserved for instances in which all other options have been exhausted [95, 96].

Hemorrhoids in Crohn's Disease

As many patients with Crohn's disease have loose stools, engorged hemorrhoids may occasionally be seen and require surgical intervention. These are specifically distinguished from Crohn-related perianal skin tags. Patient selection is very important. In the background of rectal inflammation, conservative management is indicated. Older literature describes a high rate of poor wound healing and complications with hemorrhoidectomy in Crohn's disease. Some patients with anorectal Crohn's disease describe a hemorrhoidectomy with poor outcome immediately preceding their inflammatory bowel disease diagnosis. However, in appropriately selected patients who are well controlled medically and have no rectal inflammation or other anorectal disease, a

good outcome can be attained. Wolkomir and Luchtefeld reported healing in 90% of patients who underwent hemorrhoidectomy in the setting of well-controlled ileocolonic Crohn's disease [97]. Karin reported on a group of 13 patients with Crohn's disease without rectal involvement who had symptomatic grade 3 hemorrhoids. All underwent transanal hemorrhoidal dearterialization with good outcomes. At 18 months, ten patients were without hemorrhoid-related symptoms [98].

Hemorrhoids in the Immunocompromised Patient

Anorectal pathology is increasingly seen in immunocompromised patients, including those with medically induced immunosuppression, such as solid organ transplant recipients and patients receiving steroids or chemotherapy, as well as those with disease-induced immunosuppression, including human immunodeficiency virus (HIV). One must recall that this population is heterogeneous. For those in whom the immunocompromise can be expected to resolve, conservative management should be pursued aggressively until immunity is normal or nearly so. For those with an ongoing degree of immunocompromise, medical management should be the primary approach, reserving direct intervention only after medical failure and with careful consideration of the implications of complications in this population [91]. RBL and excisional hemorrhoidectomy have been shown to be safe in HIV-positive patients on highly active antiretroviral therapy with acceptable CD4 counts [99, 100].

Conclusion

In conclusion, hemorrhoidal disease is common and frequently misdiagnosed. Knowledge of associated symptoms along with anorectal and hemorrhoid anatomy is critical in securing the diagnosis and selecting the appropriate treatment (Fig. 11.17). Minimizing straining and improving hydration and fiber intake are the first step for patients with symptomatic hemorrhoids. Most office procedures are best suited for symptomatic grade I–III internal hemorrhoids or thrombosed external hemorrhoids. One's armamentarium should include a variety of techniques for symptomatic hemorrhoids to optimize outcomes and provide individualized therapy. Excisional hemorrhoidectomy continues to provide the most consistent results, while others, possibly less painful surgical interventions, are associated with higher recurrence rates. Complications of hemorrhoid surgery are rare and include urinary retention, bleeding, infection, stenosis, incontinence, and recurrence. Special considerations include pregnant patients, as well as those with Crohn's disease, the immunocompromised, or those with portal hypertension.

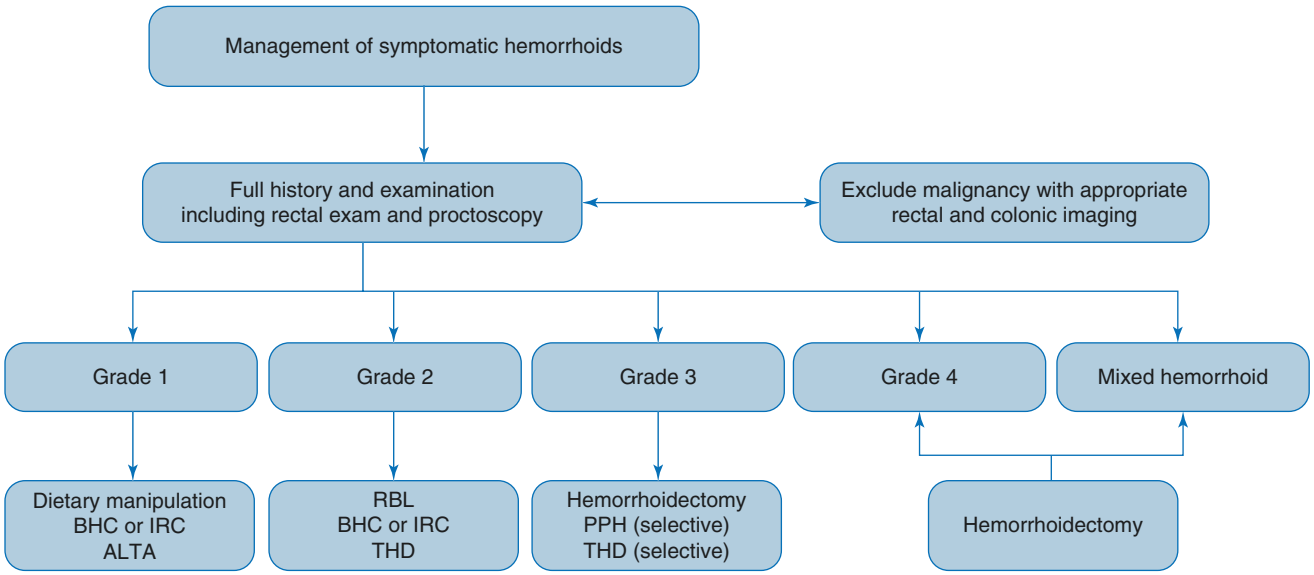

Fig. 11.17 Treatment algorithm

References

1. Kaidar-Person O, Person B, Wexner SD. Hemorrhoidal disease: a comprehensive review. J Am Coll Surg. 2007;204(1):102–17.
2. Yeung TM, D'Souza ND. Quality analysis of patient information on surgical treatment of haemorrhoids on the internet. Ann R Coll Surg Engl. 2013;95(5):341–4.
3. Qiu R, et al. Estimating disease burden using internet data. Health Informatics J. 2019;25(4):1863–77.
4. Sun Z, Migaly J. Review of hemorrhoid disease: presentation and management. Clin Colon Rectal Surg. 2016;29(1):22–9.
5. Yang JY, et al. Burden and cost of outpatient hemorrhoids in the United States employer-insured population, 2014. Am J Gastroenterol. 2019;114(5):798–803.
6. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part I: overall and upper gastrointestinal diseases. Gastroenterology. 2009;136(2):376–86.
7. Johanson JF, Sonnenberg A. The prevalence of hemorrhoids and chronic constipation. An epidemiologic study. Gastroenterology. 1990;98(2):380–6.
8. Banov L Jr, et al. Management of hemorrhoidal disease. J S C Med Assoc. 1985;81(7):398–401.
9. Coote H. On the removal of haemorrhoids by painless operations. Br Med J. 1869;1(424):138.
10. Lestar B, Penninckx F, Kerremans R. The composition of anal basal pressure. An in vivo and in vitro study in man. Int J Color Dis. 1989;4(2):118–22.
11. Riss S, et al. The prevalence of hemorrhoids in adults. Int J Color Dis. 2012;27(2):215–20.
12. Salnikova LE, Khadzhieva MB, Kolobkov DS. Biological findings from the PheWAS catalog: focus on connective tissue-related disorders (pelvic floor dysfunction, abdominal hernia, varicose veins and hemorrhoids). Hum Genet. 2016;135(7):779–95.
13. Han W, et al. Pathologic change of elastic fibers with difference of microvessel density and expression of angiogenesis-related proteins in internal hemorrhoid tissues. Zhonghua Wei Chang Wai Ke Za Zhi. 2005;8(1):56–9.
14. Chung YC, Hou YC, Pan AC. Endoglin (CD105) expression in the development of haemorrhoids. Eur J Clin Investig. 2004;34(2):107–12.
15. Idrees JJ, et al. Evaluating the accuracy of hemorrhoids: comparison among specialties and symptoms. Dis Colon Rectum. 2019;62(7):867–71.
16. Harish K, et al. Videoanoscopy: useful technique in the evaluation of hemorrhoids. J Gastroenterol Hepatol. 2008;23(8 Pt 2):e312–7.
17. Gralnek IM, et al. The role of colonoscopy in evaluating hematochezia: a population-based study in a large consortium of endoscopy practices. Gastrointest Endosc. 2013;77(3):410–8.
18. Siminoff LA, Rogers HL, Harris-Haywood S. Missed opportunities for the diagnosis of colorectal cancer. Biomed Res Int. 2015;2015:285096.
19. Wolf AMD, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018;68(4):250–81.
20. Hari Krishnan R. A review on squat-assist devices to aid elderly with lower limb difficulties in toileting to tackle constipation. Proc Inst Mech Eng H. 2019;233(4):464–75.
21. Andersson H, et al. Colonic transit after fibre supplementation in patients with haemorrhoids. Hum Nutr Appl Nutr. 1985;39(2):101–7.
22. Zhang C, et al. Meta-analysis of randomized controlled trials of the effects of probiotics on functional constipation in adults. Clin Nutr. 2020;39:2960–9.
23. Cusano F, Luciano S. Contact dermatitis from pramoxine. Contact Dermatitis. 1993;28(1):39.
24. Kawada A, et al. Fixed drug eruption induced by lidocaine. Contact Dermatitis. 1996;35(6):375.
25. Chen L, et al. Intracellular signaling pathways of inflammation modulated by dietary flavonoids: the most recent evidence. Crit Rev Food Sci Nutr. 2018;58(17):2908–24.
26. Perera N, et al. Phlebotonics for haemorrhoids. Cochrane Database Syst Rev. 2012;(8):CD004322.
27. La Torre F, Nicolai AP. Clinical use of micronized purified flavonoid fraction for treatment of symptoms after hemorrhoidectomy: results of a randomized, controlled, clinical trial. Dis Colon Rectum. 2004;47(5):704–10.
28. Barron J. Office ligation treatment of hemorrhoids. Dis Colon Rectum. 1963;6:109–13.
29. Nelson RS, et al. Risk of late bleeding following hemorrhoidal banding in patients on antithrombotic prophylaxis. Am J Surg. 2008;196(6):994–9; discussion 999
30. Hite N, et al. Clopidogrel bisulfate (Plavix) does not increase bleeding complications in patients undergoing rubber band ligation for symptomatic hemorrhoids. J Surg Res. 2018;229:230–3.
31. Dennison A, et al. A randomized comparison of infrared photocoagulation with bipolar diathermy for the outpatient treatment of hemorrhoids. Dis Colon Rectum. 1990;33(1):32–4.
32. Marques CF, et al. Early results of the treatment of internal hemorrhoid disease by infrared coagulation and elastic banding: a prospective randomized cross-over trial. Tech Coloproctol. 2006;10(4):312–7.
33. Anderson HG. The treatment of haemorrhoids by submucous injections of chemicals. Br Med J. 1924;2(3316):100–2.
34. Greca F, et al. A randomized trial to compare rubber band ligation with phenol injection for treatment of haemorrhoids. Br J Surg. 1981;68(4):250–2.
35. Gartell PC, Sheridan RJ, McGinn FP. Out-patient treatment of haemorrhoids: a randomized clinical trial to compare rubber band ligation with phenol injection. Br J Surg. 1985;72(6):478–9.
36. Perrotti P, et al. Conservative treatment of acute thrombosed external hemorrhoids with topical nifedipine. Dis Colon Rectum. 2001;44(3):405–9.
37. Bleday R, et al. Symptomatic hemorrhoids: current incidence and complications of operative therapy. Dis Colon Rectum. 1992;35(5):477–81.
38. Ferguson JA, et al. The closed technique of hemorrhoidectomy. Surgery. 1971;70(3):480–4.
39. Milone M, et al. Ferguson hemorrhoidectomy: is still the gold standard treatment? Updat Surg. 2012;64(3):191–4.
40. Milsom JW, Mazier WP. Classification and management of postsurgical anal stenosis. Surg Gynecol Obstet. 1986;163(1):60–4.
41. Lohsiriwat V, Vongjirad A, Lohsiriwat D. Value of routine histopathologic examination of three common surgical specimens: appendix, gallbladder, and hemorrhoid. World J Surg. 2009;33(10):2189–93.
42. Bhatti MI, Sajid MS, Baig MK. Milligan-Morgan (open) versus ferguson haemorrhoidectomy (closed): a systematic review and meta-analysis of published randomized, controlled trials. World J Surg. 2016;40(6):1509–19.
43. Arbman G, Krook H, Haapaniemi S. Closed vs. open hemorrhoidectomy--is there any difference? Dis Colon Rectum. 2000;43(1):31–4.
44. Carapeti EA, et al. Randomized trial of open versus closed day-case haemorrhoidectomy. Br J Surg. 1999;86(5):612–3.
45. Gencosmanoglu R, et al. Hemorrhoidectomy: open or closed technique? A prospective, randomized clinical trial. Dis Colon Rectum. 2002;45(1):70–5.

46. Ho YH, et al. Randomized controlled trial of open and closed haemorrhoidectomy. Br J Surg. 1997;84(12):1729–30.
47. Nienhuijs S, de Hingh I. Conventional versus LigaSure hemorrhoidectomy for patients with symptomatic Hemorrhoids. Cochrane Database Syst Rev. 2009;1:CD006761.
48. Sohn VY, et al. A comparison of open versus closed techniques using the harmonic scalpel in outpatient hemorrhoid surgery. Mil Med. 2008;173(7):689–92.
49. Tsunoda A, et al. Randomized controlled trial of bipolar diathermy vs ultrasonic scalpel for closed hemorrhoidectomy. World J Gastrointest Surg. 2011;3(10):147–52.
50. Fleshman J. Advanced technology in the management of hemorrhoids: stapling, laser, harmonic scalpel, and ligasure. J Gastrointest Surg. 2002;6(3):299–301.
51. Iwagaki H, et al. The laser treatment of hemorrhoids: results of a study on 1816 patients. Jpn J Surg. 1989;19(6):658–61.
52. Senagore A, et al. Treatment of advanced hemorrhoidal disease: a prospective, randomized comparison of cold scalpel vs. contact Nd:YAG laser. Dis Colon Rectum. 1993;36(11):1042–9.
53. Wang JY, et al. The role of lasers in hemorrhoidectomy. Dis Colon Rectum. 1991;34(1):78–82.
54. Watson AJ, et al. Comparison of stapled haemorrhoidopexy with traditional excisional surgery for haemorrhoidal disease (eTHoS): a pragmatic, multicentre, randomised controlled trial. Lancet. 2016;388(10058):2375–85.
55. Lumb KJ, et al. Stapled versus conventional surgery for hemorrhoids. Cochrane Database Syst Rev. 2006;(4).
56. Porrett LJ, Porrett JK, Ho YH. Documented complications of staple hemorrhoidopexy: a systematic review. Int Surg. 2015;100(1):44–57.
57. Faucheron JL, Voirin D, Abba J. Rectal perforation with life-threatening peritonitis following stapled haemorrhoidopexy. Br J Surg. 2012;99(6):746–53.
58. Morinaga K, Hasuda K, Ikeda T. A novel therapy for internal hemorrhoids: ligation of the hemorrhoidal artery with a newly devised instrument (Moricorn) in conjunction with a Doppler flowmeter. Am J Gastroenterol. 1995;90(4):610–3.
59. Lehur PA, et al. Cost-effectiveness of new surgical treatments for hemorrhoidal disease: a multicentre randomized controlled trial comparing transanal doppler-guided hemorrhoidal artery ligation with mucopexy and circular stapled hemorrhoidopexy. Ann Surg. 2016;264(5):710–6.
60. Pucher PH, et al. Clinical outcome following Doppler-guided haemorrhoidal artery ligation: a systematic review. Color Dis. 2013;15(6):e284–94.
61. Brown S, et al. The HubBLe trial: haemorrhoidal artery ligation (HAL) versus rubber band ligation (RBL) for symptomatic second- and third-degree haemorrhoids: a multicentre randomised controlled trial and health-economic evaluation. Health Technol Assess. 2016;20(88):1–150.
62. Xu L, Chen H, Gu Y. Stapled hemorrhoidectomy versus transanal hemorrhoidal dearterialization in the treatment of hemorrhoids: an updated meta-analysis. Surg Laparosc Endosc Percutan Tech. 2019;29(2):75–81.
63. Emile SH, et al. Transanal hemorrhoidal dearterialization (THD) versus stapled hemorrhoidopexy (SH) in treatment of internal hemorrhoids: a systematic review and meta-analysis of randomized clinical trials. Int J Color Dis. 2019;34(1):1–11.
64. Xu L, et al. Transanal hemorrhoidal dearterialization with mucopexy versus open hemorrhoidectomy in the treatment of hemorrhoids: a meta-analysis of randomized control trials. Tech Coloproctol. 2016;20(12):825–33.
65. Collins JB, Song J, Mahabir RC. Onset and duration of intradermal mixtures of bupivacaine and lidocaine with epinephrine. Can J Plast Surg. 2013;21(1):51–3.
66. Haas E, et al. A double-blind, randomized, active-controlled study for post-hemorrhoidectomy pain management with liposome bupivacaine, a novel local analgesic formulation. Am Surg. 2012;78(5):574–81.
67. Little A, et al. A cost-minimization analysis evaluating the use of liposomal bupivacaine in reconstructive plastic surgery procedures. Plast Reconstr Surg. 2019;143(4):1269–74.
68. Gatherwright J, et al. Prospective, randomized, controlled comparison of bupivacaine versus liposomal bupivacaine for pain management after unilateral delayed deep inferior epigastric perforator free flap reconstruction. Plast Reconstr Surg. 2018;141(6):1327–30.
69. Kalogera E, et al. Abdominal incision injection of liposomal bupivacaine and opioid use after laparotomy for gynecologic malignancies. Obstet Gynecol. 2016;128(5):1009–17.
70. Brummett CM, et al. New persistent opioid use after minor and major surgical procedures in US adults. JAMA Surg. 2017;152(6):e170504.
71. Van Backer JT, et al. Preemptive analgesia decreases pain following anorectal surgery: a prospective, randomized, double-blinded, placebo-controlled trial. Dis Colon Rectum. 2018;61(7):824–9.
72. Wanis KN, et al. Systemic metronidazole may not reduce post-hemorrhoidectomy pain: a meta-analysis of randomized controlled trials. Dis Colon Rectum. 2017;60(4):446–55.
73. Lu P, et al. Opioid prescriptions after hemorrhoidectomy. Dis Colon Rectum. 2020;63:1118–26.
74. Meyer DC, Hill S, McDade JA, Harnsberger CR, Davids JS, Sturrock PR, Maykel JA, Alavi K. Opioid consumption patterns after anorectal operations: development of an institutional prescribing guideline. J Am Coll Surg. 2021;64:103–11.
75. Ala S, et al. Effect of topical baclofen 5% on post-hemorrhoidectomy pain: randomized double blind placebo-controlled clinical trial. J Gastrointest Surg. 2020;24:405–10.
76. Ratnasingham K, et al. Meta-analysis of the use of glyceryl trinitrate ointment after haemorrhoidectomy as an analgesic and in promoting wound healing. Int J Surg. 2010;8(8):606–11.
77. Vahabi S, et al. Comparative Study of 0.2% glyceryl trinitrate ointment for pain reduction after hemorrhoidectomy surgery. Surg J (N Y). 2019;5(4):e192–6.
78. Perrotti P, et al. Topical nifedipine with lidocaine ointment versus active control for pain after hemorrhoidectomy: results of a multicentre, prospective, randomized, double-blind study. Can J Surg. 2010;53(1):17–24.
79. Linares-Gil MJ, et al. Topical analgesia with lidocaine plus diclofenac decreases pain in benign anorectal surgery: randomized, double-blind, and controlled clinical trial. Clin Transl Gastroenterol. 2018;9(11):210.
80. Vinson-Bonnet B, et al. Ambulatory haemorrhoidal surgery: systematic literature review and qualitative analysis. Int J Color Dis. 2015;30(4):437–45.
81. Toyonaga T, et al. Postoperative urinary retention after surgery for benign anorectal disease: potential risk factors and strategy for prevention. Int J Color Dis. 2006;21(7):676–82.
82. Chen HH, et al. Effective management of posthemorrhoidectomy secondary hemorrhage using rectal irrigation. Dis Colon Rectum. 2002;45(2):234–8.
83. Chen HH, et al. Risk factors associated with posthemorrhoidectomy secondary hemorrhage: a single-institution prospective study of 4,880 consecutive closed hemorrhoidectomies. Dis Colon Rectum. 2002;45(8):1096–9.
84. Rosen L, et al. Outcome of delayed hemorrhage following surgical hemorrhoidectomy. Dis Colon Rectum. 1993;36(8):743–6.
85. Farrer FE. Delayed postoperative anorectal hemorrhage. Dis Colon Rectum. 1961;4:50–5.
86. Yano T, et al. The outcome of postoperative hemorrhaging following a hemorrhoidectomy. Surg Today. 2009;39(10):866–9.

87. Milito G, et al. Haemorrhoidectomy with Ligasure vs conventional excisional techniques: meta-analysis of randomized controlled trials. Color Dis. 2010;12(2):85–93.
88. Carditello A, et al. Surgical treatment of anal stenosis following hemorrhoid surgery. Results of 150 combined mucosal advancement and internal sphincterotomy. Chir Ital. 2002;54(6):841–4.
89. Eu KW, et al. Anal stricture following haemorrhoidectomy: early diagnosis and treatment. Aust N Z J Surg. 1995;65(2):101–3.
90. Rasmussen OO, et al. Emergency haemorrhoidectomy compared with incision and banding for the treatment of acute strangulated haemorrhoids. A prospective randomised study. Eur J Surg. 1991;157(10):613–4.
91. Rakinic J, Poola VP. Hemorrhoids and fistulas: new solutions to old problems. Curr Probl Surg. 2014;51(3):98–137.
92. Ferdinande K, et al. Anorectal symptoms during pregnancy and postpartum: a prospective cohort study. Color Dis. 2018;20(12):1109–16.
93. Bernstein WC. What are hemorrhoids and what is their relationship to the portal venous system? Dis Colon Rectum. 1983;26(12):829–34.
94. Chawla Y, Dilawari JB. Anorectal varices--their frequency in cirrhotic and non-cirrhotic portal hypertension. Gut. 1991;32(3):309–11.
95. Montemurro S, et al. Inferior mesocaval shunt for bleeding anorectal varices and portal vein thrombosis. Hepato-Gastroenterology. 2001;48(40):980–3.
96. Rahmani O, Wolpert LM, Drezner AD. Distal inferior mesenteric veins to renal vein shunt for treatment of bleeding anorectal varices: case report and review of literature. J Vasc Surg. 2002;36(6):1264–6.
97. Wolkomir AF, Luchtefeld MA. Surgery for symptomatic hemorrhoids and anal fissures in Crohn's disease. Dis Colon Rectum. 1993;36(6):545–7.
98. Karin E, et al. Doppler-guided haemorrhoidal artery ligation in patients with Crohn's disease. Color Dis. 2012;14(1):111–4.
99. Moore BA, Fleshner PR. Rubber band ligation for hemorrhoidal disease can be safely performed in select HIV-positive patients. Dis Colon Rectum. 2001;44(8):1079–82.
100. Ramanujam PS, et al. Perianal abscesses and fistulas. A study of 1023 patients. Dis Colon Rectum. 1984;27(9):593–7.
101. Cintron JR, Abcarian H. Benign anorectal: hemorrhoids. In: Wolff BG, Fleshman JW, Beck DE, Pemberton JH, Wexner SD, Church JM, Garcia-Aguilar J, Roberts PL, Saclarides TJ, Stamos MJ, editors. The ASCRS textbook of colon and rectal surgery: Springer Nature; London, UK, 2007.
102. Wexner SD, Fleshman JW, editors. Colon and rectal surgery: anorectal operations: Wolters Kluwer Health, Inc.; Philadelphia, Pennsylvania, USA, 2018.

Anal Fissure and Anal Stenosis

12

V. Liana Tsikitis and Slawomir Marecik

Key Concepts

- Acute anal fissures (symptoms <6 weeks) are typically treated first with nonoperative, conservative management with high healing rates.
- Calcium channel blockers have similar efficacy rates with topical nitrates and fewer side effects. They are considered first line of treatment for chronic fissures.
- Botulinum toxin injection has slighter higher efficacy in addressing symptomatology than topical therapy, and it is considered second line of treatment for chronic anal fissures.
- Lateral internal sphincterotomy (LIS) has superior healing rates than pharmacologic treatment for chronic anal fissures; however, there is an increased risk for permanent minor incontinence. Open and closed techniques of LIS yield similar healing rates.
- Anocutaneous flaps represent a safe surgical alternative for anal fissures with decreased anal sphincter tone. In addition, advancement flaps can be used in combination with botulinum toxin injection and LIS for expediting primary wound healing.
- Ninety percent of anal stenosis cases are a result of inappropriately performed hemorrhoidectomy.
- Mild anal stenosis can frequently be managed with nonoperative treatment.
- Moderate and severe anal stenosis will require surgical treatment.
- Sphincterotomy, stricturotomy, and stricturectomy should be followed by reconstructive procedures reintroducing the epithelial or mucosal coverage into the anal canal.
- Reconstructive options involve the rectal advancement flap and several flaps utilizing the anoderm and perirectal skin.
- Management of anal stenosis in Crohn's disease should be based on optimization of medical therapy combined with dilations; however, a significant number of patients will require diversion.

Anal Fissure

Definition, Clinical Presentation, and Etiology

An anal fissure is a linear tear of the anal mucosa, usually extending from the dentate line to the anal verge. Even though anal fissures are encountered frequently, there are no population studies that elucidate their exact incidence (Fig. 12.1). The chief complaints from patients with an anal fissure include anal pain and bleeding associated with defecation. Most patients with anal fissures will seek consultation due to the severity of pain and negative impact on quality of life [1].

Anal fissures affect all age groups, and the majority of fissures (90%) occur at the posterior anal midline (90%) [2–4]. The incidence of anterior midline fissures is higher in female patients (10–25%) than male patients (1–8%) [2–4]. The incidence of concomitant anterior and posterior fissures is 3% [4]. Atypical fissures including lateral fissures should raise concern for inflammatory bowel disease, tuberculosis, human immunodeficiency virus (HIV), or syphilis (Fig. 12.2).

Acute anal fissures are thought to be secondary to anoderm trauma due to either constipation with hard stools or frequency from diarrhea. The pain is described as most severe during the act of defecation although it may last several hours following a bowel movement. Although constipation and hard stools are commonly considered the culprit, only 13% of patients with fissuring disease report constipa-

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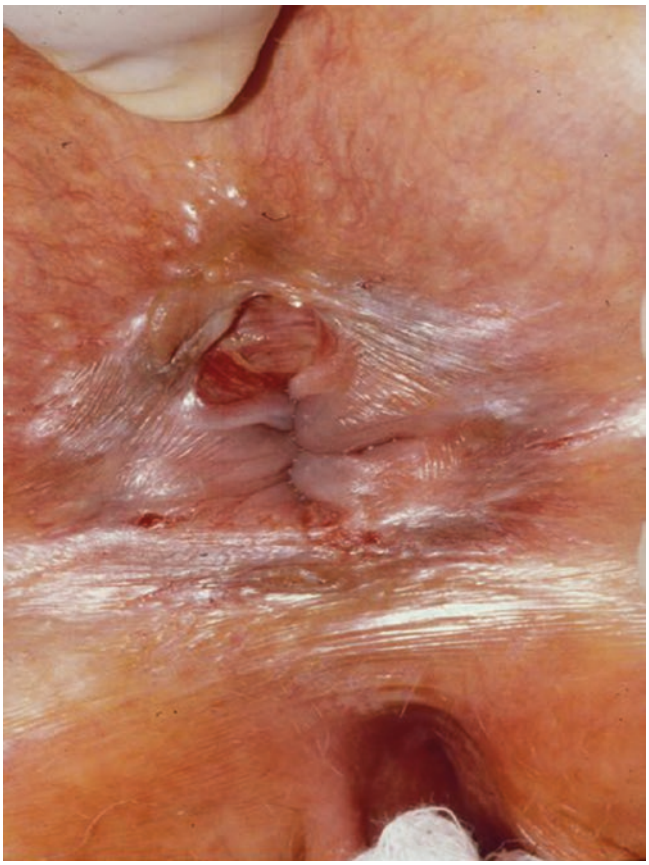

Fig. 12.1 Anal fissure

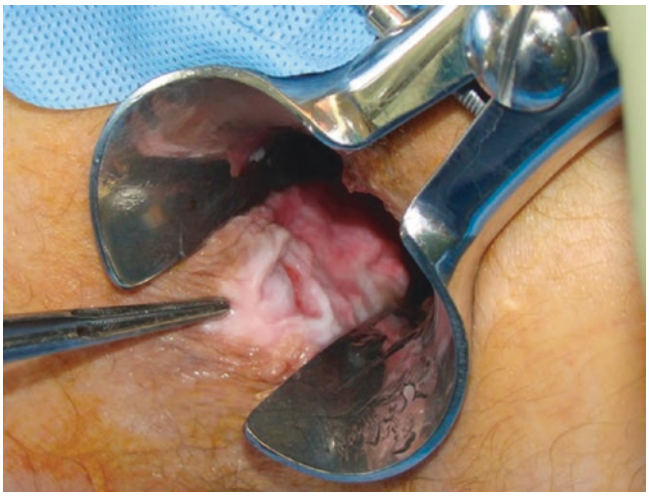

Fig. 12.2 Atypical fissure with skin changes, broad base, and lateral location. (Courtesy of Sam Atallah, MD)

tion [2]. Chronic fissures are persistent, long-lasting fissures that continue for more than 6 weeks. In particular, the persistently high internal sphincter tone leads to chronicity of fissures, and they can cause pain even after a local anesthetic is applied [1]. Chronic fissures may be found at an outpatient clinic examination, although examination and visualization

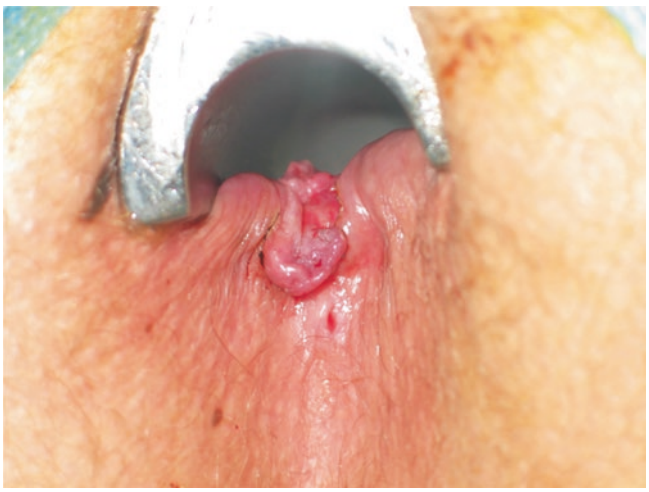

Fig. 12.3 Acute fissure with clear edges and no signs of chronicity of sphincter hypertrophy. (Courtesy of Richard P. Billingham, MD)

may be difficult due to pain and internal sphincter spasm. Inspection classically reveals indurated edges, visible sphincter muscle at the base, associated hypertrophic papilla proximally, and a sentinel tag distally (Fig. 12.3).

It is speculated that the lack of normal activity of nitric oxide synthase (NOS) is responsible for the chronicity of long-standing fissures. One study aimed to compare the presence of NOS in patients with and without chronic anal fissures. Internal sphincter biopsies were taken from patients with chronic anal fissures at the time of lateral internal sphincterotomy and from patients that were undergoing abdominoperineal resections that acted as the control group. Internal sphincter specimens from patients with chronic fissures contained little or no NOS compared to the internal sphincters from the abdominoperineal resection specimens [5]. In addition, the increased internal sphincter tone associated with anal fissures is thought to cause local ischemia which prevents the fissure from healing. When the topography of the inferior rectal arteries was examined using postmortem angiography, the anoderm is supplied by the inferior rectal arteries after traversing the internal sphincter, and it clearly illustrated that the arterial perfusion is inversely related to the pressure of the internal sphincter [6]. High tonicity of the internal sphincter muscle will lead to lower perfusion of the anal canal, suggesting the fissure represents a nonhealing ischemic ulcer. Likewise, cadaver studies have demonstrated a paucity of arterioles in the posterior midline of the anal canal, also explaining the propensity for the posterior location of fissures [7, 8].

Anal fissures can also occur in women during labor and delivery due to shear forces and local trauma. In fact, 11% of chronic fissures are associated with difficult or instrumented deliveries and are most common in the anterior midline [3]. Interestingly, these chronic fissures are not associated with

increased sphincter tone, but normal or even low pressures. It is important to distinguish the etiology of chronic fissures, so treatment is appropriately tailored [9].

Medical/Pharmaceutical Treatment

Topical Agents

First-line treatment of anal fissures consists of conservative medical treatment including stool softeners, psyllium fiber and other bulking agents, sitz baths, and the application of topical analgesics such as lidocaine gel for pain control. Most studies show healing rates of 16–31% in acute and chronic fissures with conservative management [3]. The application of local lidocaine does not increase fissure healing rates when compared to placebo; however, lidocaine can provide symptomatic pain relief [4, 10]. In addition, maintenance therapy with fiber decreases the risk of fissure recurrence [11].

The goal of medical treatment of anal fissures is to decrease the internal sphincter tone and allow healing. Topical nitrate use leads to healing of chronic anal fissures in about 50% of patients and demonstrates a 13.5% improvement in healing over placebo; however, recurrence rates are high [4]. In particular, close to 50% of the patients who had their fissures healed with nitrates will experience a recurrence. Commonly used topical nitrates include isosorbide dinitrate and glyceryl trinitrate. However, these nitrates are rarely used today due to their unpleasant side effects, primarily headaches [3, 4].

Application of topical calcium channel blockers including nifedipine and diltiazem has been associated with healing close to 90% of chronic anal fissures [12]. In addition, a double-blinded, multicenter, randomized trial comparing the application of nifedipine (treatment group) to hydrocortisone and lidocaine (control group) found that the nifedipine treatment healed acute fissures within 21 days in 95% of patients compared to 50% in the control group [13]. In this study, anal manometry confirmed that nifedipine decreased the resting anal pressure by 30% compared to the control group [13]. Data suggest that the cure rate of anal fissures is higher with three times' daily application of calcium channel blockers and with a 3-month treatment duration [14].

Botulinum Toxin Injection

When conservative management with topical ointment fails, a second-line treatment still under the medical management umbrella is the injection of botulinum toxin (Botox). Interestingly, Botox injection has better results when used as a second-line treatment [3, 15]. Treatment with Botox has healing rates ranging from 27% to 96% [3]. The most common side effect related to Botox injection is temporary incontinence, particularly to flatus, that can occur in up to 18% of patients [3]. Multiple dosages (ranging from 20 to 100 international units (IU) or more) have been described, and varied injection sites have been proposed [3, 4]. One advantage of Botox injection over topical nitrates and calcium channel blockers is that it does not require a frequent application schedule and does not cause similar unpleasant side effects [4, 16]. However, its efficacy is questionable with one meta-analysis showing that Botox injection had no significant advantage over nitrate topical application or placebo [10]. Another meta-analysis comparing Botox to sphincterotomy reported that Botox has lower healing rates but also lower rates of incontinence [17].

A Cochrane review of 77 studies and 5031 participants showed that nitrates are marginally more efficacious than placebo (48% healed versus 35%) in healing fissures [18]. Botulinum toxin injections and calcium channel blockers were equivalent to nitrates in efficacy but had fewer side effects [18]. No arms of medical therapy compared favorably to surgical treatment; however, they all carry a lower risk of permanent incontinence [10, 18].

Operative Treatment

Anal dilation is possibly the oldest treatment for anal fissures and is only mentioned here for historic purposes. There is substantial variance in the surgical technique with a wide range of outcomes. A 2011 Cochrane review examining seven randomized controlled trials comparing anal dilation to sphincterotomy reported that anal dilation was less effective and resulted in higher rates of incontinence (OR: 4.03, 95% CI: 2.04–7.46) [19]. More recently pneumatic balloon dilation has been described for anal fissure therapy. In one study, a 40-mm-diameter and 60-mm-long anal balloon was inserted into the anal canal after adequate lubrication and was positioned with 10 mm protruding from the anus. The balloon was rapidly inflated to a 20 psi pressure (1.4 atm) and maintained in situ for 6 min. The balloon was then deflated and removed. The fissure-healing rates were 83.3 percent in the pneumatic balloon dilatation and 92 percent in the lateral internal sphincterotomy group. At anal manometry, mean resting pressure decrements obtained after pneumatic balloon dilatation and lateral internal sphincterotomy were 30.5 and 34.3 percent, respectively. At 24-month follow-up, the incidence of incontinence, irrespective of severity, was 0 percent in the pneumatic balloon dilatation group and 16 percent in the lateral internal sphincterotomy group ($P < 0.0001$) [20].

Lateral Internal Sphincterotomy (LIS)

Lateral internal sphincterotomy (LIS) is considered the gold standard for treatment of chronic anal fissures with multiple randomized studies showing its superior effectiveness in

treating the symptomatology when compared to conservative medical management [21–32]. LIS has healing rates of 88–100%, but it can be associated with incontinence rates of 8–30% [4]. This incontinence can be transient (less than 2 months) or prolonged (over 2 months) in 3–7% of patients [3]. However, these incontinence rates are reported with traditional LIS, when the sphincterotomy is carried up to the dentate line. Such a traditional sphincterotomy has a lower rate of recurrence and a higher risk of permanent incontinence when compared to the "tailored" sphincterotomy [33], which is defined as a sphincterotomy to the apex of the fissure. The "tailored" sphincterotomy has been shown to preserve more of the sphincter and lowers incontinence rates [19, 34]. Older randomized trials comparing traditional and tailored sphincterotomy showed statistically higher healing rates with the traditional technique, with relatively similar reported incidences of minor incontinence (<3% incontinence rate) [35, 36]. Accordingly, the tailored sphincterotomy is as the preferred surgical approach which provides symptom relief and decreased risk of permanent incontinence. LIS may be considered as first-line surgical treatment in patients without prior obstetrical injury, inflammatory bowel disease, prior anorectal operations, or sphincter weakness [4]. In particular, patients with chronic anal fissures and without underlying fecal incontinence may benefit from LIS as the first line of treatment.

Technique

LIS is performed with either an open or closed technique. In the open technique, an incision is made distal to the dentate line exposing the intersphincteric groove. The surgeon then elevates and divides the internal sphincter muscle to the height of the fissure and closes the wound with an absorbable stitch. In the closed technique, the intersphincteric groove is not exposed but delineated. A narrow-bladed scalpel, flat side adjacent to the muscle, is introduced through the skin in either right- or left-lateral position of the intersphincteric groove, and the tip is advanced submucosally to the dentate line. The sharp edge of the knife is turned toward the internal sphincter muscle, and the muscle is divided, releasing the tension and creating a palpable defect. The skin opening can be left open or closed with a chromic stitch. In a recent Cochrane review comparing the open and closed techniques, no difference in outcomes including persistence of the fissure or fecal incontinence was demonstrated between the two techniques (Figs. 12.4 and 12.5) [19].

Outcomes

Reported recurrence rates range from 0% to 15% after LIS, which are usually attributed to insufficient length of the division of the internal sphincter muscle [3]. LIS can be repeated and offered as a treatment of recurrent fissures and performed on the contralateral side of a prior sphincterotomy site [4]. There is a paucity of data regarding recurrent fissures after LIS. A recent study including 57 patients evaluated repeated LIS for recurrent fissures with a mean follow-up of 12.5 ± 4.2 years. They reported a 98% healing rate and a 4% minor incontinence rate including incontinence to flatus and seepage. The authors used the modified Cleveland Clinic Incontinence Questionnaire to report patients' symptoms, and 2 female patients out of 57 reported varied incontinence to flatus and seepage [37]. Overall, one should consider LIS as the standard surgical treatment for chronic anal fissures with increased sphincter tone when medical management has failed.

Local Advancement Flaps

Local advancement flaps are the first line of surgical treatment for chronic anal fissures associated with normal or low anal pressures. These patients are usually female patients that have developed fissures after a prolonged and difficult vaginal delivery. These flaps are usually anocutaneous flaps (dermal V-Y or house flap) which have been described using a variety of techniques (see below in the "Anal Stenosis" segment). Giordano et al. demonstrated a 98% healing rate after anorectal advancement flap surgery independent of anal tonicity [38]. At a 6-month follow-up, there was no reported fissure recurrence or fecal incontinence [38]. Interestingly, the authors reported a 6% rate of fissure formation at a new site [38]. A smaller study showed similar successful results after local advancement flap surgery for fissures in the setting of hypotonicity with a median follow-up of 7 months [39].

Anocutaneous flaps have been combined with sphincterotomy or Botox injection to simultaneously address the chronic nonhealing wound and the underlying sphincter hypertonicity [4]. One randomized study allocated 50 patients to receive LIS, 50 patients to receive V-Y advancement flap, and 50 patients to receive a combination of LIS and V-Y flap (see diagram in "Anal Stenosis" segment). At the 1-year follow-up, healing rates for patients who received LIS, V-Y advancement flap, and a combination of LIS and V-Y flap were 84%, 48%, and 94% ($p = 0.001$), and recurrence rates were 4%, 22%, and 2% ($p = 0.01$), respectively [40].

Fissurotomy and Fissurectomy

Fissurotomy and fissurectomy are not considered standard treatment options for anal fissure. Chronic fissures frequently present with subcutaneous tracts that extend distally from the chronic fissure to the sentinel tag. Fissurotomy involves incising and dividing that tract to expose the chronic underlying cavity and release the perianal skin, resulting in widening of the anal canal. The wound remains open to heal by secondary intention. One prospective trial of 109 patients undergoing fissurotomy had resolution of symptoms in 98% of patients, with the other 2% requiring subsequent sphinc-

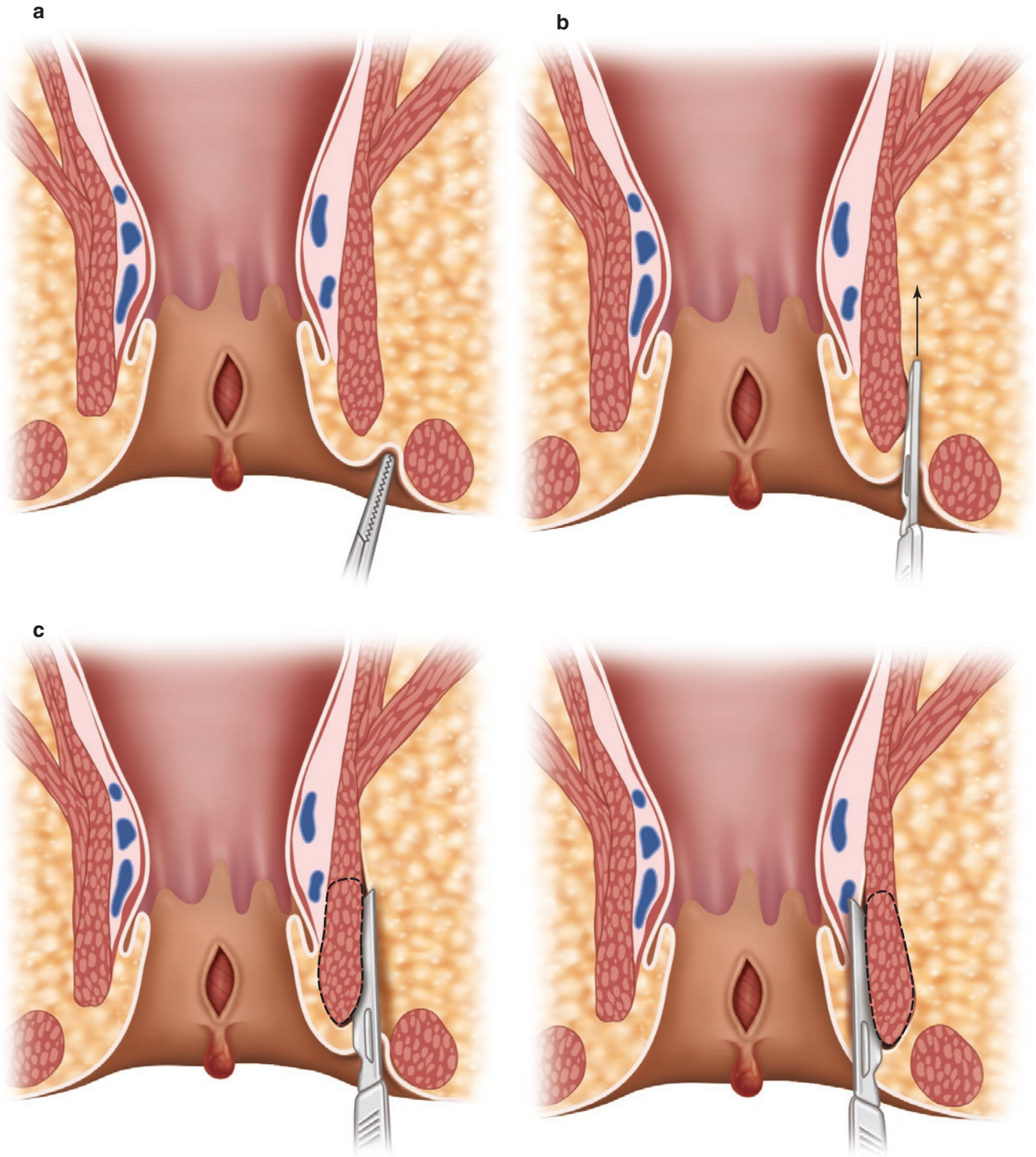

Fig. 12.4 Closed lateral sphincterotomy. (**a**). Location of the intersphincteric groove. (**b**). Insertion of the knife blade in the intersphincteric plane. (**c**). Lateral to medial division of the internal anal sphincter (*inset:* medial to lateral division of the muscle)

terotomy [41]. In contrast, fissurectomy is defined as the excision of the chronic fissure wound with excision of the sentinel pile, if present. In a recent Cochrane review on operative procedures for fissure in ano, the authors commented on two studies which compared fissurectomy with sphincterotomy [19]. These studies comprised of total of 162 patients and found that sphincterotomy was significantly less likely to result in treatment failure compared to fissurectomy (OR 8.07 [1.42–45.84]). One of the two studies concluded that fissurectomy is not a procedure of choice because of its asso-

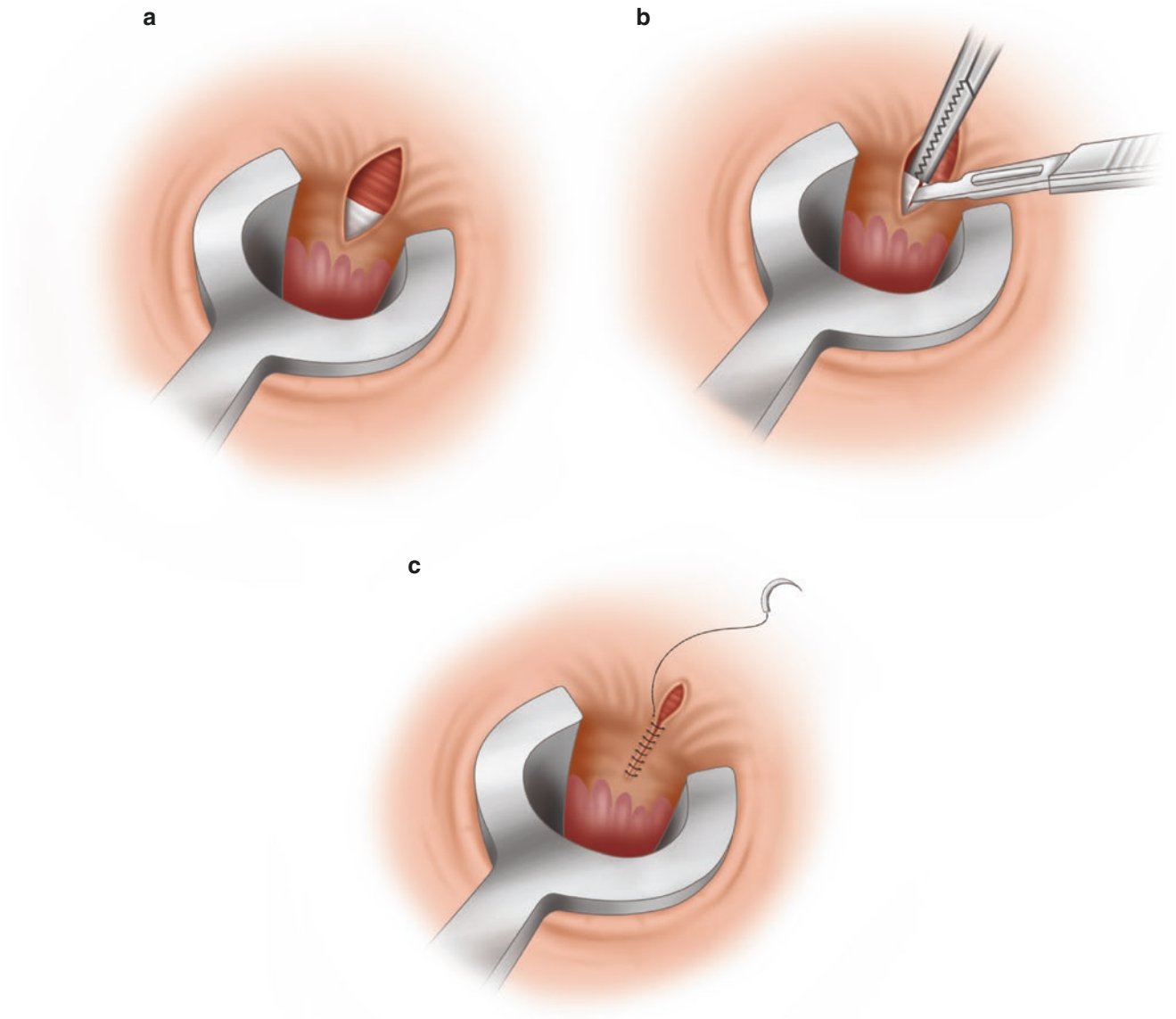

Fig. 12.5 Open lateral internal sphincterotomy. (**a**). Radial skin incision distal to the dentate line exposing the intersphincteric groove. (**b**). Elevation and division of the internal sphincter. (**c**). Primary wound closure

ciated recurrence risk (3%) and the high rate of incontinence (6%) [42]. Another study reported that fissurectomy, in combination with isosorbide dinitrate cream, resulted in 100% healing within 10 weeks without recurrence and without incontinence complaints [43]. A third study showed that fissurectomy with concurrent Botox injection led to 100% improvement of symptoms with objective wound healing in 93% of patients [44].

Atypical Fissures

Atypical fissures are most commonly seen in patients with Crohn's disease and patients with sexually transmitted diseases. Fissures in Crohn's patients usually present as deep, painful ulcerations and are treated with Crohn's medical therapies. Crohn's fissures are rarely treated surgically because of perceived poor wound healing that may lead to significant perianal deformity and potentially to incontinence. Multidisciplinary care is instrumental in addressing anorectal Crohn's pathology, and optimal medical management may lead to resolution in more than half of the cases [45, 46]. Treatment of atypical fissures associated with sexually transmitted diseases is dictated by identifying the causative organism after a biopsy of the fissure. HIV-related fissures are the most commonly encountered and may present either as deep, broad-based ulcers or as typical appearing fissures. These fissures are not associated

with internal sphincter hypertonicity. Short-term successful treatment options include surgical debridement and intralesional steroid injection; however, in the long term, optimizing antiretroviral therapy is instrumental for improving symptomatology [47].

Anal Fissure, Conclusion

Anal fissures are common and can be effectively treated with conservative medical management. When fissure symptomatology is long-standing (more than 6 weeks), topical calcium channel blockers in combination with sitz baths and the use of psyllium fiber or other bulking agents are the first lines of treatment. Botulinum toxin injection can be added when medical management fails to provide a resolution of symptoms. LIS is considered the standard surgical treatment for chronic anal fissures with a hypertonic internal sphincter and can be considered first-line treatment for patients that have no underlying fecal incontinence. Advancement flaps remain an option for patients with symptomatic chronic anal fissures with associated hypotonicity and/or compromised continence.

Anal Stenosis

Introduction, Definition, and Types

Anal stenosis is an uncommon but potentially serious condition characterized by abnormal narrowing of the anorectal junction, anal canal, or the anal margin. It occurs when the physiologic capacity of the anal canal is lost and the pliable tissues are replaced with fibrotic connective tissue [48]. This leads to an abnormally tight and inelastic anal canal and can also involve the internal anal sphincter [49]. Anal stenosis commonly results from the loss of anodermal coverage distal to the dentate line and less frequently can occur in the proximal anal canal [50].

Anal stenosis can be classified as congenital, primary, or secondary [51]. Congenital stenosis is related to developmental abnormalities, which are frequently associated with imperforate anus, anal atresia, or Hirschsprung disease. Conversely, primary stenosis occurs later in life and is related to rare involutional (senile) changes. Lastly, secondary anal stenosis is the most common presentation. Historically, it has been connected to an improperly performed surgical hemorrhoidectomy, in particular a now almost abandoned technique proposed by Whitehead [52]. Anal stenosis can also, however, be encountered after any anorectal procedure or disease process resulting in repetitive trauma or excessive destruction of anoderm and hemorrhoidal tissue.

Incidence and Causes

Post-hemorrhoidectomy (secondary) anal stenosis or stricture is present in 1.5–4% of cases with some recent reports quoting even higher incidence of 19% [53–55]. Hemorrhoidectomy accounts for approximately 90% of all anal stenosis cases [41, 42]. One of the more common scenarios occurs during excessive removal of acute, swollen, and partially necrotic grade IV hemorrhoids while failing to preserve adequate anoderm. Secondary anal stenosis following a pull-through procedure can occur in up to 16% of cases and occurs most often following mucosectomy and/or anastomotic dehiscence [56, 57]. Pull-through procedures or sagittal anorectoplasties performed on children in order to treat congenital anal stenosis can lead to secondary anastomotic anal stenosis [58, 59]. Stapling procedures for hemorrhoids (PPH) have also been associated with scarring and stenosis in the area of the anorectal junction [60]. Finally, Crohn's disease can lead to stricture formation at many levels [61, 62], often with transmural disease frequently involving the internal sphincter. Stricture at the anorectal junction occurs when deep fissures of the rectal mucosa converge at the anorectal ring. More distal strictures of the anal canal are related to fissuring and fistulizing disease involving the anus and perianal region or simply from chronic inflammation caused by chronic diarrhea. The potential causes of anal stenosis are summarized in Table 12.1.

Symptoms

Symptoms of anal stenosis include difficult, painful, or incomplete evacuation, fecal impaction, constipation, decrease in stool caliber, tenesmus, bleeding, overflow diarrhea, fecal seepage, and incontinence.

Evaluation

Initial diagnosis of anal stenosis can frequently be made in the office during physical examination, although anatomic findings may not directly correlate with the severity of patient symptoms. Findings can reveal narrowing of the anal opening with common circumferential fissure formation [51]. However, the true extent and severity of the stenosis often has to be investigated and identified with the patient under anesthesia to avoid unnecessary pain or discomfort. An exam under anesthesia will also enable the physician to differentiate between the anatomical and functional cause of the stenosis and allow for biopsy of any suspicious lesions [63]. Relaxation of the anus during anesthesia is characteristic for functional stenosis, while the persistence of stricture points to anatomical stenosis caused by the scarring of the anoderm and potentially the underlying internal sphincter. A thorough

Table 12.1 Potential causes of anal stenosis

Anorectal procedure	
	Hemorrhoidectomy
	Excision and fulguration of condylomas
	Wide local excision of Paget's and Bowen's disease
	Transanal excision of anorectal polyp or cancer
	Sphincteroplasty
Anastomotic type	
	Coloanal
	Ileal pouch anal anastomosis
	Mucosectomy
	Pull-through for Hirschsprung's disease
Inflammatory bowel disease	
	Involving lower rectum, anal canal, and anal verge
Trauma	
Chronic laxative use	
Fissure(s)	
	Being a result and/or a reason
Radiation	
Suppurative processes	
	Complex abscess/fistula
	Hidradenitis
Infectious	
	Sexually transmitted diseases
	Tuberculosis
Neoplastic	
Congenital	

Table 12.2 Classification of anal stenosis

Severity	Location	Extent
Mild: Exam can be completed with a finger or medium Hill-Ferguson retractor	*Low:* At least 0.5 cm distal to the dentate line	*Localized*: One level or quadrant of the anal canal
Moderate: Dilation needed to examine with a finger or medium Hill-Ferguson retractor	*Mid*: Within 0.5 cm distal and proximal to the dentate line	*Diffuse*: More than one level or quadrant
Severe: Unable to examine with little finger or small Hill-Ferguson retractor, unless forcefully dilated	*High*: At least 0.5 cm proximal to the dentate line	*Circumferential*: Entire circumference

evaluation of the anorectum will allow for determination of the degree, extent, and level of the stricture, circumferential distribution of fibrosis, and any sphincter involvement.

Classification

Based on the above findings, the severity of stricture can be classified and appropriate treatment chosen. The most commonly used Milsom and Mazier classification is presented in Table 12.2 [50]. This classification divides the stenosis into mild, moderate, and severe and low (65% of patients), mid-level (18.5% of patients), and high (8.5% of patients). In addition, stenosis can be "diaphragmatic" (after inflammatory bowel disease, characterized by a thin strip of constrictor tissue), "ringlike" (annular, lesions <2 cm), or "tubular" (length > 2 cm).

Treatment

The treatment of anal stenosis is based on patient symptoms and varies depending on the severity, location, and cause of the stenosis. Inflammatory and infectious etiology should always be treated with appropriate medical therapy first.

Nonoperative Treatment

This option is typically used for patients with mild and occasionally moderate stenosis (as an initial step) and is based on dietary modifications, stool softeners, and "bulking therapy" with dietary fiber supplementation [49]. Assuring that the stool is soft enough to pass through the stenosis, it allows for the natural, repetitive stretch of the anal canal by a fecal bolus. At a minimum, this can prevent further stricture formation. In many cases, this therapy is successful and can lead to effective widening of the anal canal lumen [64].

If the bulking therapy is not successful, or the patient experiences a significant amount of pain during elimination, digital or mechanical dilation can be performed [51]. This can be attempted in the office with the use of local anesthetic gel and a set of Hegar dilators, followed by at-home dilations. Alternatively, the patient can undergo the first dilation under anesthesia (with digital, Hegar, or pneumatic technique), followed by regular gradual dilations at home. A set of metal or plastic dilators can be acquired for between $15 and $100. Historically, candles or other similarly shaped household objects have also been used.

Any dilation under anesthesia should be performed carefully and follow two main principles. The first is to allow for only minimal trauma to the already strictured anoderm and to avoid creation of deep fissures. The second principle requires no disruption of the underlying internal sphincter muscle. If the dilation procedure cannot meet the above principles, it should be avoided, and the patient should be advised of other corrective techniques described later in the text.

Aggressive dilation with deep fissure creation and trauma to the internal sphincter will likely lead to a brief improvement in symptoms. However, in the long term, it will also lead to worsening of the anoderm and sphincter fibrosis [51]. Dilations can be successfully performed in patients with Crohn's disease, postradiation stenosis, or anastomotic strictures [49]. They are routinely used following pull-through procedures for Hirschsprung's disease in children [65]. It is important to identify any anastomotic strictures as early as

possible. In fact, it is the author's routine practice to check for them during the rectal exam within the first 2 weeks after surgery. Early recognition of not-yet fibrotic strictures allows for early, frequent digital dilations in the office or home, thereby avoiding the need for forceful mechanical dilation later.

Dilations of chronic and fibrotic strictures require compliant and highly motivated patients. Approximately half of patients with anal Crohn's stenosis will respond to medical therapy and dilations, while the other half will require proctectomy or proximal diversion [66, 67]. Dilations are more effective for shorter strictures. Pain related to dilations is a major factor that can limit the effectiveness of the therapy. Sphincter damage leading to fecal incontinence is a major concern after repeated dilations [68]. If the stenosis is refractory to safe dilations, other surgical options should be considered.

Anal stenosis is often associated with anal fissure disease, which can be a result of or cause for the stenosis. For this reason, it is important to first address the fissure, as described earlier in this chapter. Lastly, it is important to note that because many patients initially present relying on laxatives, enemas, suppositories, and even manual disimpaction maneuvers, this can lead to additional trauma of the already stenotic anal canal in the long term [51, 68].

Surgical Treatment

Operative treatment is reserved for severe and persistent moderate anal stenosis, as well as for rare refractory cases of mild symptomatic stenosis [49–51, 54, 63, 68]. Sphincter function evaluation with anorectal manometry and pudendal nerve motor latency can also be attempted before the surgical correction if indicated; however, it will not likely change the course of treatment and may be either painful or difficult to perform. Endoanal ultrasound is not typically an option.

All corrective cases are performed under general anesthesia or under sedation with local anesthesia allowing for sufficient retraction and exposure of the anal area. The main challenge is to provide the initial access to the strictured anal canal, which will frequently require using a small-size Hill-Ferguson retractor. Often, a gentle pneumatic or Hegar dilation is necessary to open the lumen. Any suspicious areas should be biopsied to rule out malignancy since chronic wounds have a higher propensity for malignant transformation. The extent and radial distribution of the scar should also be ascertained since further treatment will be determined by these findings [50]. The internal sphincter involvement, and its fibrosis, is evaluated for possible functional stenosis, which may require lateral internal sphincterotomy [51]. Any fibrotic stenosis of the internal sphincter muscle should be addressed by concomitant sphincterotomy (unilateral or bilateral) to improve chances of successful outcome [63].

The Lone-Star retractor is frequently used to bring the anus into the effective operating field. Release or excision of the scar tissue enables further access into the anal canal.

Reconstruction of the anodermal defect can then be performed with a fragment of a healthy rectal wall (commonly referred to as rectal mucosa), anoderm of the anal verge, or the perianal and gluteal skin including the underlying subcutaneous tissues.

Transverse Closure Following Excision of Scar (With Possible Sphincterotomy)

For short strictures involving the internal sphincter, an incision or excision of the scar with internal sphincterotomy can be attempted. This will create a diamond-shape defect. Transverse closure of this wound can then be attempted, as long as there is no excessive tension on the tissues [69]. Absorbable and long-lasting 2-0 and 3-0 sutures should be used (e.g., Vicryl). If there is too much tension on the edges of the defect, the patient should be considered for a Y-V advancement flap (see below) [69]. Simple stricture release without any reconstruction attempt can lead to temporary improvement in symptoms but will likely result in stricture recurrence [49].

Rectal Advancement Flap

Advancement of the healthy rectal tissue is primarily reserved for proximal and mid-anal canal stenosis [70–72]. It is performed as a modification of Martin's anoplasty following the incision or excision of the scar and optional concomitant internal sphincterotomy (preferably in the lateral position) [73]. In the literature, this is described as "rectal mucosal flap"; however, this term is a misnomer. The flap is often not created, but rather the rectal wall is stretched to cover the defect. And if the flap is created, to prevent ischemia of the flap, the dissection should also involve the deeper tissues, including one or both layers of the muscularis propria of the rectum (potentially including some fragments of the distal internal sphincter) or even a thin layer of the mesorectal tissue, which can fill in the sphincterotomy defect. One of the important stipulations of this technique is to advance the flap only to the level of the intersphincteric groove, thus preventing mucosal ectropion creation. A potential defect distal to the intersphincteric groove is usually left open for secondary healing. Rahkmanine reported very good results with this technique [74] (Fig. 12.6).

Y-V Advancement Flap

This procedure, as with the techniques described below, is used for mid- and distal anal stenosis [48, 75–77]. It involves the advancement of the anoderm or the perianal skin into the anal canal. After gentle dilation of the anus, a small- or medium-size Hill-Ferguson retractor is used for the expo-

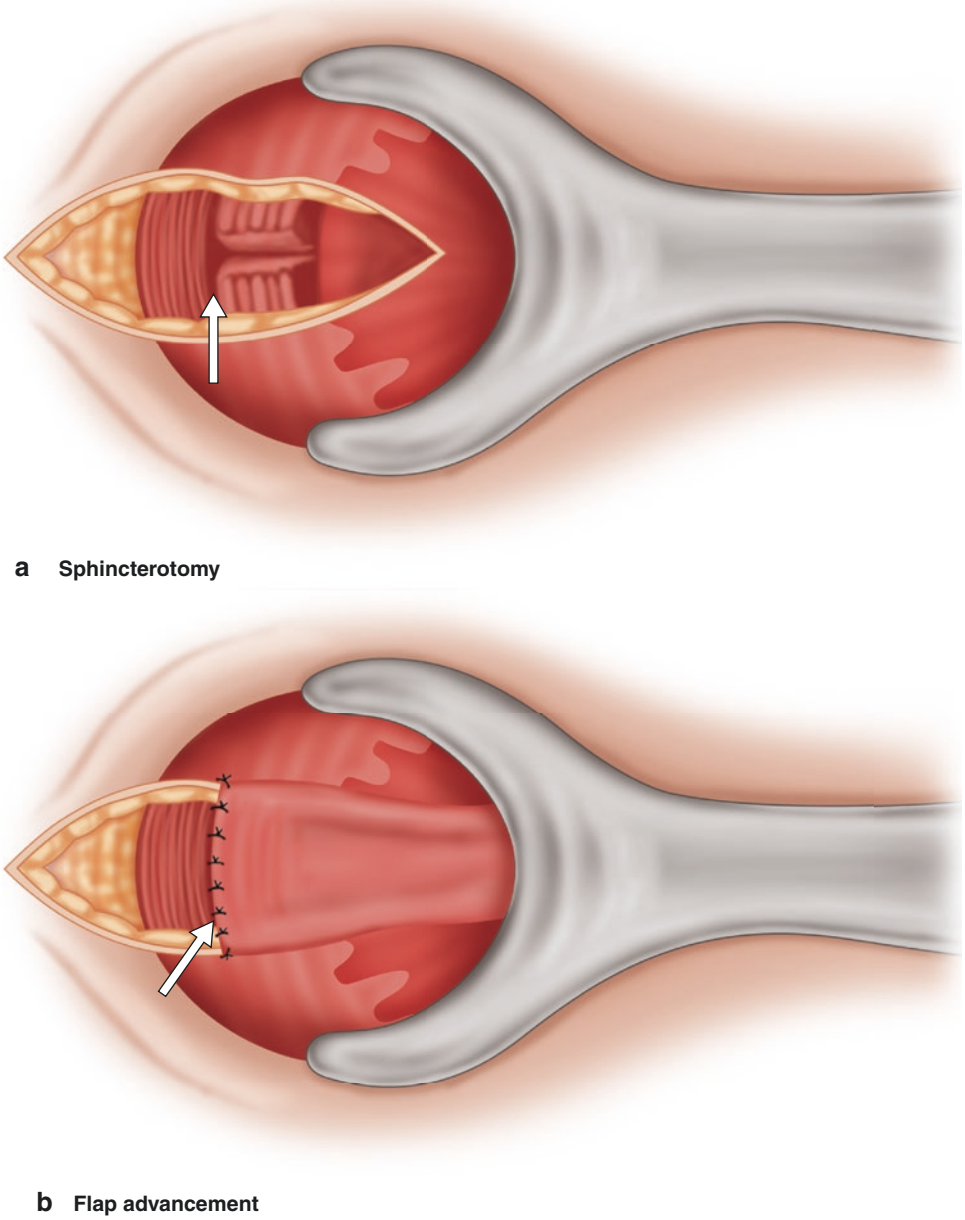

Fig. 12.6 Rectal advancement flap

sure. The scar is longitudinally incised or removed, and concomitant internal sphincterotomy can then be performed. The vertical limb incision of the Y is extended proximally, beyond the stenosed area, into the anal canal. Subsequently, two incisions constituting the oblique limbs of the Y are created, starting at the distal end of the defect and extending into the anal margin, for a total length of at least 5 cm. The created V flap should include the underlying subdermal tissue. In thinner patients, it can also include the subcutaneous layer of the external sphincter muscle in order to provide adequate blood supply and mobility. The flap is then stretched proximally into the anal canal. The tip of the V flap is anchored to the internal sphincter and the anal canal mucosa at the proximal end of the defect. The edges of the flap are sutured to the corresponding edges of the defect. Long-lasting absorbable sutures are used. The V-Y flap can be used to cover no more than 25% of the anal circumference and can be performed bilaterally (similar to most advancement flaps). It should be noted that the tip of the flap is prone to ischemia. Healing rate between 64% and 100% has been reported (Fig. 12.7) [75–78].

V-Y Advancement Flap

This technique involves the creation of a triangular island flap using the skin, anoderm, and subdermal tissue, with the proximal base of the flap directly adjacent to the defect from the scar excision (and potentially the sphincterotomy) [50]. The foundation can also involve the subcutaneous layer of

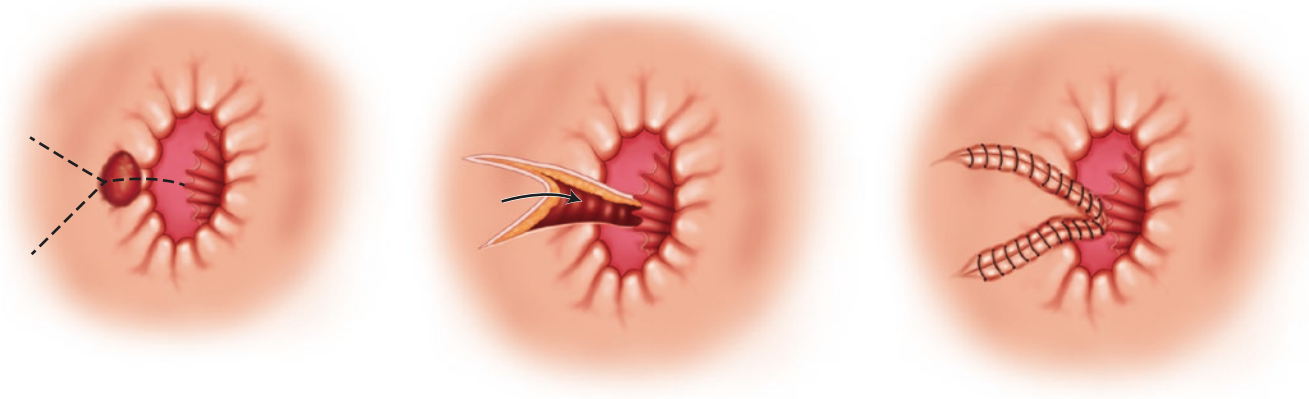

Fig. 12.7 Y-V advancement flap

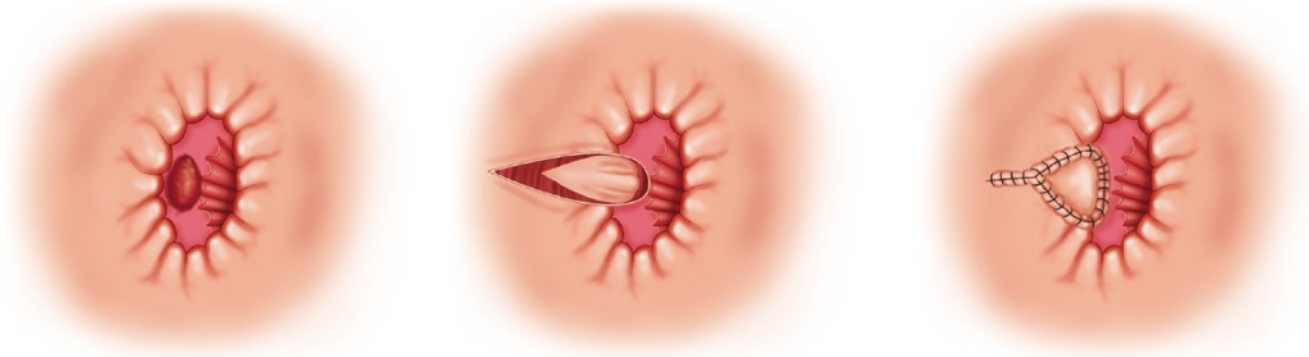

Fig. 12.8 V-Y advancement flap

the external sphincter [79]. The tethering of the flap is only dependent upon its deeper layers, while all edges are free. The flap is then advanced into the resulting defect and sutured circumferentially, while the donor site is closed. This effectively pushes the flap into the anal canal. This technique was initially developed as the treatment for anal ectropion but later became an option in treating anal stenosis (Fig. 12.8) [80].

Diamond (Rhomboid) Flap

This technique, described by Caplin and Kodner, involves advancement of the rhomboid skin and subcutaneous flap into the defect formed by stricturotomy in the distal anal canal [81]. It can also include the fibers of the subcutaneous layer of the external sphincter to increase its thickness and reach. The flap is moved into the defect, while attached by its deeper layers which provide the vascular supply. It is then sutured circumferentially to the surrounding tissues. The donor site defect is closed, effectively pushing the flap into the anal canal. Excellent healing rates after diamond anoplasty have been reported (Fig. 12.9) [76, 78, 81].

House Flap

This technique was first described by Christensen et al. [82]. The house flap anoplasty involves proximal advancement of the perianal skin into the area of the stricturotomy, located distally to the dentate line. The concept is similar to the V-Y flap or diamond flap techniques; however, the formation of a wider flap allows for more effective treatment of the stenosis. In order to accomplish this, the initial longitudinal incision through the stenosed area is supplemented by two transverse incisions of equal length at both ends, centered on the longitudinal incision. This may also involve the internal sphincter. Alternatively, the scar can be excised in the form of a square. Subsequently, a house-shape flap is created using the adjacent skin and subcutaneous tissue. Occasionally this can include the subcutaneous layer of the external sphincter for better vascularity and further reach. The base of the (house) flap equals the length of the transverse incisions, and the height of the house walls equals the length of the defect. The flap is moved into the defect, while only tethered by its deeper layers, which provide the vascular supply. It is then sutured circumferentially to the surrounding tissues while the donor site defect is closed, thus effectively pushing the

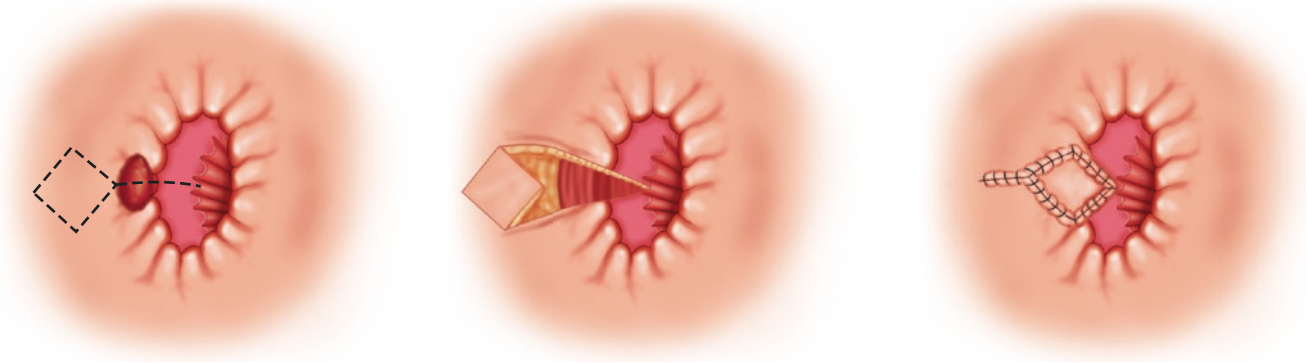

Fig. 12.9 Diamond (rhomboid) flap

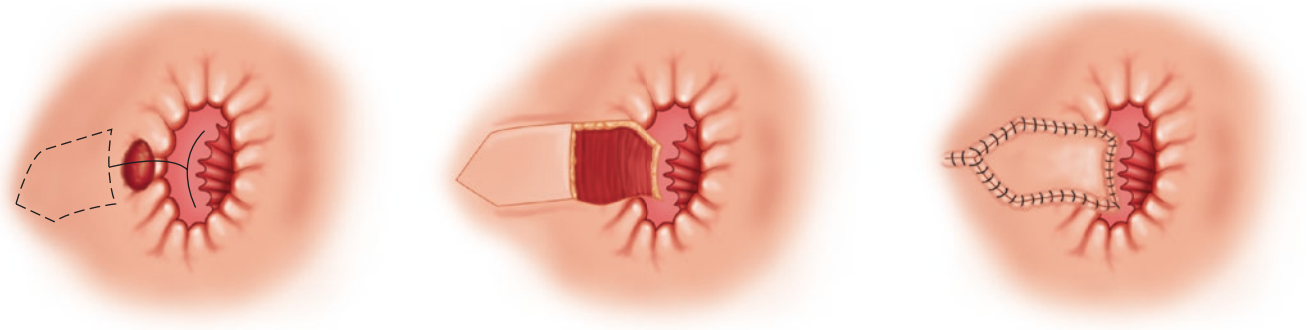

Fig. 12.10 House flap

flap into the anal canal. Clinical improvement or healing of the stenosis was reported in more than 90% of patients (Fig. 12.10) [83–85].

U Flap (Island Flap Anoplasty)

This technique was developed by Pearl et al. and can also be used in the treatment of ectropion as well as distal fistula in ano [86]. The U flap provides a wide-base island flap that can cover a large area of anodermal defect, similar to the previously described techniques. The important difference, however, is that the donor site in this technique is not closed but is left open for secondary healing. Initially, wet to dry gauze application is required to allow the area to granulate. Dry gauze can then be used to allow the wound to epithelialize. Of 25 patients treated with this flaps (20 for anal stenosis and 5 for mucosal ectropion), 16 reported excellent and 7 reported good results [86].

Rotational S Flap

This technique is used most often to cover larger defects resulting from the excision of perianal Paget's or Bowen's disease. The rotational S flap (S-plasty) can also be used to effectively move a significant amount of perianal skin into the anus in order to cover a large defect after circumferential excision of the stenotic scar in the distal anal canal. In this technique, two full-thickness, well-vascularized cutaneous flaps with an appropriate amount of underlying subcutaneous tissue (sometimes as fascio-cutaneous flaps) are created by the S-shape incision and centered around the anal opening. The flaps are subsequently advanced, rotated into the distal anus along the incision, and sutured to the non-strictured rectal mucosa, as well as to the corresponding edges of the defect (Fig. 12.11) [87, 88].

Technical Aspects

Reconstructive flap procedures are performed after mechanical bowel preparation. A complete bowel preparation may be difficult to accomplish in patients with anal stenosis. Frequently, a prolonged 1–2-day bowel preparation is required in addition to a roughage-free diet for several days prior to the procedure. If the patient is found to have a large amount of liquid stool in the colon immediately before the procedure, an ad hoc colonoscopic washout and aspiration can be performed.

The mechanical bowel preparation can be supplemented with oral antibiotic administration. This is in line with current recommendations for proctectomy cases, since the anas-

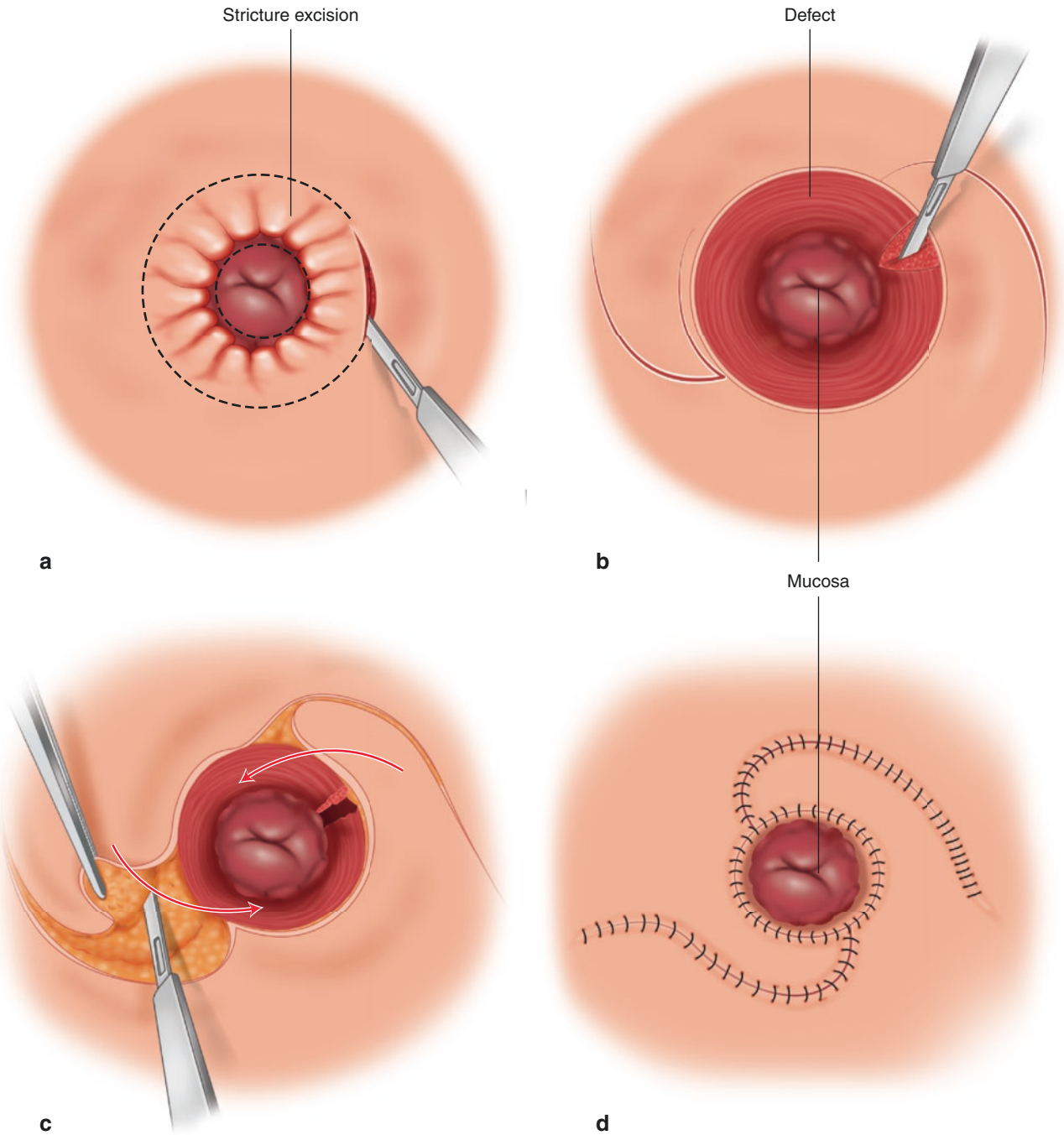

Fig. 12.11 Rotational flap (**a**) scar excision, (**b**) internal sphincterotomy, (**c**) flap creation, (**d**) flap fixation in place

tomosis (suture line) is created in the flap cases. Perioperative antibiotics are given. In cases with large amount of contamination, a low-concentration chlorhexidine solution jet irrigation can be used (Irrisept®). The choice of post procedure antibiotics (IV, oral, or none) is dependent upon the complexity of the case, bowel preparation, and surgeon preference.

Most of the flap procedures are performed with the patient in the prone jackknife position, with the exception of posterior rectal advancement flaps. The buttocks are initially taped apart and the Lone-Star retractor can be useful. Low wattage cautery and sharp knife dissection are used.

In the current era of effective hemostasis, hemostatic epinephrine solution injection is primarily reserved for cases of stubborn bleeding from the scar tissue. Alternatively, epinephrine-soaked gauze application can be utilized. Additionally, injection of epinephrine into the flap can lead to ischemia of its terminal parts, whereas injection into the dissected tissues can disturb the surgical planes or even decrease the effective space in an already tight anal canal.

Excision of the scar requires precision and should avoid thermal injury to the underlying healthy tissues. Frequently a thin layer of the scar can be infiltrated with saline or epinephrine solution and removed sharply.

It is important that the minimal amount of absorbable suture material is used, typically 2-0 Vicryl for strength and 3-0 Vicryl or Chromic for tissue approximation. Occasionally, a few non-absorbable strength sutures can be placed. Care should be taken to avoid dead space formation underneath the flaps.

In selected cases, the flap reconstruction can be protected using a diverting ostomy, most often created with laparoscopic assistance at the end of the procedure. Tenuous repairs with poor bowel preparation and negative predictive healing factors can be the determinants for prophylactic diversion.

Flap Aftercare

The majority of flap procedures are performed on an outpatient basis. Patients are instructed to not sit directly on the repair site. Showering or rinsing with water is recommended, particularly when soiling with stool occurs. The wounds should then be covered with dry dressings to prevent tissue maceration. Wet to dry dressings are suggested for the open wounds.

Close follow-up is necessary to observe for any flap ischemia, suture line breakdown, granulomas, or wound dehiscence. Localized dehiscence is not uncommon but can be effectively monitored and treated in the office setting and by thorough wound care. Not healed wound dehiscence can lead to chronic fissures, especially when associated with flap ischemia. Patients should be seen in the office within 5 days from surgery in order to check on wound healing and to reinforce the aftercare instructions.

Postoperative bowel rest can be beneficial and is frequently used by surgeons for complex and repeat repairs. Pharmacological bowel rest with antimotility and narcotic agents can be used; however, the consequences of subsequent stool buildup, fecal impaction, and its effect on the healing wound should be carefully weighed. Today, an available option is total or peripheral parenteral nutrition (TPN or PPN), which can often be administered in the home setting via the PICC line or Medline®, respectively. This route of nutrition can be effectively combined with a liquid diet high in fat and protein to provide sufficient nutrition during the first 1–2 weeks of healing. The cost of this approach is more favorable compared to the option of protective diverting ostomy (author's observation).

Alternatively, patients can be restarted on a soft high-fiber diet with an appropriate amount of water to bulk up the stools and prevent constipation (similar to the bowel regimen for the fissure patients). Local antibiotic ointments (e.g., triple antibiotic ointment) can be used for topical application.

Postoperative pain control can be provided by intraoperative injection of liposomal bupivacaine (e.g., Exparel®) as well as oral analgesia (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, Lyrica®). Stool softeners are recommended during opioid analgesia. Diarrhea should be prevented, since liquid stool appears to be more detrimental to flap repairs than bulky or firm stool.

A successful flap procedure rarely requires further dilation maneuvers. However, if recurrent stricture formation is identified, dilations should be performed.

Choosing the Right Procedure

The ideal procedure should be simple, effective, and free from serious morbidity and should restore the anal function for a good long-term outcome. Unfortunately, there is no one-fits-all solution. The choice of procedure should also depend on the surgeon's comfort level. The involvement of the scar tissue needs to be determined. Repair of the stenosed anoderm will fail if the concomitant internal sphincter fibrosis is not addressed. Conversely, the lateral internal sphincterotomy will not be successful if the problem of the concomitant anodermal stenosis is not corrected [63].

Not every stenosis needs correction. Patients with asymptomatic stenosis found during digital rectal exam should only be instructed about dietary modifications and the potential need for dilations should symptoms occur. The possibility of underlying malignancy must also be excluded.

The simplest form of anoplasty involves longitudinal incision of the involved tissue with transverse closure of the resulting diamond-shape defect in a Heineke-Mikulicz fashion. This approach can be utilized for stenosis at different levels in the anal canal and performed more than once around the circumference. It is reserved for small areas of stenosis, has a high chance for restenosis, and may require additional dilations [69]. For proximal and mid-anal stenosis, rectal advancement flaps should be considered.

Mid and distal anastomosis can be successfully treated with Y-V flaps; however, the tip of the flap can be at risk for ischemia if significant tension is applied. If the Y-V flap cannot reach into the desired location without excessive tension; it can be converted into the diamond island flap [69]. Insufficient release of the stenosis with one diamond flap can be addressed by a repeated procedure on the contralateral site.

For scenarios that require advancement of a larger amount of tissue in both transverse and longitudinal aspects, the V-Y, house, and U flap (island flap anoplasty) are more appropriate. They can also be performed bilaterally. Circumferential excision of the distal anoderm is best addressed by the rotational S-plasty or larger skin flaps, based on the named vascular pedicles [79, 87–89].

It is extremely difficult to comparatively interpret the results of many case series involving various reconstructive procedures. The only randomized study by Farid compared the house flap, rhomboid flap, and Y-V anoplasty in anal stenosis patients. The average operative times were the longest in the house flap group (62 min) and the shortest in the Y-V anoplasty (35 min). The anal caliber at 1 year was the largest in the house flap group, together with the highest quality of life score and a significant improvement of symptoms ($p < 0.05$) [83]. Helpful summaries of the flap procedures with their respected outcomes have been presented by Brisinda and Shawki [48, 54].

Few complications have been reported with most of these techniques. They can include infection, flap failure, recurrence of the stenosis, fecal incontinence, and impaction [54]. In cases where no satisfactory results can be obtained using the abovementioned procedures, a diverting colostomy remains the last resort option.

Anal Stenosis in Crohn's Disease

Anal stenosis in Crohn's disease is common and does not frequently manifest itself clinically due to the liquid nature of stools in this patient population. The stricturing, fistulizing, and fissuring nature of the disease, with subsequent healing attempts, can lead to the possibility of anal stenosis at any level of the anal canal and frequently involves the anorectal junction. Poor wound healing, constant inflammation, and scar tissue formation pose a significant challenge for the possibility of surgical correction.

In a study of 224 patients with anorectal complications of Crohn's disease, 65 patients presented with anal stenosis, and 4 patients went on to develop anal stenosis during the study [67]. Most of these patients specifically indicated that anal stenosis was their only complaint, and only a small number of patients from this group required absolutely no surgical intervention. Another 16 patients underwent mechanical dilatation, and 17 patients ultimately underwent proctectomy or diverting stoma within a mean follow-up of 19 months. In another study of 44 patients with anal stenosis secondary to Crohn's disease, 75% underwent mechanical dilatation and 43% eventually required proctectomy [66]. Brochard reported successful healing in Crohn's-related anorectal stricture in 59% over the course of 8.9 years [90].

These results highlight the significant risk of loss of bowel continence in patients with Crohn's disease and anal stenosis. Some authors have suggested that manual anal dilatation may result in further scarring and progressive stenosis or incontinence and should thus be avoided in patients with Crohn's disease [51, 61, 68].

Prevention

Avoidance of several crucial mistakes during hemorrhoidectomy, which is the procedure responsible for 90% of all stenosis cases, should decrease the chance of this complication occurring. In particular, overzealous removal of all abnormal hemorrhoidal tissue should be avoided, and the mucocutaneous bridges of viable tissue should be preserved (>1 cm strips). Some of the remaining abnormal hemorrhoidal tissue can be incorporated into the closure suture line, thus eliminating the need to remove it altogether.

Other devascularization techniques (suture ligation, supplemental rubber band ligation) can also be used to address the remaining engorged hemorrhoidal tissue. Three-quadrant hemorrhoidectomy can often be replaced by two-quadrant excision, with the addition of limited resection or rubber banding of the third remaining hemorrhoidal pedicle. Often, the remaining smallest third pedicle is so devascularized after the two other columns are removed that no resection is needed. Techniques of vascular plexus resection with preservation of the anoderm or hemorrhoidopexy can also be utilized.

Finally, treatment of acute grade IV hemorrhoidal disease should be done with caution, since the majority of the anoderm is abnormally swollen at the time of the resection and will return to normal after the acute process is resolved. Injection of a local anesthetic before the resection of the hemorrhoid or a skin tag artificially "inflates" the tissues. In the end, this can result in excessive resection. In many cases, the rectal mucosa can be anchored to the internal sphincter at the level of the dentate line, or even more distally, thereby avoiding the need to close each wound in the vertical fashion. Similarly, some of the remaining anoderm of the anal verge can be anchored into the sphincter in order to prevent its outward retraction.

Resection of the hemorrhoidal tissue in the anterior or posterior midline can lead to poor wound healing, fissure formation, and anal stenosis and thus should be avoided if possible. Care should be taken to minimize the thermal injury to the non-resected tissues in the anal canal.

Anal Stenosis, Conclusions

Anal stenosis is a rare but serious problem, which every colorectal surgeon will encounter. Prevention of this complication is crucial among any surgeon who is addressing the anorectal pathology. Appropriately performed hemorrhoidectomy should minimize the risk of anal stenosis. Conservative management is reserved for mild stenosis cases. Several surgical options for moderate and severe stenosis include sphincterotomy, stricturotomy or stricturectomy, and appropriate flap anoplasty.

References

1. Keck JO, Staniunas RJ, Coller JA, Barrett RC, Oster ME. Computer-generated profiles of the anal canal in patients with anal fissure. Dis Colon Rectum. 1995;38(1):72–9.
2. Hananel N, Gordon PH. Re-examination of clinical manifestations and response to therapy of fissure-in-ano. Dis Colon Rectum. 1997;40(2):229–33.
3. Poh A, Tan KY, Seow-Choen F. Innovations in chronic anal fissure treatment: a systematic review. World J Gastrointest Surg. 2010;2(7):231–41.
4. Stewart DB Sr, Gaertner W, Glasgow S, Migaly J, Feingold D, Steele SR. Clinical practice guideline for the management of anal fissures. Dis Colon Rectum. 2017;60(1):7–14.
5. Lund JN. Nitric oxide deficiency in the internal anal sphincter of patients with chronic anal fissure. Int J Colorectal Dis. 2006;21(7):673–5.
6. Schouten WR, Briel JW, Auwerda JJ. Relationship between anal pressure and anodermal blood flow. The vascular pathogenesis of anal fissures. Dis Colon Rectum. 1994;37(7):664–9.
7. Klosterhalfen B, Vogel P, Rixen H, Mittermayer C. Topography of the inferior rectal artery: a possible cause of chronic, primary anal fissure. Dis Colon Rectum. 1989;32(1):43–52.
8. Lund JN, Binch C, McGrath J, Sparrow RA, Scholefield JH. Topographical distribution of blood supply to the anal canal. Br J Surg. 1999;86(4):496–8.
9. Corby H, Donnelly VS, O'Herlihy C, O'Connell PR. Anal canal pressures are low in women with postpartum anal fissure. Br J Surg. 1997;84(1):86–8.
10. Nelson R. A systematic review of medical therapy for anal fissure. Dis Colon Rectum. 2004;47(4):422–31.
11. Jensen SL. Maintenance therapy with unprocessed bran in the prevention of acute anal fissure recurrence. J R Soc Med. 1987;80(5):296–8.
12. Sanei B, Mahmoodieh M, Masoudpour H. Comparison of topical glyceryl trinitrate with diltiazem ointment for the treatment of chronic anal fissure: a randomized clinical trial. Acta Chir Belg. 2009;109(6):727–30.
13. Antropoli C, Perrotti P, Rubino M, Martino A, De Stefano G, Migliore G, et al. Nifedipine for local use in conservative treatment of anal fissures: preliminary results of a multicenter study. Dis Colon Rectum. 1999;42(8):1011–5.
14. Samim M, Twigt B, Stoker L, Pronk A. Topical diltiazem cream versus botulinum toxin a for the treatment of chronic anal fissure: a double-blind randomized clinical trial. Ann Surg. 2012;255(1):18–22.
15. Brisinda G, Cadeddu F, Brandara F, Marniga G, Vanella S, Nigro C, et al. Botulinum toxin for recurrent anal fissure following lateral internal sphincterotomy. Br J Surg. 2008;95(6):774–8.
16. Berkel AE, Rosman C, Koop R, van Duijvendijk P, van der Palen J, Klaase JM. Isosorbide dinitrate ointment vs botulinum toxin A (Dysport) as the primary treatment for chronic anal fissure: a randomized multicentre study. Colorectal Dis. 2014;16(10):O360–6.
17. Chen HL, Woo XB, Wang HS, Lin YJ, Luo HX, Chen YH, et al. Botulinum toxin injection versus lateral internal sphincterotomy for chronic anal fissure: a meta-analysis of randomized control trials. Tech Coloproctol. 2014;18(8):693–8.
18. Nelson RL, Thomas K, Morgan J, Jones A. Non surgical therapy for anal fissure. Cochrane Database Syst Rev. 2012;(2):CD003431.
19. Nelson RL, Chattopadhyay A, Brooks W, Platt I, Paavana T, Earl S. Operative procedures for fissure in ano. Cochrane Database Syst Rev. 2011;(11):CD002199.
20. Renzi A, Izzo D, Di Sarno G, Talento P, Torelli F, Izzo G, et al. Clinical, manometric, and ultrasonographic results of pneumatic balloon dilatation vs. lateral internal sphincterotomy for chronic anal fissure: a prospective, randomized, controlled trial. Dis Colon Rectum. 2008;51(1):121–7.
21. Arroyo A, Perez F, Serrano P, Candela F, Lacueva J, Calpena R. Surgical versus chemical (botulinum toxin) sphincterotomy for chronic anal fissure: long-term results of a prospective randomized clinical and manometric study. Am J Surg. 2005;189(4):429–34.
22. Brown CJ, Dubreuil D, Santoro L, Liu M, O'Connor BI, McLeod RS. Lateral internal sphincterotomy is superior to topical nitroglycerin for healing chronic anal fissure and does not compromise long-term fecal continence: six-year follow-up of a multicenter, randomized, controlled trial. Dis Colon Rectum. 2007;50(4):442–8.
23. Davies I, Dafydd L, Davies L, Beynon J. Long term outcomes after lateral anal sphincterotomy for anal fissure: a retrospective cohort study. Surg Today. 2014;44(6):1032–9.
24. de Rosa M, Cestaro G, Vitiello C, Massa S, Gentile M. Conservative versus surgical treatment for chronic anal idiopathic fissure: a prospective randomized trial. Updates Surg. 2013;65(3):197–200.
25. Gandomkar H, Zeinoddini A, Heidari R, Amoli HA. Partial lateral internal sphincterotomy versus combined botulinum toxin A injection and topical diltiazem in the treatment of chronic anal fissure: a randomized clinical trial. Dis Colon Rectum. 2015;58(2):228–34.
26. Iswariah H, Stephens J, Rieger N, Rodda D, Hewett P. Randomized prospective controlled trial of lateral internal sphincterotomy versus injection of botulinum toxin for the treatment of idiopathic fissure in ano. ANZ J Surg. 2005;75(7):553–5.
27. Katsinelos P, Papaziogas B, Koutelidakis I, Paroutoglou G, Dimiropoulos S, Souparis A, et al. Topical 0.5% nifedipine vs. lateral internal sphincterotomy for the treatment of chronic anal fissure: long-term follow-up. Int J Colorectal Dis. 2006;21(2):179–83.
28. Mentes BB, Irkorucu O, Akin M, Leventoglu S, Tatlicioglu E. Comparison of botulinum toxin injection and lateral internal sphincterotomy for the treatment of chronic anal fissure. Dis Colon Rectum. 2003;46(2):232–7.
29. Nasr M, Ezzat H, Elsebae M. Botulinum toxin injection versus lateral internal sphincterotomy in the treatment of chronic anal fissure: a randomized controlled trial. World J Surg. 2010;34(11):2730–4.
30. Richard CS, Gregoire R, Plewes EA, Silverman R, Burul C, Buie D, et al. Internal sphincterotomy is superior to topical nitroglycerin in the treatment of chronic anal fissure: results of a randomized, controlled trial by the Canadian Colorectal Surgical Trials Group. Dis Colon Rectum. 2000;43(8):1048–57; discussion 57–8.
31. Sileri P, Stolfi VM, Franceschilli L, Grande M, Di Giorgio A, D'Ugo S, et al. Conservative and surgical treatment of chronic anal fissure: prospective longer term results. J Gastrointest Surg. 2010;14(5):773–80.
32. Valizadeh N, Jalaly NY, Hassanzadeh M, Kamani F, Dadvar Z, Azizi S, et al. Botulinum toxin injection versus lateral internal sphincterotomy for the treatment of chronic anal fissure: randomized prospective controlled trial. Langenbecks Arch Surg. 2012;397(7):1093–8.
33. Garcia-Granero E, Sanahuja A, Garcia-Botello SA, Faiz O, Esclapez P, Espi A, et al. The ideal lateral internal sphincterotomy: clinical and endosonographic evaluation following open and closed internal anal sphincterotomy. Colorectal Dis. 2009;11(5):502–7.
34. Littlejohn DR, Newstead GL. Tailored lateral sphincterotomy for anal fissure. Dis Colon Rectum. 1997;40(12):1439–42.
35. Ho KS, Ho YH. Randomized clinical trial comparing oral nifedipine with lateral anal sphincterotomy and tailored sphincterotomy in the treatment of chronic anal fissure. Br J Surg. 2005;92(4):403–8.
36. Mentes BB, Ege B, Leventoglu S, Oguz M, Karadag A. Extent of lateral internal sphincterotomy: up to the dentate line or up to the fissure apex? Dis Colon Rectum. 2005;48(2):365–70.
37. Liang J, Church JM. Lateral internal sphincterotomy for surgically recurrent chronic anal fissure. Am J Surg. 2015;210(4):715–9.
38. Giordano P, Gravante G, Grondona P, Ruggiero B, Porrett T, Lunniss PJ. Simple cutaneous advancement flap anoplasty for

resistant chronic anal fissure: a prospective study. World J Surg. 2009;33(5):1058–63.
39. Kenefick NJ, Gee AS, Durdey P. Treatment of resistant anal fissure with advancement anoplasty. Colorectal Dis. 2002;4(6):463–6.
40. Magdy A, El Nakeeb A, El Fouda Y, Youssef M, Farid M. Comparative study of conventional lateral internal sphincterotomy, V-Y anoplasty, and tailored lateral internal sphincterotomy with V-Y anoplasty in the treatment of chronic anal fissure. J Gastrointest Surg. 2012;16(10):1955–62.
41. Pelta AE, Davis KG, Armstrong DN. Subcutaneous fissurotomy: a novel procedure for chronic fissure-in-ano. A review of 109 cases. Dis Colon Rectum. 2007;50(10):1662–7.
42. Mousavi SR, Sharifi M, Mehdikhah Z. A comparison between the results of fissurectomy and lateral internal sphincterotomy in the surgical management of chronic anal fissure. J Gastrointest Surg. 2009;13(7):1279–82.
43. Engel AF, Eijsbouts QA, Balk AG. Fissurectomy and isosorbide dinitrate for chronic fissure in ano not responding to conservative treatment. Br J Surg. 2002;89(1):79–83.
44. Lindsey I, Cunningham C, Jones OM, Francis C, Mortensen NJ. Fissurectomy-botulinum toxin: a novel sphincter-sparing procedure for medically resistant chronic anal fissure. Dis Colon Rectum. 2004;47(11):1947–52.
45. Ouraghi A, Nieuviarts S, Mougenel JL, Allez M, Barthet M, Carbonnel F, et al. Infliximab therapy for Crohn's disease anoperineal lesions. Gastroenterol Clin Biol. 2001;25(11):949–56.
46. Sweeney JL, Ritchie JK, Nicholls RJ. Anal fissure in Crohn's disease. Br J Surg. 1988;75(1):56–7.
47. Viamonte M, Dailey TH, Gottesman L. Ulcerative disease of the anorectum in the HIV+ patient. Dis Colon Rectum. 1993;36(9):801–5.
48. Shawki S, Costedio M. Anal fissure and stenosis. Gastroenterol Clin North Am. 2013;42(4):729–58.
49. Liberman H, Thorson AG. How I do it. Anal stenosis. Am J Surg. 2000;179(4):325–9.
50. Milsom JW, Mazier WP. Classification and management of postsurgical anal stenosis. Surg Gynecol Obstet. 1986;163(1):60–4.
51. Khubchandani IT. Anal stenosis. Surg Clin North Am. 1994;74(6):1353–60.
52. Maria G, Alfonsi G, Nigro C, Brisinda G. Whitehead's hemorrhoidectomy. A useful surgical procedure in selected cases. Tech Coloproctol. 2001;5(2):93–6.
53. Bonello JC. Who's afraid of the dentate line? The Whitehead hemorrhoidectomy. Am J Surg. 1988;156(3 Pt 1):182–6.
54. Brisinda G, Vanella S, Cadeddu F, Marniga G, Mazzeo P, Brandara F, et al. Surgical treatment of anal stenosis. World J Gastroenterol. 2009;15(16):1921–8.
55. Lehmann JP, Johansson HO, Graf W. Long-term functional results after excisional haemorrhoidectomy. Colorectal Dis. 2020;22:824–30.
56. Sagar PM, Pemberton JH. Intraoperative, postoperative and reoperative problems with ileoanal pouches. Br J Surg. 2012;99(4):454–68.
57. Kumar A, Daga R, Vijayaragavan P, Prakash A, Singh RK, Behari A, et al. Anterior resection for rectal carcinoma - risk factors for anastomotic leaks and strictures. World J Gastroenterol. 2011;17(11):1475–9.
58. Couto RA, Zequeira JJ, Vicente HL. Recalcitrant coloanal strictures in children managed by transanal circular stapled reanastomosis. J Pediatr Surg. 2014;49(11):1686–8.
59. Halleran DR, Sanchez AV, Rentea RM, Ahmad H, Weaver L, Reck C, et al. Assessment of the Heineke-Mikulicz anoplasty for skin level postoperative anal strictures and congenital anal stenosis. J Pediatr Surg. 2019;54(1):118–22.
60. Ravo B, Amato A, Bianco V, Boccasanta P, Bottini C, Carriero A, et al. Complications after stapled hemorrhoidectomy: can they be prevented? Tech Coloproctol. 2002;6(2):83–8.
61. Bouchard D, Abramowitz L, Bouguen G, Brochard C, Dabadie A, de Parades V, et al. Anoperineal lesions in Crohn's disease: French recommendations for clinical practice. Tech Coloproctol. 2017;21(9):683–91.
62. Galandiuk S, Kimberling J, Al-Mishlab TG, Stromberg AJ. Perianal Crohn disease: predictors of need for permanent diversion. Ann Surg. 2005;241(5):796–801; discussion -2.
63. Katdare MV, Ricciardi R. Anal stenosis. Surg Clin North Am. 2010;90(1):137–45, Table of Contents.
64. Crapp AR, Alexander-Williams J. Fissure-in-ano and anal stenosis. Part I: conservative management. Clin Gastroenterol. 1975;4(3):619–28.
65. Jenetzky E, Reckin S, Schmiedeke E, Schmidt D, Schwarzer N, Grasshoff-Derr S, et al. Practice of dilatation after surgical correction in anorectal malformations. Pediatr Surg Int. 2012;28(11):1095–9.
66. Linares L, Moreira LF, Andrews H, Allan RN, Alexander-Williams J, Keighley MR. Natural history and treatment of anorectal strictures complicating Crohn's disease. Br J Surg. 1988;75(7):653–5.
67. Michelassi F, Melis M, Rubin M, Hurst RD. Surgical treatment of anorectal complications in Crohn's disease. Surgery. 2000;128(4):597–603.
68. MacDonald A, Smith A, McNeill AD, Finlay IG. Manual dilatation of the anus. Br J Surg. 1992;79(12):1381–2.
69. Duieb Z, Appu S, Hung K, Nguyen H. Anal stenosis: use of an algorithm to provide a tension-free anoplasty. ANZ J Surg. 2010;80(5):337–40.
70. Khubchandani IT. Mucosal advancement anoplasty. Dis Colon Rectum. 1985;28(3):194–6.
71. Nickell WB, Woodward ER. Advancement flaps for treatment of anal stricture. Arch Surg. 1972;104(2):223–4.
72. Casadesus D, Villasana LE, Diaz H, Chavez M, Sanchez IM, Martinez PP, et al. Treatment of anal stenosis: a 5-year review. ANZ J Surg. 2007;77(7):557–9.
73. Martin EG. The plastic use of skin in simple anal stricture, reconstruction of anal lining, pilonidal disease. Tr Am Proct Soc. 1944;44:195–200.
74. Rakhmanine M, Rosen L, Khubchandani I, Stasik J, Riether RD. Lateral mucosal advancement anoplasty for anal stricture. Br J Surg. 2002;89(11):1423–4.
75. Aitola PT, Hiltunen KM, Matikainen MJ. Y-V anoplasty combined with internal sphincterotomy for stenosis of the anal canal. Eur J Surg. 1997;163(11):839–42.
76. Angelchik PD, Harms BA, Starling JR. Repair of anal stricture and mucosal ectropion with Y-V or pedicle flap anoplasty. Am J Surg. 1993;166(1):55–9.
77. Gingold BS, Arvanitis M. Y-V anoplasty for treatment of anal stricture. Surg Gynecol Obstet. 1986;162(3):241–2.
78. Maria G, Brisinda G, Civello IM. Anoplasty for the treatment of anal stenosis. Am J Surg. 1998;175(2):158–60.
79. Borsuk DJ, Melich G, Sugrue J, Calata J, Seitz IA, Park JJ, et al. Wide local excision of perianal Paget's disease with gluteal flap reconstruction: an interdisciplinary approach. J Vis Surg. 2016;2:159.
80. Rosen L. Anoplasty. Surg Clin North Am. 1988;68(6):1441–6.
81. Caplin DA, Kodner IJ. Repair of anal stricture and mucosal ectropion by simple flap procedures. Dis Colon Rectum. 1986;29(2):92–4.
82. Christensen MA, Pitsch RM Jr, Cali RL, Blatchford GJ, Thorson AG. "House" advancement pedicle flap for anal stenosis. Dis Colon Rectum. 1992;35(2):201–3.
83. Farid M, Youssef M, El Nakeeb A, Fikry A, El Awady S, Morshed M. Comparative study of the house advancement flap, rhomboid flap, and y-v anoplasty in treatment of anal stenosis: a prospective randomized study. Dis Colon Rectum. 2010;53(5):790–7.

84. Sentovich SM, Falk PM, Christensen MA, Thorson AG, Blatchford GJ, Pitsch RM. Operative results of House advancement anoplasty. Br J Surg. 1996;83(9):1242–4.
85. Alver O, Ersoy YE, Aydemir I, Erguney S, Teksoz S, Apaydin B, et al. Use of "house" advancement flap in anorectal diseases. World J Surg. 2008;32(10):2281–6.
86. Pearl RK, Hooks VH 3rd, Abcarian H, Orsay CP, Nelson RL. Island flap anoplasty for the treatment of anal stricture and mucosal ectropion. Dis Colon Rectum. 1990;33(7):581–3.
87. Handaya Y, Sunardi M. Bilateral rotational S flap technique for preventing restenosis in patients with severe circular anal stenosis: a review of 2 cases. Ann Coloproctol. 2019;35:221–4.
88. Koscinski T. Treatment of iatrogenic anal stricture. Pol Przegl Chir. 2007;79(4):280–5.
89. Orkin BA. Perineal reconstruction with local flaps: technique and results. Tech Coloproctol. 2013;17(6):663–70.
90. Brochard C, Siproudhis L, Wallenhorst T, Cuen D, d'Halluin PN, Garros A, et al. Anorectal stricture in 102 patients with Crohn's disease: natural history in the era of biologics. Aliment Pharmacol Ther. 2014;40(7):796–803.

Cryptoglandular Abscess and Fistula

13

Eric K. Johnson and Greta Bernier

Key Concepts

- Anorectal abscess should be treated with surgical drainage, not antibiotic therapy.
- At least one-third of cryptoglandular abscesses will progress to fistula.
- Anal fistula in the typical patient should be evaluated with examination under anesthesia. Subsequent management will be dictated by anatomic findings in the operating room.
- Priorities of management are control of sepsis, maintenance of continence, and cure without recurrence, generally in that order.
- While there are many new and emerging methods of treatment, the surgeon should be critical of the published literature and base their informed consent discussion on their observed results over time. Most studies would indicate that at least 12 months of follow-up is required to determine success.

Introduction

Anorectal abscess and fistula-in-ano are commonly encountered in a colorectal surgery clinic. It is imperative for the surgeon to fully understand the pathophysiology of this disease process, the anatomy of the anal canal and pelvis with respect to cryptoglandular abscess and fistula, and how to appropriately individualize care for each patient.

As stated by Dr. Herand Abcarian, "It is difficult if not impossible to accurately assess the incidence of anorectal abscesses because they often drain spontaneously or are incised and drained in a physician's office, emergency room or surgicenter" [1]. Similarly, our estimates do not account for those treated with antibiotics alone in the primary care setting. This is further complicated by the misdiagnosis of many common anorectal pathologies as "hemorrhoids," both by patients and referring physicians.

The incidence of anorectal abscess is documented as 8.6–20 patients per 100,000 people, with males being more affected than females at an incidence of 2.4–3:1 and presentation at a mean age of 40 years [2–4]. The most common etiology is cryptoglandular, accounting for 90% of anorectal abscesses, although both abscess and fistula can arise from a multitude of etiologies, including Crohn's disease, obstetric injury, fissure, and infectious etiologies such as tuberculosis, sarcoid, and HIV. These etiologies are outside the scope of this chapter but will be discussed in further detail in subsequent chapters.

Cryptoglandular Pathophysiology

Cryptoglandular abscess and fistula-in-ano arise from glands at the dentate line, nestled between the anal papilla and the columns of Morgagni. These glands extend into the submucosal space, internal sphincter, intersphincteric space, and external sphincter to varying degrees. When bacteria and debris become inspissated in these glands, an infection develops, and this will track along the course of the gland or follow to the path of least resistance from its origin (Fig. 13.1) [5, 6]. This theory was described and popularized by Eisenhammer in the 1950s [5].

Cryptoglandular Abscess

As described above, anorectal abscesses occur in multiple spaces in the pelvis and are so classified by these locations: perianal, ischiorectal, intersphincteric, and supralevator

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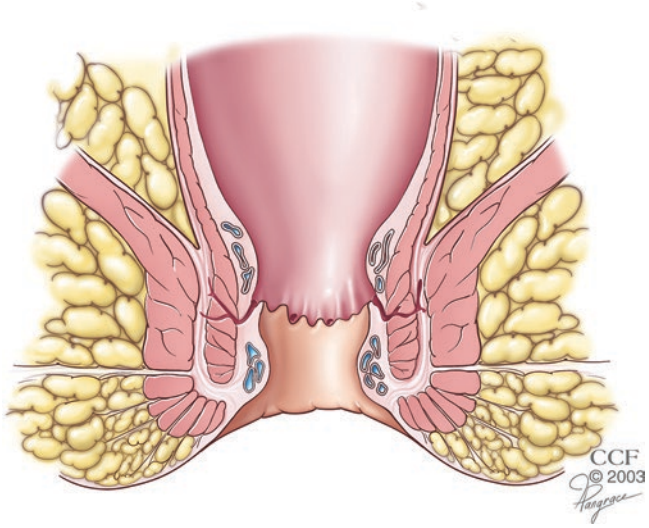

Fig. 13.1 Image depicting the anal canal with surrounding musculature and crypt glands in cross section coursing through the internal anal sphincter. (Reprinted with permission, The Cleveland Clinic Center for Medical Art & Photography © 2009–2020. All Rights Reserved)

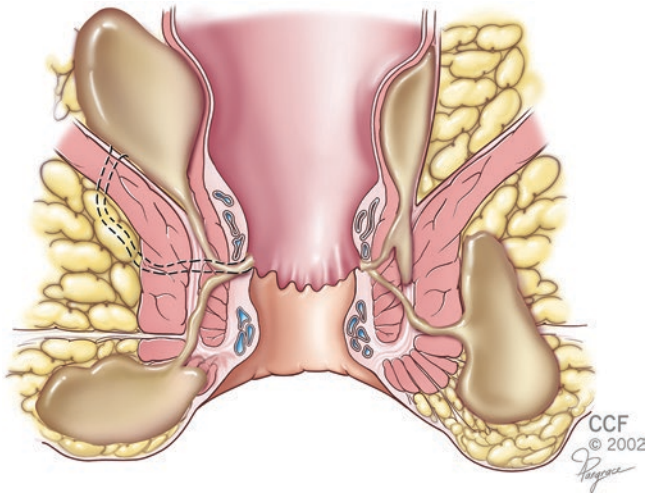

Fig. 13.2 Cross-sectional image showing abscess formation in the different potential spaces. (Reprinted with permission, The Cleveland Clinic Center for Medical Art & Photography © 2009–2020. All Rights Reserved)

(Fig. 13.2). Another classification, horseshoe abscess, describes an abscess that courses posteriorly through the deep postanal space to involve the bilateral ischiorectal spaces.

Both perianal abscesses and ischiorectal abscesses typically present with perianal pain, swelling, and fluctuance, with possible spontaneous drainage of purulent fluid. Intersphincteric abscesses typically do not have any external manifestations but rather present as intense anal pain, such that the patient will often not tolerate a digital rectal exam, without any other clear pathology to account for these symptoms such as a fissure, thrombosed hemorrhoid, sexually transmitted infection, or malignancy. Supralevator abscesses may arise from cephalad extension of a cryptoglandular origin but, however, are more commonly associated with an intraabdominal process such as diverticular disease, malignancy, or Crohn's disease. Perianal and ischiorectal abscesses represent the majority of anorectal abscess, 65–80% [7, 8]. Ramanujam et al. further described the incidence of each subtype of anorectal abscess in their evaluation of 1023 patients presenting over a 5.5-year period. In their series, perianal abscesses accounted for 42.7% of anorectal abscesses, ischiorectal for 22.7%, intersphincteric for 21.4%, and supralevator for 7.3%.

Diagnosis

History and physical examination are generally sufficient to diagnose perianal and ischiorectal abscesses. Imaging adjuncts, such as CT scan, MRI, fistulogram, and endoanal ultrasound, are not indicated for the patient with classic uncomplicated presentation, without diagnostic dilemma or comorbidity, and a fluctuant area is appreciated on examination [3, 9]. Imaging may be beneficial in the workup of those with an unclear diagnosis, such as those with isolated intersphincteric abscess or those that have other complicating factors, such as history of malignancy, radiation, Crohn's disease, prior anorectal operations, or trauma, or those with concern for complex abscesses such as horseshoe or supralevator extension. Imaging adjuncts may also be useful in select cases for management of associated fistula-in-ano, as discussed later in this chapter.

Treatment

The primary treatment for anorectal abscess is expeditious incision and drainage. Perianal and ischiorectal abscesses should be drained through the skin overlying the area of fluctuance. If the abscess cavity is large, the incision should be made over the area of the cavity that is closest to the anal verge. With this technique, if the patient develops a resultant fistula-in-ano, the tract will not be unnecessarily long. This consideration is important, as approximately one-third of acute anorectal abscesses persist as a fistula-in-ano [8, 10, 11].

Intersphincteric abscesses and supralevator abscesses require special considerations both for effective drainage and to avoid iatrogenic injury. Intersphincteric abscesses typically require internal drainage at the dentate line via sphincterotomy if there is no external area of fluctuance.

The route of drainage is of particular importance for supralevator abscesses. Those that arise from an intraabdom-

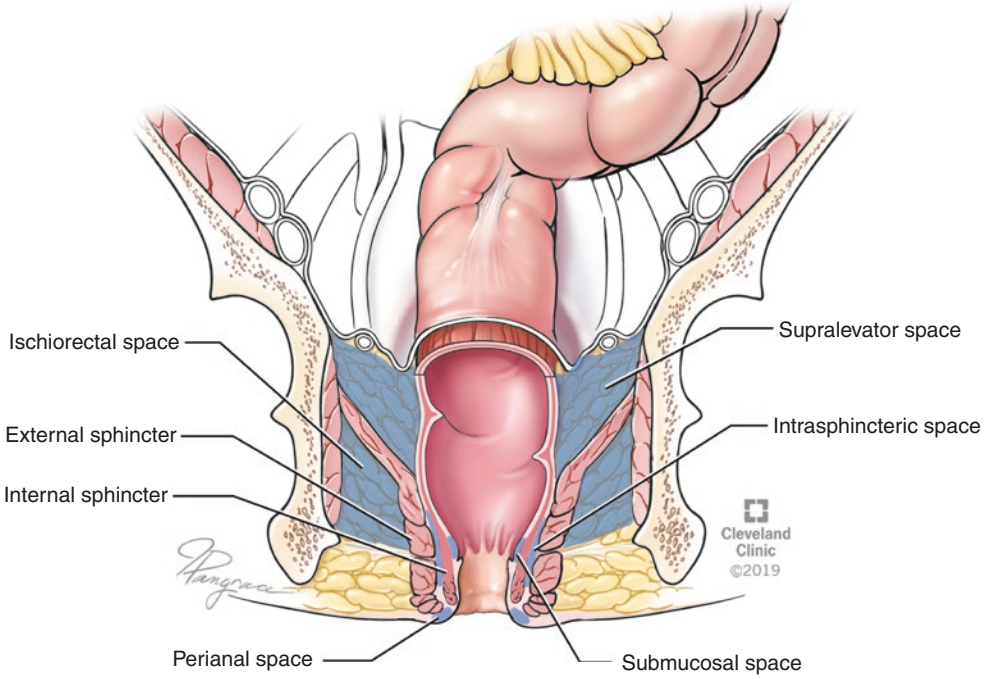

Fig. 13.3 Image showing different potential spaces for abscess formation, with emphasis on appropriate drainage route for supralevator abscess. (Reprinted with permission, The Cleveland Clinic Center for Medical Art & Photography © 2009–2020. All Rights Reserved)

inal source should be drained either transabdominally using interventional radiology assistance or transrectally, while those arising from cephalad extension of a cryptoglandular source via the intersphincteric space should be drained transrectally. Those that arise from a cephalad extension of an ischiorectal abscess should be drained transcutaneously. These principles are important in order to avoid iatrogenic creation of a suprasphincteric fistula (Fig. 13.3).

Another special case is drainage of the horseshoe abscess. As stated previously, these typically arise from extension of an ischiorectal abscess via the deep postanal space. In order to adequately drain these abscesses, there must be both bilateral transcutaneous ischiorectal drainage and posterior drainage via division of the anococcygeal ligament to access the deep postanal space. Other examples of a horseshoe abscess include those arising from a perianal abscess extending through the superficial postanal space, those extending through the anterior perianal space, or a supralevator abscesses coursing through the posterior supralevator space (Fig. 13.4).

Acute Fistula Management

By definition, 100% of anorectal abscesses of cryptoglandular etiology will have a path from the dentate line to the drained abscess cavity. At the time of acute abscess presentation, 30–70% of patients will have an identifiable tract [8, 12–14]; however, this tract is not mature and will only become a fistula tract in ~30–35% of patients. There is also a risk of creating a false passage while attempting to identify a fistula tract in the setting of acute inflammation. If a tract is identified, some advocate for primary fistulotomy at the time of abscess drainage to reduce recurrent abscess or need for second operation were a fistula to develop. And while some have shown a decrease in both abscess recurrence and fistula formation with primary fistulotomy [12], this approach results in occasionally unnecessary sphincter division in patients who would not have ultimately developed a chronic fistula. In addition, inflammation from the concomitant abscess will make it more difficult to discern the degree of muscle involvement, precluding appropriate surgical judgment, thereby potentially increasing the risk of incontinence [12, 15]. Given this controversy and potential risks, it is not generally recommended to definitively manage this tract at the time of abscess drainage.

Incision and drainage in the clinic instead of the operating room is preferred as it expedites the time to control of sepsis. In order to perform this procedure in clinic, the provider must have an adequate setup with anesthetic, instruments, patient positioning, and an amenable patient. In many cases, patients will tolerate in office drainage. This can be facilitated by injecting a wheal of anesthetic at the intended site of drainage, decompressing the cavity through the wheal with a larger needle prior to injecting additional anesthetic, and then completing drainage via a small incision. Complex perianal abscesses, such as those that are deep/nonpalpable, those that are associated with tissue necrosis, and those inpatients who are intolerant of a bedside procedure, are better managed in the operating room.

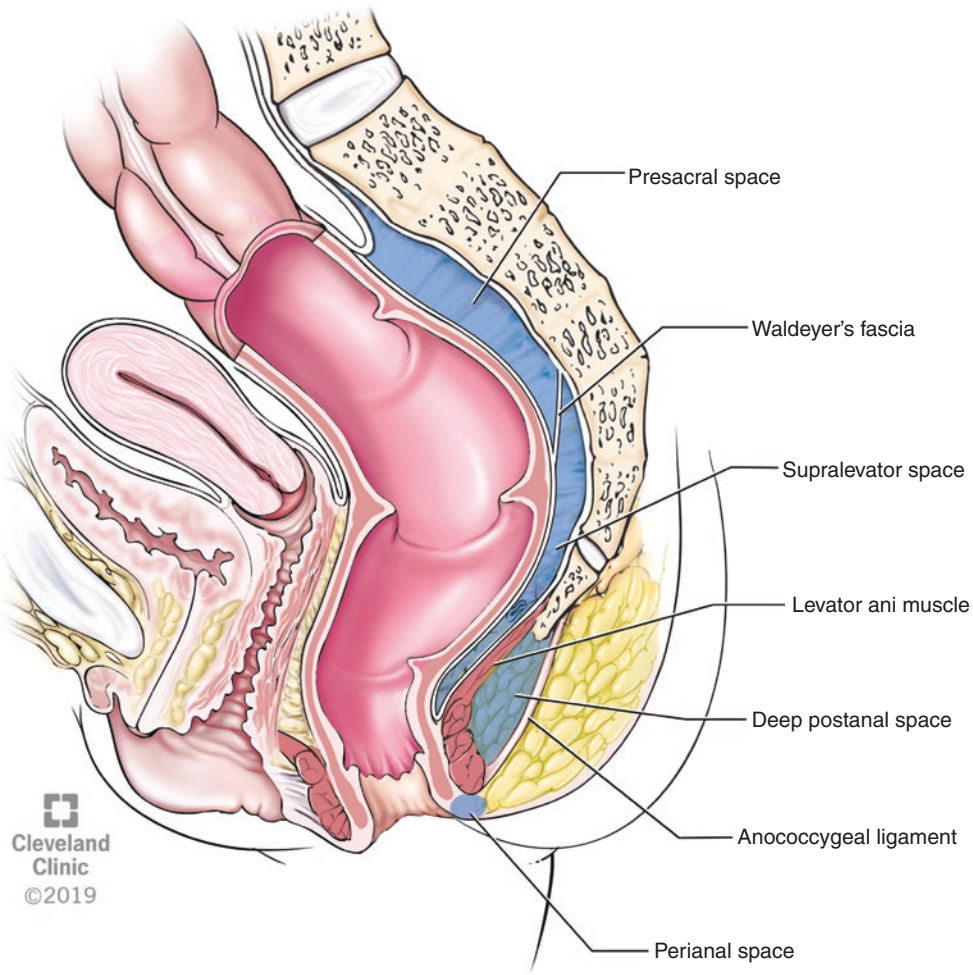

Fig. 13.4 Sagittal image showing potential abscess spaces. (Reprinted with permission, The Cleveland Clinic Center for Medical Art & Photography © 2009–2020. All Rights Reserved)

Post-drainage Care

After transcutaneous drainage, packing the abscess cavity is not recommended as wounds left unpacked are more manageable to care for with less pain and faster healing [16–18]. A catheter, such as a mushroom-tip catheter, may be placed in an abscess cavity to promote drainage and to maintain the external opening. This is of particular help in those with large or deep abscess cavities to ensure adequate drainage of the cavity and to minimize the size of external incision. Warm water soaks (i.e., sitz baths) for 10–15 minutes two to three times per day and external gauze for drainage are all that are required for wound care.

Post-drainage Antibiotics

Traditionally antibiotics were recommended only for those with extensive cellulitis, signs of sepsis, or immunocompromised state [19]. While we lack definitive evidence to direct antibiotic therapy, in general, a broad-spectrum antibiotic that offers gram-negative and anaerobic coverage while providing additional coverage of typical gram-positive skin-associated bacteria is adequate. Typical oral regimens would include augmentin alone, trimethoprim-sulfamethoxazole alone, and a quinolone combined with metronidazole. In a patient with prior history of methicillin-resistant *S. aureus* infection, use of trimethoprim-sulfamethoxazole or clindamycin will often cover a community-acquired form of the infection. This is more controversial in recent years as there is data to suggest post-drainage antibiotic treatment may decrease fistula formation. Ghahramani et al. randomized 307 patients to operative drainage with or without postoperative ciprofloxacin and metronidazole. They found a significant decrease in fistula formation from 30% in the control group to 14.1% in the antibiotic group ($P < 0.001$) [20]. Likewise, Lohsiriwat found a decrease in fistula formation from 48% to 17% in those that received antibiosis vs. those that didn't, respectively [11]. In a subsequent meta-analysis, Mocanu et al. found a 36% decreased rate of fistula formation in those with post-drainage antibiotics than those who received no antibiotics or placebo [21]. These studies are not uniformly reproducible, as there are similar studies which showed no protective effect of antibiotic treat-

ment with fistula formation [10, 22]. Given this inconclusive evidence, guidelines still recommend against routine antibiotics [19].

Without plans for post-drainage antibiotics, it is not necessary to send a bacterial culture, as this data would not be actionable. If antibiotics are planned, then a bacterial culture at the time of drainage may help guide antimicrobial selection, in particular when treating a patient with history of drug-resistant bacteria such as MRSA.

Anal Fistula

Presentation/Symptoms

As previously discussed, anorectal abscess persists as an anal fistula in approximately 30–35% of patients. Interestingly, this rate increases in nondiabetics and those less than age 40, with no significant difference identified based on sex, smoking status, HIV status, or administration of perioperative antibiotics [10, 11]. Patients with fistula-in-ano present to the colorectal surgery clinic with a wide range of complaints, including "hemorrhoids," history of anorectal abscess with spontaneous or surgical drainage, external bump that becomes irritated and bleeds, chronic external drainage, and cyclical perianal pain and swelling that is relieved with expression of fluid. Given the variety of complaints in patients with fistula-in-ano as well as those of any anorectal patient, a good physical exam is of the utmost importance to appropriate diagnosis, medical decision-making, and patient counseling.

Classification

The most common etiology of fistula-in-ano is cryptoglandular progression. The course of the offending gland through the sphincter complex or the path the bacteria travels through the tissues as its path of least resistance determines the type of resultant fistula. Fistulas are categorized based on degree of sphincter involvement: subcutaneous/submucosal (2–3%), intersphincteric (24–45%), transsphincteric (30–60%), and suprasphincteric (2–20%) [23–25].

Subcutaneous or submucosal fistulas begin at the dentate line and course just deep to the anoderm without any sphincter involvement. Intersphincteric fistulas track through the internal sphincter alone before traveling through the intersphincteric space to reach the perianal skin. Transsphincteric fistulas travel through both the internal sphincter and external sphincter and are further subdivided based on degree of external sphincter involvement. Those fistulas involving 30% or less of the external sphincter are considered low transsphincteric fistulas, whereas those involving more than 30% of the external sphincter are termed high transsphincteric fistulas. This is of particular importance in the decision regarding sphincter-dividing vs. sphincter-sparing techniques and risk of postoperative fecal incontinence. This will be discussed in further detail in a later section. Suprasphincteric fistulas begin at the dentate line, course through the internal sphincter, travel cephalad in the intersphincteric space, and cross the skeletal muscle above the external sphincter to enter the ischiorectal space.

A fifth class of anorectal fistula is also described: the extrasphincteric fistula. These fistulas do not arise from a cryptoglandular origin and do not involve the sphincter complex. These fistulas arise from an intraabdominal source such as diverticulitis or malignancy, are associated with a separate etiology of fistulizing disease such as Crohn's disease, or may arise from iatrogenic injury or inappropriate drainage of a supralevator abscess. Extrasphincteric fistulas are mentioned here to fully understand the classification of fistula-in-ano; however, their management will be discussed in another chapter (Fig. 13.5).

Neither the location of the initial abscess cavity nor the location of external opening of a fistula tract can predict the degree of sphincter involvement. The internal opening can be somewhat reliably predicted for cryptoglandular fistulas based on the location of the external opening following Goodsall's principle. Overall this principle correctly corresponds to actual patient disease in ~80% of those with cryptoglandular fistula [26]. This is most accurate for posterior and intersphincteric fistulas, 91% and 93%, respectively, than for anterior and transsphincteric fistulas, 69% and 68%, respectively (Fig. 13.6) [27].

In this principle, any external opening involving the posterior half of the anoderm (posterior to the transverse anal line) will curve medially to involve an internal opening in the posterior midline. External openings involving the anterior half of the anal verge (anterior to the transverse anal line) will correspond to a radially located internal opening. Exceptions to this rule include posteriorly arising fistula tracts that extend anteriorly in their curved path prior to communicating with the perianal skin.

Preoperative Imaging for Fistula Characterization

As mentioned previously, there are several imaging adjuncts that may be used to define a fistula tract, such as CT scan, MRI, fistulography, and endoanal ultrasound. The majority of patients with uncomplicated cryptoglandular disease are diagnosed with fistula-in-ano based on symptoms and physical exam findings alone, and there is no additional benefit to adding imaging in the initial workup. Gonzalez-Ruiz et al. demonstrated 93% ability to identify internal fistula opening

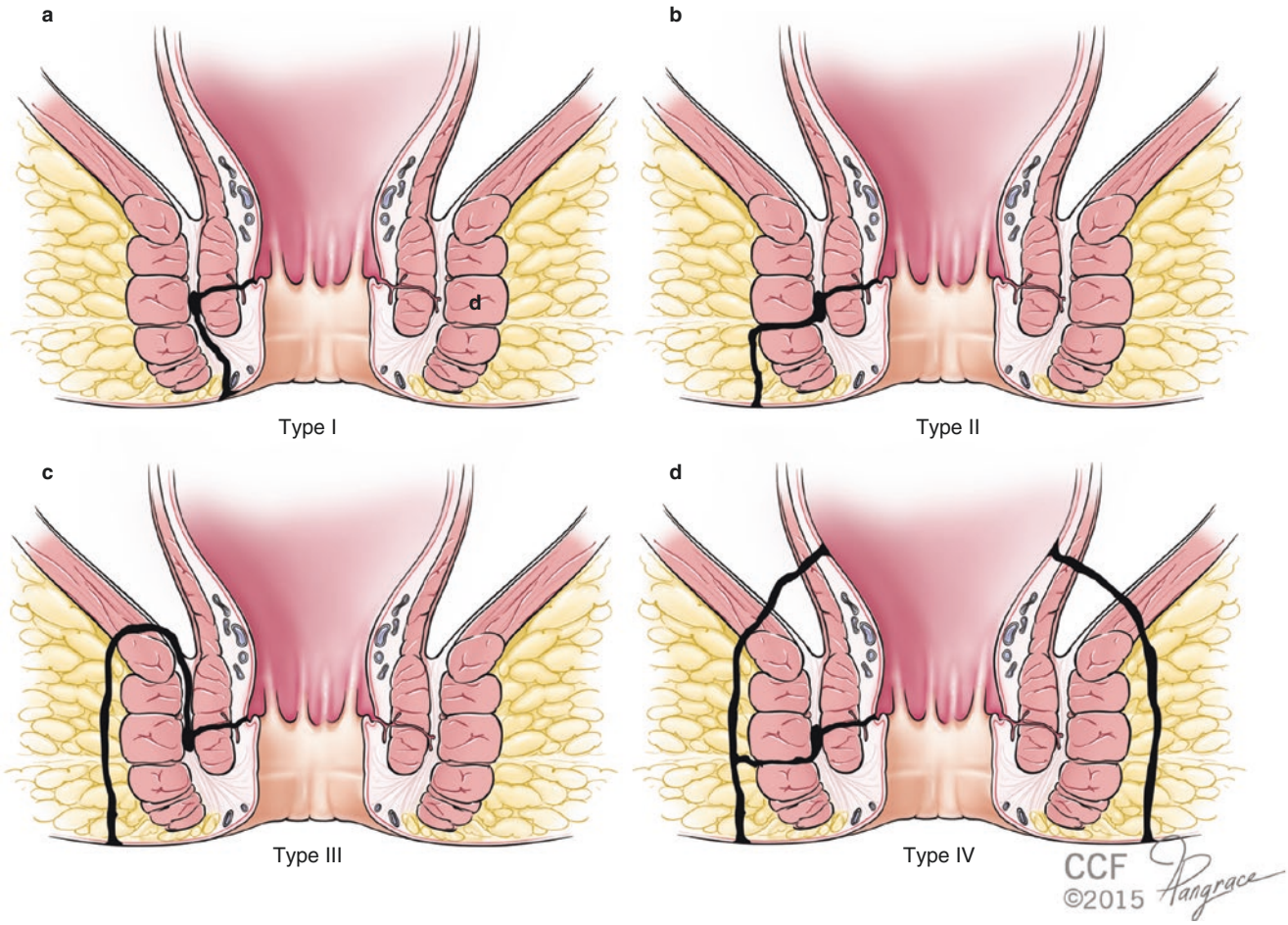

Fig. 13.5 Cross-sectional images showing the anatomy of various fistula tracts. Type 1, intersphincteric; type 2, transsphincteric; type 3, suprasphincteric; type 4, extrasphincteric, combined transsphincteric/extrasphincteric. (Reprinted with permission, The Cleveland Clinic Center for Medical Art & Photography © 2009–2020. All Rights Reserved)

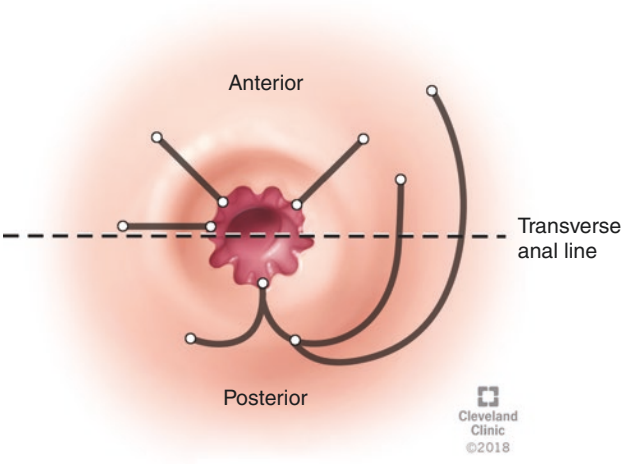

Fig. 13.6 Goodsall's rule, which has come into question more recently. It still remains a decent guideline for determining the location of an internal opening. (Reprinted with permission, The Cleveland Clinic Center for Medical Art & Photography © 2009–2020. All Rights Reserved)

with direct palpation [26]. Imaging is reasonable to consider for those with non-cryptoglandular disease, such as Crohn's, those with recurrent disease or history of prior fistula operation, and those in whom the tract was not readily identifiable on examination under anesthesia.

The imaging modality selected is highly dependent on surgeon preference, comfort with interpretation, access to certain modalities, and, in the case of ultrasound, surgeon skill.

Fistulography

Fistulography is performed by injection of water-soluble contrast into the external fistula opening followed by plain X-ray or fluoroscopy imaging. A modified technique described by Pomerri et al. may also be used during which contrast is placed into the rectum via a Foley catheter [28]. With this method, the authors were able to identify 100% of primary tracts, 74.2% of internal openings, 91.8% of secondary tracks, and 87.8% of abscesses. Despite relative accuracy, both fistulography techniques have been surpassed by

other modalities, due to the lack of radiologist expertise, anatomic information provided with plain X-ray alone, and discomfort to the patient [29]. These may still have a role for those without access to more advanced 3D imaging options.

Computed Tomography (CT)

Standard computerized tomography (CT) is typically not a helpful modality to evaluate fistula characteristics [30]. CT may be helpful, as previously stated, in the evaluation of complex abscess cavities, including supralevator abscesses, or to define aberrant anatomy from prior surgery, prior infection or inflammatory disease, or congenital aberrancies. CT with fistulography, however, does have the ability to characterize a fistula tract with relatively good accuracy [31]. Proponents of this technique cite the increased availability of CT and decreased cost as compared to MRI. There is also no interobserver variability. Negatives of this modality include exposure to radiation, procedural cannulation of the fistula tract which often requires surgeon presence in radiology, and decreased accuracy as compared to MRI. CT fistulography is less accurate at fistula classification (73.1% vs. 92.7%, $p < 0.001$) and identification of internal opening (68.2% vs. 85.3%, $p < 0.001$) as compared to MRI, with similar ability to identify secondary extensions and similar correlation with intraoperative findings [31].

Magnetic Resonance Imaging (MRI)

The use of MRI to evaluate anal fistulas was first described in the 1992 by Lunniss et al. [32]. In the initial reports, MRI was highly accurate, sensitive, and concordant with operative findings [33, 34]. Many consider MRI the preferred imaging modality to characterize anal fistulas given its accuracy, reproducibility, and no need for instrumentation of the fistula tract by the radiologist or surgeon, which leads to improved patient tolerance [29]. MRI is also preferred due to its ability to both localize abscesses and characterize fistulas with depiction of the surrounding anatomy.

A more important determination may not be which modality to use, but when to use imaging. In a study of 136 patients undergoing preoperative 3T MRI, Konan et al. identified an 83.1% concordance with operative findings; however, the contribution of that finding to clinical evaluation was only significant in 33.8% of patients [35]. Applicable and treatment changing information was more common in those with complex fistulas (54.4% vs. 5.2%, $p < 0.001$) and with external opening >2 cm from the anal verge (47.1% vs. 10.2%, $p < 0.001$) and when a horseshoe fistula was present (66.7% vs. 30.6%, $p = 0.021$). This again supports the earlier assertion that imaging adjuncts are unnecessary with straightforward cryptoglandular disease.

MRI can be performed with either an endoanal coil or a body coil. There was initial support for the endoanal coil with studies showing improved accuracy as compared to an external coil [36]. This technique however is poorly tolerated by patients and has decreased ability to delineate anatomy further from the anal verge. In addition, with improvements in MRI technology with both 1.5 Tesla and 3.0 Tesla magnets, body coil MRI findings surpassed endoanal coil MRI in concordance to surgical findings [37, 38].

Endoanal Ultrasound (EAUS)

While MRI is currently considered the gold standard for fistula evaluation, cost and access are often prohibitive for patients. In these situations, endoanal ultrasound provides a reasonable alternative for preoperative evaluation. Endoanal ultrasound is similar to MRI in ability to accurately identify internal opening, each with rates of 80–90% accuracy [37, 39, 40]. Endoanal ultrasound is less accurate at identifying secondary extensions, 67–80% vs. 90% [37, 39, 40]. Notably there is no difference between these two modalities in evaluation of simple fistula tracts [40]; however, most would argue that neither adjunct is indicated for the simple fistula tract.

Injection of dilute hydrogen peroxide into the fistula tract via the external opening is often used as an ultrasonic contrast agent during endoanal ultrasound to improve visibility of fistula. Peroxide contrast enhancement increases identification of internal openings, accuracy of fistula classification, and ability to identify supralevator extension and abscess [41–44].

Endoanal ultrasound remains an accurate and cost-effective modality for fistula evaluation. However, given the poor patient tolerance, variability of accuracy based on operator skill, and limited view of anatomy further from the anal canal, MRI continues to be the standard of care for preoperative imaging assessment when available and when indicated in select patients. One advantage of ultrasound is that it can be performed as an adjunct in the OR, which may have immediate impact upon treatment.

Treatment Strategies

There are three main goals in management of fistula-in-ano: (1) control of sepsis, (2) definitive repair of fistula without recurrent disease, and (3) maintenance of continence [45, 46]. The first step in treatment is rectal exam under anesthesia, to evaluate the fistula, surrounding anatomy, and degree of ongoing infection and to classify the fistula with respect to sphincter involvement.

There is little to no role for medical management alone without surgical management in the treatment of cryptoglandular fistula-in-ano. Exceptions to this include those that are minimally symptomatic and have other comorbidities precluding surgical management. In these patients, control of sepsis remains a goal of treatment which may require placement of a draining seton as described below. They must also

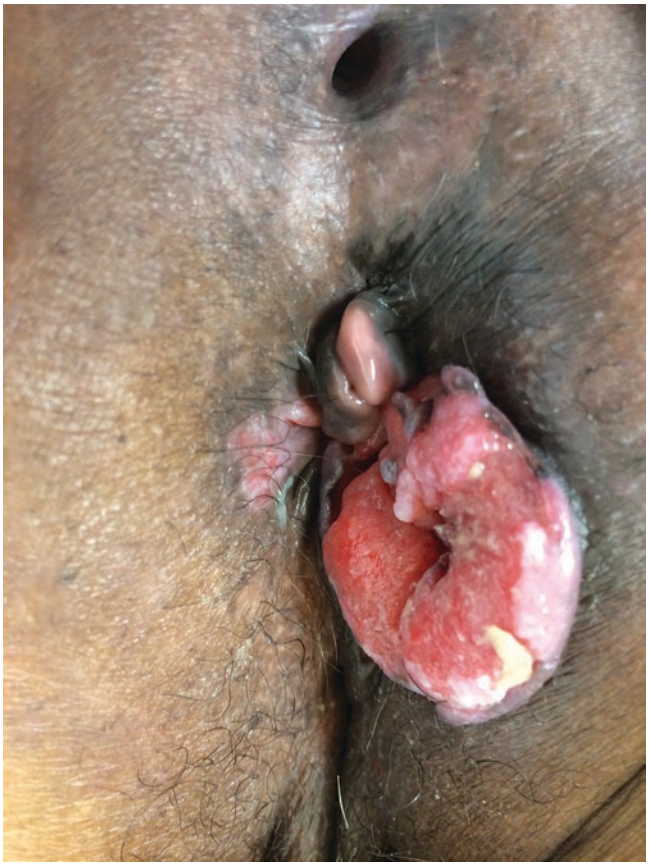

Fig. 13.7 Image showing malignant degeneration/transformation in a chronic fistula tract

be monitored long term due to the rare but documented incidence of malignant degeneration of chronic anal fistula (Fig. 13.7) [47]. Medical management is well described for fistula-in-ano related to Crohn's disease, as will be discussed in the following chapter.

Intraoperative Fistula Identification

The first step in surgical management is intraoperative identification and characterization of the fistula. Even in those with preoperative imaging, these findings are merely guidance and must be confirmed with intraoperative findings. To this end, rectal examination under anesthesia is performed. The authors prefer monitored anesthesia care with sedation and prone jackknife position; however, this procedure can be performed in high lithotomy or under general anesthesia depending on surgeon preference and patient comorbidities.

The procedure begins with digital rectal exam and anoscopic exam both to palpate internal opening and rule out other anal canal pathologies previously unidentified during examination in clinic. The external opening is gently probed with a blunt-tipped fistula probe. These probes can be single or double armed, straight or curved, and malleable or non-malleable, depending on both surgeon preference and the limitations of the individual fistula tract. The probe is passed along the tract until it communicates with the internal opening. This can be facilitated by palpation of the internal opening with the opposite hand at the time of probe passage to guide direction. The probe should move smoothly and without significant force through the fistula tract, so as to avoid creation of a false passage.

A commonly encountered situation is that in which the fistula probe passes through the sphincter complex but does not pass through the mucosal opening. While tempting to "pop through" this final layer of mucosa, inaccurate identification of the internal opening leads to increased risk of recurrent fistula, and therefore this should be avoided [48].

It can be challenging to identify the internal opening in some patients. Intraoperative hydrogen peroxide or methylene blue may be injected via the external fistula opening to aid in identification of the exact site of internal opening. In a study by Gonzalez-Ruiz et al., internal openings were accurately identified in 83% of cases when methylene blue or hydrogen peroxide injections were used [26]. Even if the internal opening is identified, it may be difficult to pass the probe if there is significant angulation or branching or if you encounter unexpected complex anatomy. In these cases, the surgeon may choose to gently probe the internal opening outward to attempt to connect with the externally passed probe.

Alternatively, intraoperative ultrasound with or without hydrogen peroxide contrast enhancement may be used. Just as with preoperative endoanal ultrasound, the surgeon may choose to add hydrogen peroxide as ultrasonic contrast enhancement. Some show that the addition of hydrogen peroxide significantly increases the ability to identify internal opening (94%) and determine curvilinear vs. linear anatomy (85%) [49, 50]. Others found endoanal ultrasound with hydrogen peroxide and endoanal ultrasound alone were equivocal in identifying internal opening, primary tract and secondary tract, although both were still highly accurate at 90 and 86%, 81 and 71%, and 68 and 63%, respectively [51].

It is important to remember that, like any ultrasound, endoanal ultrasound is highly user dependent. These aforementioned degrees of accuracy are in the hands of experienced users. If a surgeon is anticipating use of this modality in the operating room, then it is advised to initially perform endoanal ultrasound intraoperatively on all fistula-in-ano patients, whether simple or complex, to improve their skill and interpretation.

Other techniques have been described to aid in internal opening identification and complete probe passage. One such technique describes partial fistulectomy or fistulotomy from the external opening to the level of the external sphincter followed by traction on the transsphincteric portion of the fistula to identify dimpling of the anal mucosa at the site of

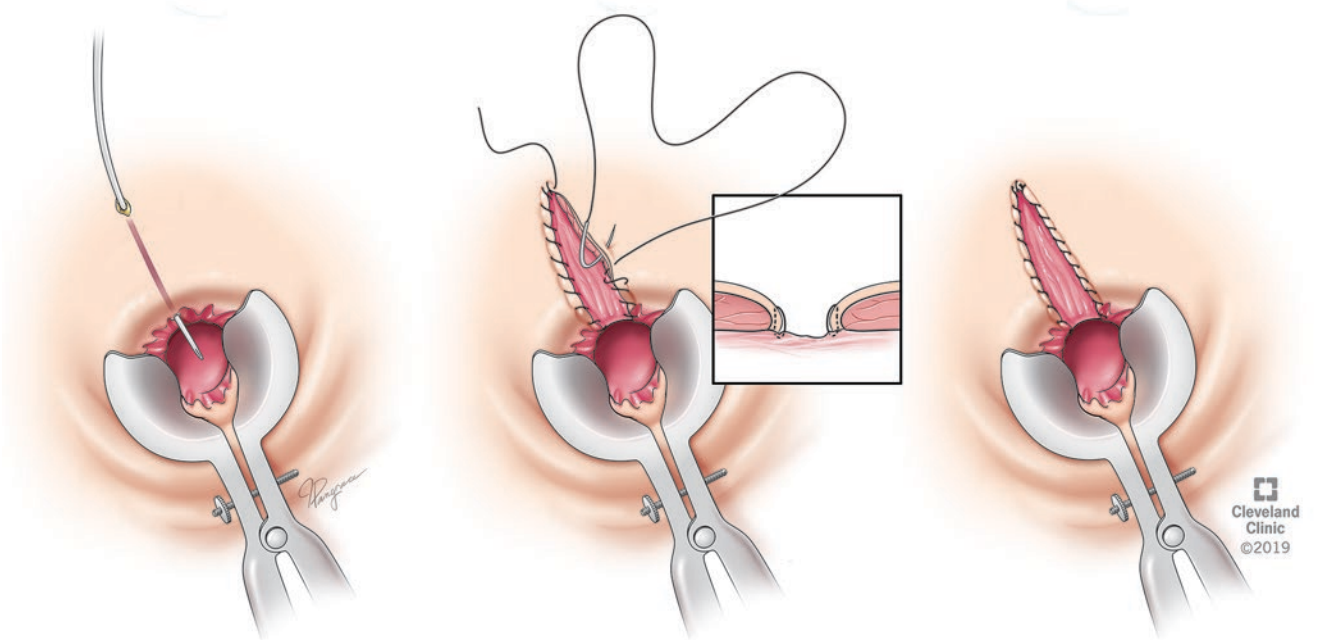

Fig. 13.8 Image showing a simple fistulotomy with marsupialization of the wound edges. (Reprinted with permission, The Cleveland Clinic Center for Medical Art & Photography © 2009–2020. All Rights Reserved)

internal opening [52]. These techniques should be used with caution as they may interfere with appropriate and definitive treatment in the future. Occasionally, one should abandon the procedure if an internal opening is not identified, preserving a future opportunity to identify the fistula tract without injury to the anal canal or sphincter complex.

Once clearly identified, fistulas are commonly classified as simple or complex based on the risk for incontinence after a sphincter-dividing operation. Complex fistulas are described by the American Society of Colon and Rectal Surgeons Standard Practice Task Force (SPTF) as involving more than 30% of external sphincter (high transsphincteric, suprasphincteric, and extrasphincteric), anterior location in a female, multiple tracts, recurrent fistula, preexisting incontinence, local irradiation, and Crohn's disease [53]. Fistulas that clearly fall in the simple classification may be treated with definitive sphincter-dividing surgery at the time of initial presentation. All others should undergo a sphincter preserving technique, typically beginning with placement of a draining seton.

Fistulotomy

Fistulotomy is generally safe in simple fistulas with recurrence rate of 0–9% and incontinence rate between 0% and 37% [24, 48, 54]. The wide range in findings is likely due to variable inclusion criteria of simple vs. complex fistula type in these studies of patients undergoing fistulotomy. Overall, in appropriately selected patients, fistulotomy is safe and has low risk of recurrence and resultant incontinence. For this reason, it is the only surgical option recommended for simple fistulas.

Fistulotomy entails laying open the fistula tract including all secondary tracts for complete and adequate drainage. In some situations, fistulotomy of the primary tract with counter-drainage of the secondary tract/s will provide a reliable result but can simplify healing and postoperative care (Fig. 13.8). This is most easily performed by dividing the tissue overlying the fistula probe with electrocautery. The underlying fistula tract is debrided with electrocautery or curetting. Marsupialization of the wound edges after fistulotomy has been shown to decrease overall resultant wound size, shorten time to healing (6 weeks vs. 10 weeks, $p < 0.001$), and reduce incidence of postoperative bleeding (36% vs. 46%, $p < 0.05$) [55, 56].

Concomitant fistulectomy was initially theorized to improve healing by removal of the dense fibrotic tissue of a chronic fistula. This technique, while having similar recurrence and incontinence rates as compared to fistulotomy, also carries with it increased wound size, increased size of postoperative sphincter defect, and increased time to healing [45, 57, 58]. Therefore, we do not recommend fistulectomy over fistulotomy for simple fistula-in-ano. Fistulectomy may have a role for chronic blind ending sinus tracts, especially one that does not cross the sphincter complex and travels cephalad into the ischiorectal space, for which fistulotomy is not feasible. A drain may be placed in this scenario to facilitate fluid drainage, in particular for tracts that are narrow and penetrate deeply into the tissues.

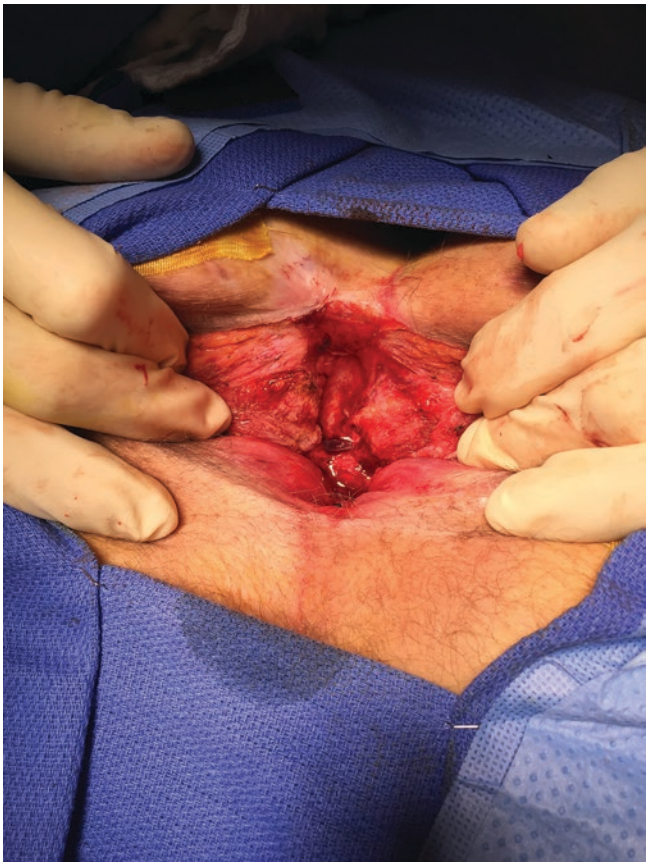

Fig. 13.9 Transsphincteric fistulotomy into the deep postanal space in a patient who failed sphincter-sparing management. This individual did not have any alteration in continence after healing, which is a relatively common result in this setting

While fistulotomy is typically reserved for low lying and simple fistulas, the modified Hanley procedure [59] (posterior midline fistulotomy into the deep postanal space using primary fistulotomy or a cutting seton combined with counter-drainage of bilateral horseshoe tracts) has been associated with successful treatment of deep postanal space/horseshoe fistulas that would generally be considered as complex (Fig. 13.9). It is the opinion of the authors that this procedure should be reserved for failures of sphincter-sparing approaches; however, despite the significant amount of external sphincter divided, incontinence rates are relatively low.

Setons

The word seton originates from *seta*, the Latin word for bristle. In fact, the earliest described setons were horsehair or "seta equina." These setons were used to drain infection and fell out over time. Currently there are many materials that may be used as a seton: nonabsorbable sutures, vessel loops, Penrose drains, silastic catheters, rubber bands, wire, electrical cable tie, etc. The main differentiation between setons is not the material chosen but the goal of treatment. Setons are characterized as draining setons or cutting setons.

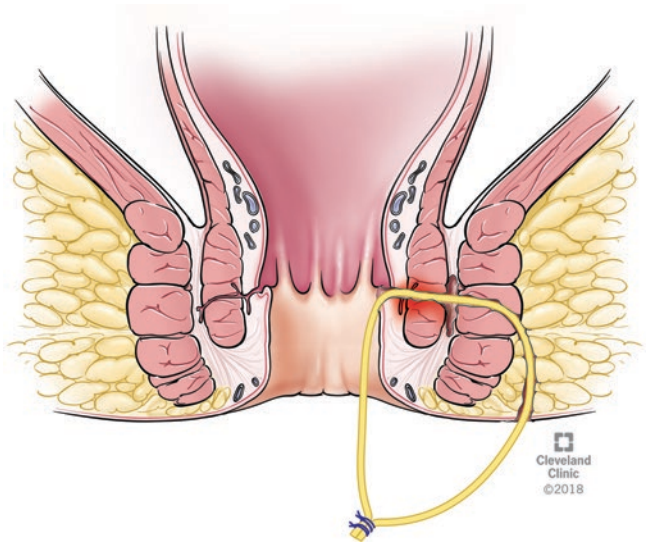

Fig. 13.10 Loose seton placed through a transsphincteric fistula. (Reprinted with permission, The Cleveland Clinic Center for Medical Art & Photography © 2009–2020. All Rights Reserved)

Draining Seton

A draining seton is secured loosely to itself (Fig. 13.10) such that there is no significant tension on the involved tissues. This type of seton is placed if there is complex disease with significant sphincter involvement or significant inflammation such that degree of sphincter involvement cannot be accurately elucidated. The goal of a draining seton is adequate drainage and sepsis management, as well as tract maturation, which is necessary for some types of complex repairs. This procedure is very well tolerated and carries with it very little risk.

Cutting Seton

A cutting seton is placed similarly to a draining seton; however, it is secured tightly to itself such that there is tension and compression on the involved tissues. Successful placement requires division of the anoderm overlying the fistula tract. The seton is then serially tightened in clinic and slowly "cuts" through the intervening tissues until it falls out, leaving intact scar behind and preventing a tissue defect from developing. The time to healing, thereby time to extrusion of seton, may last weeks to months and is dependent on the amount of tissue to be divided. Setons are tightened as frequently as every other day or as infrequent as just once postoperatively. Recurrence rates are low with this procedure (0–10%); however, there remains a significant risk of incontinence, reported between 0 and 67% [60–66]. This observed variability in incontinence rates is attributed to differing surgical techniques, duration of follow-up, and variable surveillance records in follow-up.

Ritchie et al. evaluated a large series of patients ($n = 1460$) and concluded a rate of incontinence of 12% after cutting seton [65]. This rate was based on all included manuscripts; however, one-third of manuscripts did not include a

description of incontinence, and when these are excluded, average incontinence rate increases to 32%. Likewise, several large studies used only medicated cutting setons. When these studies are excluded, incontinence rate rises to 22%. Incontinence rate also increases with more proximal location of the internal opening.

In a review by Vial et al., authors compared rates of recurrence and incontinence with or without division of the internal anal sphincter [66]. They identified similar recurrence rates between preserved and divided internal anal sphincter (5% vs. 3%) and significant difference in rates of incontinence (5.6% vs. 25.2%). These authors concluded that division of internal anal sphincter was not necessary to improve recurrence rate and worsened postoperative function and should therefore be avoided when using a cutting seton.

Overall, cutting setons have high enough incontinence rates to recommend preferential use of other sphincter-sparing approaches for complex fistulas, unless in the setting of recurrent disease with exhaustion of other options or when the anatomy is not amenable to other options.

Loose Seton as Definitive Treatment and External Anal Sphincter-Sparing Seton

Loose draining setons were traditionally seen as a mechanism for sepsis control and bridge to definitive repair in cryptoglandular anal fistula; more recent studies show promising results with the use of draining seton as definitive repair. The mechanism for this treatment is not fully understood; however, proponents of this technique cite eventual erosion of the seton such that the internal opening migrates distally out of the high pressure zone, allowing ultimate healing [67]. Emile et al. reported ~10% recurrence rate with risk of incontinence of 3% [68]. Risks for recurrence include previously recurrent fistula, supralevator extension, and anterior fistula. In their multicenter review of 200 patients undergoing loose seton placement for definitive management of fistula, Kelly et al. identified 100% initial clearance of fistula, with overall 6% recurrence rate and 96% patient tolerance [69]. In their described technique, setons were changed electively every 3 months until the fistula resolved. The median number of seton replacement for each patient was 3 (range 1–8, mean 2.84).

In a recent study by Omar et al., 60 patients with complex anal fistula were randomized to conventional drainage seton or external anal sphincter-sparing seton using a rerouting technique [70]. They identified persistence or recurrence rates of 13% and 3% for conventional and external sphincter-sparing techniques, respectively ($p = 0.35$), and no difference in physical, social, or sexual activities ($p = 0.7$, 0.59, 0.67). Importantly they identified significant decrease in time to healing from 103 ± 47 days in the conventional group, as compared to 46 ± 18 days in the external sphincter-sparing group ($p < 0.0001$). These studies are promising for the use of loose draining seton as a means of definitive treatment and warrant further investigation.

Fibrin Glue

The use of fibrin glue for obliteration of an anal fistula tract was first described in the 1990s as a means to treat complex anal fistulas without impairment of incontinence [71]. In this initial series, Hjortrup et al. reported a 50% success rate, which they argued was reasonable given the procedure's repeatability, ease of performance, and minimal patient risk. With this procedure, the primary fistula tract is identified and debrided, followed by injection of fibrin glue (Fig. 13.11). While none have been associated with change in recurrence rate, variations to this procedure include the use of preoperative setons, degree of tract debridement, use of intra-adhesive antibiotics, and suture closure of internal or external openings [72]. Since this initial study, success rates remain variable at a range of 14–94% [72–76]. Healing rates decrease with increasing fistula complexity [76, 77]. Given the variable success rates, fibrin glue is not recommended as a first-line treatment for complex fistula-in-ano; however, with low risk of complication or incontinence, it is a reasonable second-line treatment or alternative when other surgical options are not feasible [19, 29].

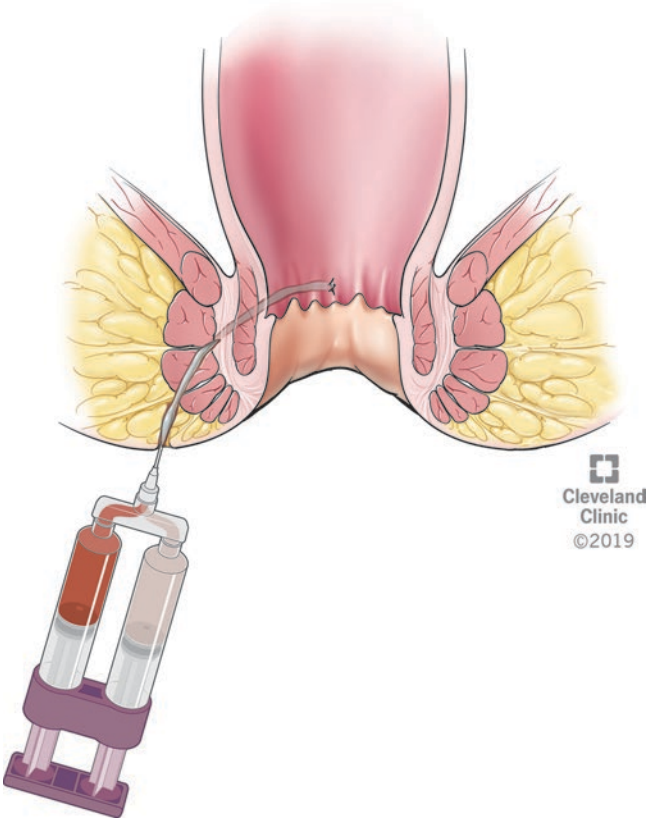

Fig. 13.11 Fibrin glue being injected into a transsphincteric fistula tract. (Reprinted with permission, The Cleveland Clinic Center for Medical Art & Photography © 2009–2020. All Rights Reserved)

Fistula Plug

The anal fistula plug was developed with similar goals to fibrin glue treatment: fistula healing by obliteration of the tract without sphincter division and resultant risk of incontinence. This procedure entails identification of primary fistula tract, passage of a biologic or synthetic plug through the fistula tract, and securement of this prosthesis to the internal opening with successful obliteration of the internal opening (Fig. 13.12a–c). The first study describing the use of graft material as an anal fistula plug, as compared to fibrin glue, occurred in 2006 by Johnson et al. [78]. In this initial series of 15 patients with bioprosthetic mesh plug, they observed an 87% closure rate. Based on this promise, commercially available plugs were created, all with the same goal: creating a scaffolding in which native tissue could grow to close a fistula tract. Subsequent studies observed widely variable success rates of 24–88% [79–82]. Decreased success was attributed to many things: inadequate tract debridement, excessive tract debridement, inadequately secured plug, and presence or lack of preoperative seton, none of which have been shown to be significant factors of success. These mixed success rates as well as increased cost have kept fistula plug from becoming a widely accepted first-line treatment for complex fistula-in-ano [19, 29].

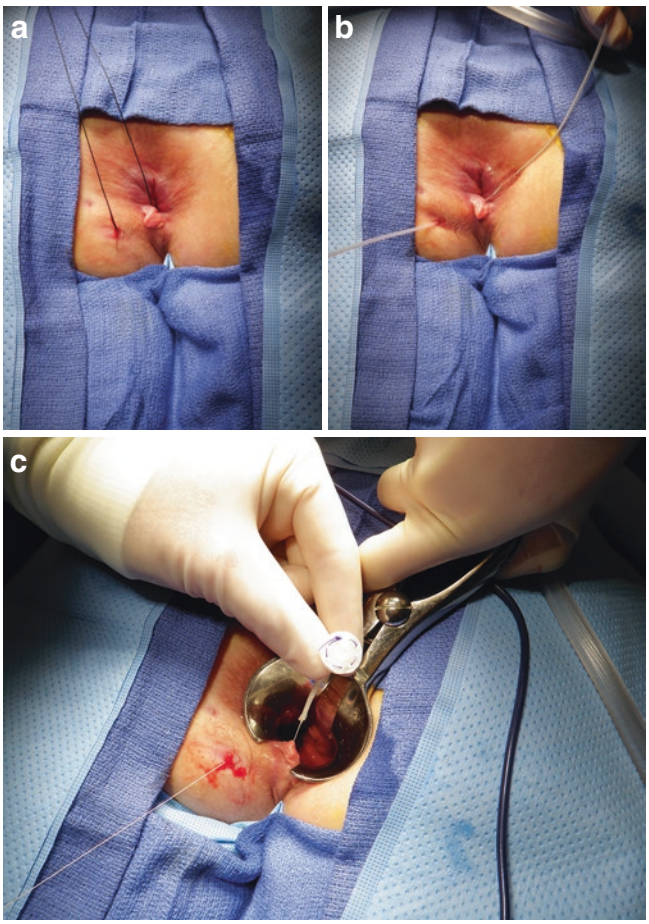

Fig. 13.12 (**a**): Transsphincteric fistula with silk suture (marker suture) placed through the tract. This will be used to pull the fistula brush through the tract. (**b**): Fistula brush being pulled through the tract to gently debride granulation tissue. (**c**): Fistula plug being pulled retrograde through the tract

While its role as a solitary treatment for complex fistula is limited, some have evaluated the role of fistula plug as an adjunct to other complex repairs, such as endorectal advancement flap (ERAF) and ligation of intersphincteric fistula tract (LIFT), as discussed below.

Endorectal Advancement Flap (ERAF)

Endorectal advancement flap entails debridement or excision of the fistula tract and mobilization of a wide-based mucosal/submucosal rectal flap, followed by coverage of the internal opening after removal of overlying tissues and suture closure of the internal opening (Fig. 13.13a–d). Based on its reproducible reasonable success rates of 60–100% [83–91], endorectal advancement flap has been accepted as a first-line treatment option for complex anal fistulas. Keys to successful flap survival include adequate blood supply, via the wide-based submucosal plexus, and lack of tension, requiring adequate length of mobilization. There is variability regarding degree of circular muscle (internal sphincter) included in the mucosal and submucosal flap, with a direct correlation between degree of muscle involvement and flap viability [92]. Importantly, however, there is an inverse relationship between degree of muscle involvement and subsequent incontinence. Recurrence is associated with smoking, recurrent disease, Crohn's disease, prior horseshoe abscess, and elevated BMI [93–97]. Contraindications include Crohn's disease, undrained sepsis, persistent secondary tracts, fistula diameter greater than 3 cm, malignancy or radiation-related etiology, and anorectal stricture [98]. Recently, Yellinek et al. evaluated flap configuration and did not show significant difference in recurrence between rhomboid designed flap (64%) and elliptical flap (62%) [99]. Likewise, there is no change in success between standard curette debridement and fistulectomy excision of fistula tract[86]. Repeat endorectal advancement flap is feasible and carries with it good success rates; however, it is also associated with a higher rate of recurrence than initial ERAF repair [100, 101].

Importantly, while this procedure does not directly divide sphincter muscle, incorporation of sphincter fibers in the advancement flap to varying degrees does lead to worsening continence in up to 35% of patients [86, 102].

Both anal fistula plug and fibrin glue have been suggested as adjuncts to endorectal advancement flap to improve success. Studies evaluating addition of fibrin glue to ERAF unfortunately revealed higher rates of failure than with flap alone [93, 103]. Likewise, advancement flap closure over a

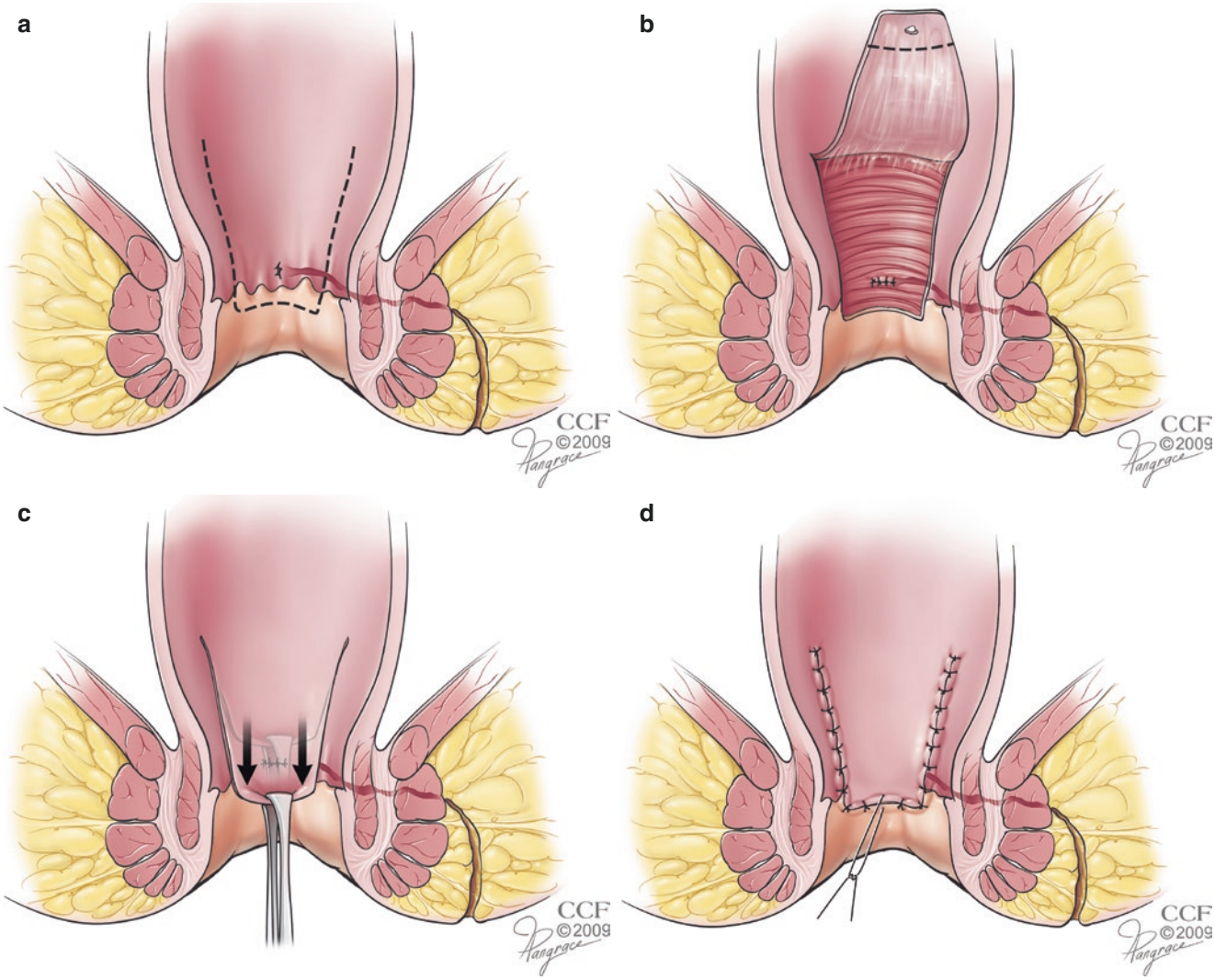

Fig. 13.13 (**a**): Dotted line represents the outline of intended tissue flap harvest. (**b**): Mucosal/submucosal flap raised with appropriate dimensions as well as area at the tip, intended for excision. (**c**): Flap being stretched into place after closing the internal opening at the muscular level. (**d**): Completed endorectal advancement flap. (Reprinted with permission, The Cleveland Clinic Center for Medical Art & Photography © 2009–2020. All Rights Reserved)

fistula plug does not confer improved healing as compared to fistula plug alone. It may be beneficial to incorporate platelet-rich plasma with ERAF [104]; however, additional studies are required.

An alternative flap design is described using a dermal advancement flap instead of a mucosal flap (Fig. 13.14), which carries with it the theoretical decreased risk of mucosal ectropion. Such flaps can be fashioned in a "house" or "diamond" configuration or as V-Y advancement of perianal skin. Studies evaluating this therapy are heterogeneous, making it difficult to make definitive recommendations. Overall, this procedure is safe and has low to moderate rates of incontinence (10–20%) [92, 105] and moderate rates of success (50–70%) [98, 106–109].

Ligation of Intersphincteric Fistula Tract (LIFT)

Similar to ERAF, ligation of intersphincteric tract (LIFT) is now widely accepted as a first-line treatment for complex fistula-in-ano due to reasonable success rates and sphincter preservation [19]. LIFT was developed as a "total sphincter preserving" technique in 2007 by Rojanasakul et al. [110]. This procedure entails dissection of intersphincteric space until the mature fistula tract is encountered and subsequently divided and doubly ligated (Fig. 13.15a–d). The internal and external wounds are debrided and left open to drain. In the initial description in 2007, authors reported 94.4% healing rate with 0% rate of incontinence [110]. A subsequent retrospective observational study of 251 patients by the initial authors reported 87.7% rate of healing [111]. Limitations

include lack of reporting on complications, specifically changes to continence, and varied patient population (55.8% low transsphincteric, 10.8% intersphincteric, 6.0% high transsphincteric, 25.5% semihorseshoe ischioanal, 2.0% horseshoe ischioanal). As many studies of sphincter-sparing techniques include only complex fistula-in-ano, it is important to consider that the patient population in this review was comprised of 66.6% simple anal fistulas. Overall, rates of success range from 61% to 94% with rare instances of change in continence [112–117]. Interestingly, recurrence was associated with shorter fistula tract ($p < 0.01$) [117]. When the LIFT procedure fails, it most often results in drainage via the intersphincteric incision as a persistent intersphincteric fistula which can subsequently be managed with simple fistulotomy [118–120]. Madbouly et al. randomized 70 patients to LIFT or endorectal advancement flap (ERAF) [121]. Authors observed initial success rates of 94% and 91% for the LIFT and ERAF groups, which fell to 74% and 66% after 1 year follow-up, respectively, emphasizing the importance of length of follow-up and risk of late failure. A recent meta-analysis of the topic indicates that results from ERAF and LIFT are quite similar [122].

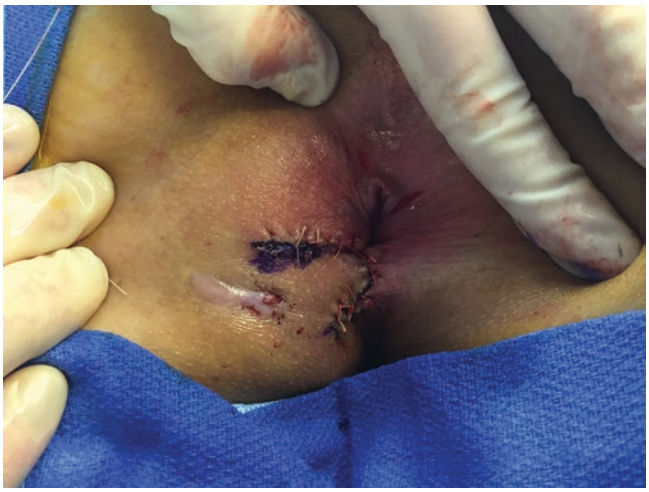

Fig. 13.14 Anocutaneous advancement flap (from outside to inside). Can be used when creating an endorectal advancement flap leading to a mucosal ectropion

Variations of the LIFT technique have been suggested: BioLIFT, LIFT plus, LIFT-PLUG, LIFT + ERAF. The BioLIFT incorporates a bioprosthetic graft placed in the inter-

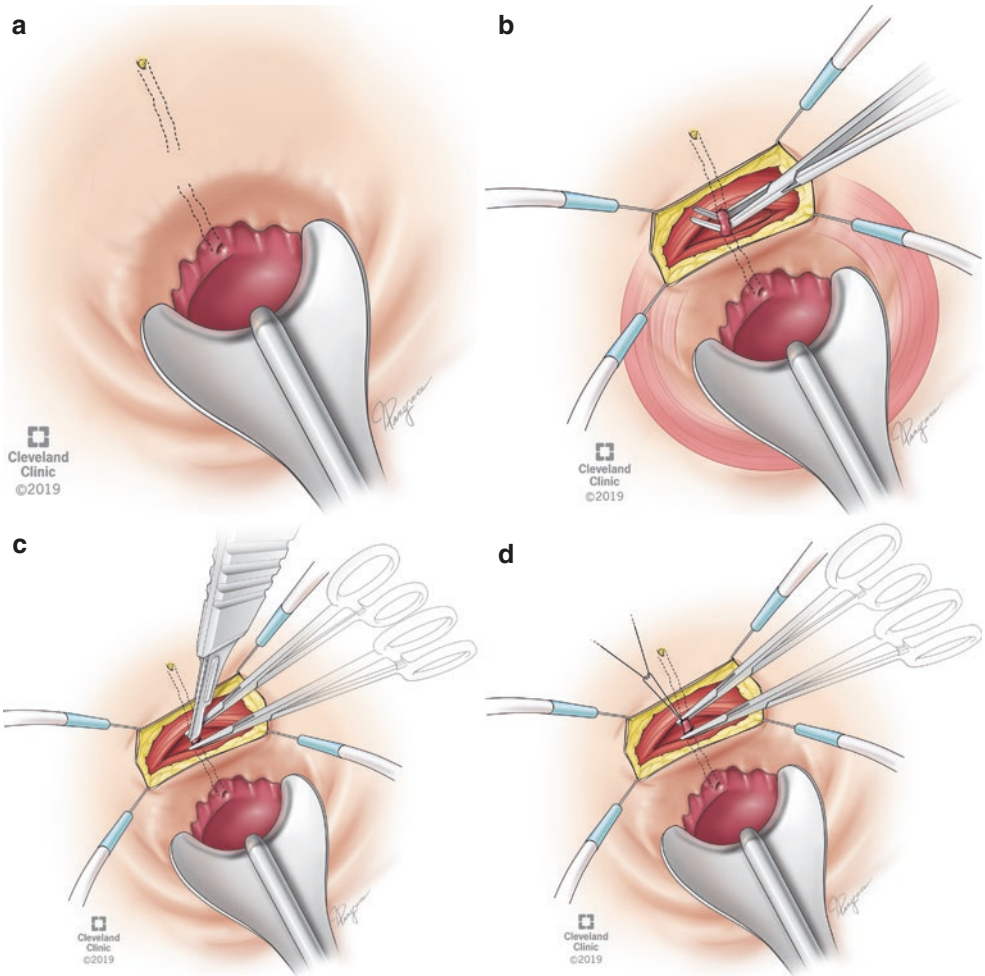

Fig. 13.15 (**a**): Transsphincteric fistula tract, illustrating the intersphincteric portion of the tract prior to incision for LIFT. (**b**): Intersphincteric incision with isolation of the intersphincteric portion of the tract. (**c**): Division of the intersphincteric portion of the tract. (**d**): Ligation of the intersphincteric portion of the fistula tract. (Reprinted with permission, The Cleveland Clinic Center for Medical Art & Photography © 2009–2020. All Rights Reserved)

sphincteric plane with the goal of decreasing communication between the two portions of the fistula tract. Concern regarding this procedure surrounds the risk of additional intersphincteric dissection to accommodate the prosthesis as well as the cost of the bioprosthetic. Lau et al. evaluated LIFT and BioLIFT and found similar success rates of 80.2 and 81.9%, respectively [123]. Thus far, BioLIFT cannot be supported as an advantage based on the cost and equivocal results.

Han et al. evaluated traditional LIFT procedure with the LIFT-PLUG procedure [124]. In this operation, a bioprosthetic plug is passed through the previously debrided external sphincter tract via the intersphincteric incision and secured in place. These authors observed shorter healing time (22 days vs. 30 days, $p < 0.001$) and higher primary healing rate (94.0% vs. 83.9%, $p < 0.001$) in the LIFT-PLUG group than the standard LIFT group, respectively.

The LIFT plus procedure incorporates a partial fistulotomy of the distal tract external to the external sphincter to promote external drainage. LIFT plus may confer an advantage over LIFT with success rates of 85% vs. 81% (0.0529) as observed by Sirikurnpiboon et al. [125]. Overall, with the current data available, none of these three techniques can be confidently recommended over standard.

Novel Surgical Therapies

Fistula Tract Laser Closure (FiLaC™)

Closure of an anal fistula tract using radially emitting laser probe was first described in 2011 and subsequently in 2014 as a novel technique to heal simple and complex anal fistulas without risk to continence [126–128]. In its initial description, the authors described mechanical tract debridement with endorectal advancement flap, followed by laser treatment of the tract with a radial fiber connected to a diode laser [126]. Subsequent descriptions did not include endorectal advancement flap. Success rates were reported at 77–82% in these initial small series with no instances of incontinence. Since then, additional studies observed a decrease in primary success rates of 33–71% [129–131]. In those with primary failure, secondary success was achieved in some with repeat-FiLaC™, fistulectomy with sphincter repair, or primary fistulotomy that was possible due to distal migration of the tract after FiLaC™. Increased success was associated with intersphincteric-type, short fistula tract (<30 mm) and history of prior seton. One study to date has described minor mucous or gas incontinence at a rate of 1.7% during their median 25.4-month follow-up [131].

Video-Assisted Anal Fistula Treatment (VAAFT)

Meinero and Mori first described the video-assisted anal fistula treatment (VAAFT) procedure in 2006, with which they observed promising success with 74% primary closure rate and 87% overall healing after 1 year of follow-up [132]. This procedure is characterized by direct visualization of the primary fistula, secondary tracts, and internal opening. A Karl Storz fistuloscope is passed through the external opening to the internal opening with continuous glycine-mannitol irrigation. Once the internal opening is identified, it is marked with a stay suture. A unipolar electrode is inserted into the fistuloscope to fulgurate the fistula walls including the openings to any secondary tracts. This is followed by debridement of necrotic material with a brush and finally closure of the internal opening, traditionally with surgical stapler, absorbable suture, or advancement flap. The closure may be further enforced by fibrin glue injection just beneath the prior internal opening. This procedure is similar in many ways to the FiLaC™ procedure but, however, has the additional benefit of direct visualization.

Garg et al. evaluated VAAFT with a meta-analysis of 8 studies including 786 patients [133]. The authors identified a 76% success rate, 16.2% complication rate, and no reports of worsening level of continence. In a subsequent meta-analysis by Emile et al. of 788 patients across 11 studies, rates of success remained high at 86.8% after medial follow-up of 9 months [134]. Complication rate remained low at 4.8% observed. Interestingly, recurrence rates varied by type of internal opening closure. Staple closure was the lowest at 15.3%, followed by suture closure 17.7%, and lastly recurrence was highest with advancement flap closure. VAAFT is a promising technique in the growing field of fistula management.

Fistulotomy with Primary Anal Sphincter Reconstruction

Fistulotomy was previously only regarded as an appropriate treatment for simple anal fistula given the increasing risk of incontinence with increasing fistula complexity. In recent years, there have been several promising studies evaluating the role of fistulotomy with primary sphincter reconstruction (Fig. 13.16a–c). These studies reveal high success rates (91–96%) and low incontinence rates (2–13%), with the post-defecation soiling being the most common type of de novo incontinence [135–138]. Risks of recurrent disease and incontinence were significantly increased in those with prior recurrent fistula, complex fistula, presence of secondary tracts, and prior seton drainage. In this technique, a primary fistulotomy is performed, with or without fistulectomy, followed by end-to-end primary sphincteroplasty with dissolvable sutures. Proponents of this technique argue its favorable success and complication profile as compared to many of the other surgical options for complex anal fistulas.

Stem Cell Therapy

There has been a lot of excitement regarding autologous stem cell therapy in the treatment of fistula-in-ano. In a phase

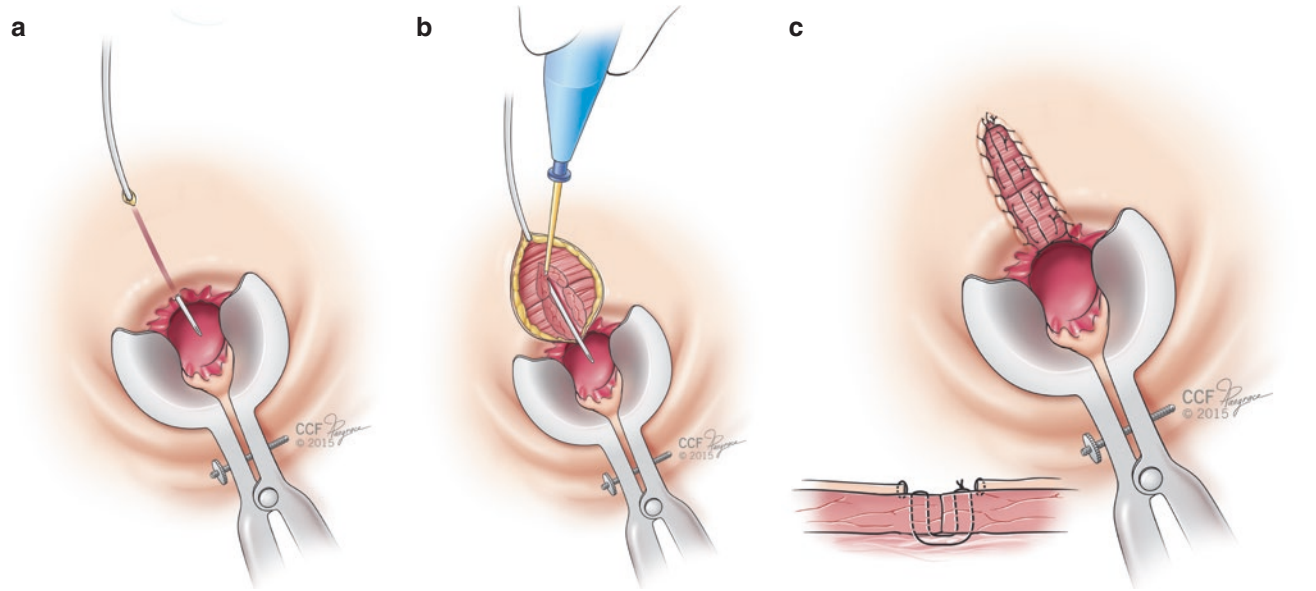

Fig. 13.16 (**a**): Transsphincteric fistula with indwelling probe prior to fistulotomy. (**b**): Fistulotomy performed over probe. There is an appreciable amount of external sphincter being divided. (**c**): Sphincter repair being performed after fistulotomy and tract debridement. (Reprinted with permission, The Cleveland Clinic Center for Medical Art & Photography © 2009–2020. All Rights Reserved)

II clinical trial, Garcia-Olmo et al. randomized 35 patients to fibrin glue alone or fibrin glue with 10 million adipose-derived stem cells [139]. Their study observed a 4.43 increased relative rate for healing (CI 1.74–11.27, $p < 0.001$) in those with adipose-derived stem cells in addition to fibrin glue (71% healing vs. 16%). Unfortunately, healing rates decreased from 71% to 62.5% in the stem cell group at 1-year follow-up. In their phase III trial, Herreros et al. on behalf of the FATT collaborative group performed a multicenter, randomized, single-blind clinical trial of 200 patients over 19 centers [140]. Participants were randomized to the following treatments after uniform closure of the internal opening: 20 million stem cells, 20 million stem cells with fibrin glue, and fibrin glue alone. There was no significant difference between groups at both 24–26-week and 1-year follow-up, ~40% and ~50%, respectively. The authors pointed out that the results were much more promising at their pioneer center, with healing rates at 24–26 weeks of 54.56%, 83.33%, and 18.18% for the stem cell alone, stem cell + fibrin glue, and fibrin glue alone groups, respectively ($p < 0.001$). Additional studies are ongoing regarding stem cell therapy including combinations with fibrin glue, plasma-rich protein, and coated fistula plugs [141–143].

Over the Scope Clip (OTSC® Proctology)

In 2012, Prosst and Ehni described the use of a clip to close the internal opening, using the OTSC® Proctology device. In this procedure, a super-elastic nitinol clip is placed with a specialized endoscope over the internal fistula opening. Initial small series observed success rates of 60–93% healing rates, with decreased healing in those with prior fistula operations. Discomfort from the clip was reported as minimal by study participants; however, the clip did require removal with the OTSC® Proctology clip cutter in the majority of cases [144–148]. This is a promising device; however, there is inadequate evidence to support its routine acceptance. Additional studies are required evaluating success, risks for failure, complication, and device cost.

Recommendation

There are a few main take-home points to consider in the management of acute anorectal abscess and anal fistula. In a patient with demonstrable abscess on physical exam, surgical drainage is the standard and can often be done in the office under local anesthesia with careful technique. Antibiotics are reserved for special circumstances including cellulitis and sepsis. Cure and preservation of continence are the overriding goals in the management of anal fistula, with continence perhaps taking precedence. A patient's quality of life would generally be better with an indwelling loose seton as opposed to living with significant incontinence. It is important to be aware of the multitude of methods that can be used to treat anal fistula. Failure rates of sphincter-sparing approaches are significant, and when one method fails, it is often useful to proceed to another. The importance of informed consent cannot be overemphasized. Failure rates should be discussed, expectations set at the onset, and patients well aware of their alternatives.

References

1. Abcarian H. Anorectal infection: abscess–fistula. Clin Colon Rectal Surg. 2011;24(1):14–21. https://doi.org/10.1055/s-0031-1272819.
2. Sainio P. Fistula-in-ano in a defined population. Incidence and epidemiological aspects. Ann Chir Gynaecol. 1984;73(4):219–24.
3. Ommer A, Herold A, Berg E, et al. German S3 guidelines: anal abscess and fistula (second revised version). Langenbecks Arch Surg. 2017;402(2):191–201. https://doi.org/10.1007/s00423-017-1563-z.
4. Adamo K, Sandblom G, Brännström F, Strigård K. Prevalence and recurrence rate of perianal abscess—a population-based study, Sweden 1997–2009. Int J Colorectal Dis. 2016;31(3):669–73. https://doi.org/10.1007/s00384-015-2500-7.
5. Eisenhammer S. The internal anal sphincter and the anorectal abscess. Surg Gynecol Obstet. 1956;103(4):501–6.
6. Parks AG. Pathogenesis and treatment of fistula-in-ano. Br Med J. 1961;1(5224):463–460.2.
7. McElwain JW, MacLean MD, Alexander RM, Hoexter B, Guthrie JF. Anorectal problems: experience with primary fistulectomy for anorectal abscess, a report of 1,000 cases. Dis Colon Rectum. 1975;18(8):646–9. https://doi.org/10.1007/bf02604266.
8. Ramanujam PS, Prasad ML, Abcarian H, Tan AB. Perianal abscesses and fistulas. A study of 1023 patients. Dis Colon Rectum. 1984;27(9):593–7. https://doi.org/10.1007/bf02553848.
9. Caliste X, Nazir S, Goode T, et al. Sensitivity of computed tomography in detection of perirectal abscess. Am Surg. 2011;77(2):166–8.
10. Hamadani A, Haigh PI, Liu I-LA, Abbas MA. Who is at risk for developing chronic anal fistula or recurrent anal sepsis after initial perianal abscess? Dis Colon Rectum. 2009;52(2):217–21. https://doi.org/10.1007/DCR.0b013e31819a5c52.
11. Lohsiriwat V, Yodying H, Lohsiriwat D. Incidence and factors influencing the development of fistula-in-ano after incision and drainage of perianal abscesses. J Med Assoc Thail Chotmaihet Thangphaet. 2010;93(1):61–5.
12. Cox SW, Senagore AJ, Luchtefeld MA, Mazier WP. Outcome after incision and drainage with fistulotomy for ischiorectal abscess. Am Surg. 1997;63(8):686–9.
13. Read DR, Abcarian H. A prospective survey of 474 patients with anorectal abscess. Dis Colon Rectum. 1979;22(8):566–8. https://doi.org/10.1007/bf02587008.
14. Vasilevsky CA, Gordon PH. The incidence of recurrent abscesses or fistula-in-ano following anorectal suppuration. Dis Colon Rectum. 1984;27(2):126–30. https://doi.org/10.1007/bf02553995.
15. Schouten WR, van Vroonhoven TJ. Treatment of anorectal abscess with or without primary fistulectomy. Results of a prospective randomized trial. Dis Colon Rectum. 1991;34(1):60–3. https://doi.org/10.1007/bf02050209.
16. O'Malley GF, Dominici P, Giraldo P, et al. Routine packing of simple cutaneous abscesses is painful and probably unnecessary. Acad Emerg Med. 2009;16(5):470–3. https://doi.org/10.1111/j.1553-2712.2009.00409.x.
17. Perera AP, Howell AM, Sodergren MH, et al. A pilot randomised controlled trial evaluating postoperative packing of the perianal abscess. Langenbecks Arch Surg. 2015;400(2):267–71. https://doi.org/10.1007/s00423-014-1231-5.
18. Tonkin DM, Murphy E, Brooke-Smith M, et al. Perianal abscess: a pilot study comparing packing with nonpacking of the abscess cavity. Dis Colon Rectum. 2004;47(9):1510–4. https://doi.org/10.1007/s10350-004-0620-1.
19. Vogel J, Johnson E, Morris A, et al. Clinical practice guideline for the management of anorectal abscess, fistula-in-ano, and rectovaginal fistula. Dis Colon Rectum. 2016;59(12):1117–33. https://doi.org/10.1097/DCR.0000000000000733.
20. Ghahramani L, Minaie MR, Arasteh P, et al. Antibiotic therapy for prevention of fistula in-ano after incision and drainage of simple perianal abscess: a randomized single blind clinical trial. Surgery. 2017;162(5):1017–25. https://doi.org/10.1016/j.surg.2017.07.001.
21. Mocanu V, Dang JT, Ladak F, et al. Antibiotic use in prevention of anal fistulas following incision and drainage of anorectal abscesses: a systematic review and meta-analysis. Am J Surg. 2019;217(5):910–7. https://doi.org/10.1016/j.amjsurg.2019.01.015.
22. Sözener U, Gedik E, Aslar AK, et al. Does adjuvant antibiotic treatment after drainage of anorectal abscess prevent development of anal fistulas? A randomized, placebo-controlled, double-blind, multicenter study. Dis Colon Rectum. 2011;54(8):923–9. https://doi.org/10.1097/DCR.0b013e31821cc1f9.
23. Parks AG, Gordon PH, Hardcastle JD. A classification of fistula-in-ano. Br J Surg. 1976;63(1):1–12. https://doi.org/10.1002/bjs.1800630102.
24. Sileri P, Cadeddu F, D'Ugo S, et al. Surgery for fistula-in-ano in a specialist colorectal unit: a critical appraisal. BMC Gastroenterol. 2011;11:120. https://doi.org/10.1186/1471-230X-11-120.
25. Subasinghe D, Samarasekera DN. Comparison of preoperative endoanal ultrasonography with intraoperative findings for fistula in ano. World J Surg. 2010;34(5):1123–7. https://doi.org/10.1007/s00268-010-0478-4.
26. Gonzalez-Ruiz C, Kaiser AM, Vukasin P, Beart RW, Ortega AE. Intraoperative physical diagnosis in the management of anal fistula. Am Surg. 2006;72(1):11–5.
27. Barwood N, Clarke G, Levitt S, Levitt M. Fistula-in-ano: a prospective study of 107 patients. Aust N Z J Surg. 1997;67(2–3):98–102. https://doi.org/10.1111/j.1445-2197.1997.tb01911.x.
28. Pomerri F, Dodi G, Pintacuda G, Amadio L, Muzzio PC. Anal endosonography and fistulography for fistula-in-ano. Radiol Med (Torino). 2010;115(5):771–83. https://doi.org/10.1007/s11547-010-0524-1.
29. Williams G, Williams A, Tozer P, et al. The treatment of anal fistula: second ACPGBI position statement – 2018. Colorectal Dis. 2018;20(S3):5–31. https://doi.org/10.1111/codi.14054.
30. Liang C, Jiang W, Zhao B, Zhang Y, Du Y, Lu Y. CT imaging with fistulography for perianal fistula: does it really help the surgeon? Clin Imaging. 2013;37(6):1069–76. https://doi.org/10.1016/j.clinimag.2013.04.014.
31. Soker G, Gulek B, Yilmaz C, et al. The comparison of CT fistulography and MR imaging of perianal fistulae with surgical findings: a case-control study. Abdom Radiol N Y. 2016;41(8):1474–83. https://doi.org/10.1007/s00261-016-0722-y.
32. Lunniss PJ, Armstrong P, Barker PG, Reznek RH, Phillips RK. Magnetic resonance imaging of anal fistulae. Lancet Lond Engl. 1992;340(8816):394–6. https://doi.org/10.1016/0140-6736(92)91472-k.
33. Joyce M, Veniero JC, Kiran RP. Magnetic resonance imaging in the management of anal fistula and anorectal sepsis. Clin Colon Rectal Surg. 2008;21(3):213–9. https://doi.org/10.1055/s-2008-1081000.
34. Halligan S. Magnetic resonance imaging of fistula-in-ano. Magn Reson Imaging Clin N Am. 2020;28(1):141–51. https://doi.org/10.1016/j.mric.2019.09.006.
35. Konan A, Onur MR, Özmen MN. The contribution of preoperative MRI to the surgical management of anal fistulas. Diagn Interv Radiol. 2018;24(6):321–7. https://doi.org/10.5152/dir.2018.18340.
36. deSouza NM, Gilderdale DJ, Coutts GA, Puni R, Steiner RE. MRI of fistula-in-ano: a comparison of endoanal coil with external phased array coil techniques. J Comput Assist Tomogr. 1998;22(3):357–63. https://doi.org/10.1097/00004728-199805000-00004.

37. West RL, Zimmerman DDE, Dwarkasing S, et al. Prospective comparison of hydrogen peroxide-enhanced three-dimensional endoanal ultrasonography and endoanal magnetic resonance imaging of perianal fistulas. Dis Colon Rectum. 2003;46(10):1407–15. https://doi.org/10.1007/s10350-004-6758-z.
38. Halligan S, Bartram CI. MR imaging of fistula in ano: are endoanal coils the gold standard? AJR Am J Roentgenol. 1998;171(2):407–12. https://doi.org/10.2214/ajr.171.2.9694465.
39. Buchanan GN, Halligan S, Bartram CI, Williams AB, Tarroni D, Cohen CRG. Clinical examination, endosonography, and MR imaging in preoperative assessment of fistula in ano: comparison with outcome-based reference standard. Radiology. 2004;233(3):674–81. https://doi.org/10.1148/radiol.2333031724.
40. Brillantino A, Iacobellis F, Reginelli A, et al. Preoperative assessment of simple and complex anorectal fistulas: tridimensional endoanal ultrasound? Magnetic resonance? Both? Radiol Med (Torino). 2019;124(5):339–49. https://doi.org/10.1007/s11547-018-0975-3.
41. Cho DY. Endosonographic criteria for an internal opening of fistula-in-ano. Dis Colon Rectum. 1999;42(4):515–8. https://doi.org/10.1007/bf02234179.
42. Ratto C, Grillo E, Parello A, Costamagna G, Doglietto GB. Endoanal ultrasound-guided surgery for anal fistula. Endoscopy. 2005;37(8):722–8. https://doi.org/10.1055/s-2005-870155.
43. Tsankov T, Tankova L, Deredjan H, Kovatchki D. Contrast-enhanced endoanal and transperineal sonography in perianal fistulas. Hepatogastroenterology. 2008;55(81):13–6.
44. Kim Y, Park YJ. Three-dimensional endoanal ultrasonographic assessment of an anal fistula with and without H2O2 enhancement. World J Gastroenterol WJG. 2009;15(38):4810–5. https://doi.org/10.3748/wjg.15.4810.
45. Bleier JI, Moloo H. Current management of cryptoglandular fistula-in-ano. World J Gastroenterol WJG. 2011;17(28):3286–91. https://doi.org/10.3748/wjg.v17.i28.3286.
46. Davis BR, Kasten KR. Anorectal abscess and fistula. In: Steele SR, Hull TL, Read TE, Saclarides TJ, Senagore AJ, Whitlow CB, editors. The ASCRS textbook of colon and rectal surgery. 3rd ed. Cham: Springer International Publishing; 2016. https://doi.org/10.1007/978-3-319-25970-3.
47. Maternini M, Guttadauro A, Ripamonti L, Chiarelli M, Gabrielli F. Malignant transformation of a chronic anorectal fistula. Ann Ital Chir. 2018;7:S2239253X18029109.
48. Garcia-Aguilar J, Belmonte C, Wong WD, Goldberg SM, Madoff RD. Anal fistula surgery. Factors associated with recurrence and incontinence. Dis Colon Rectum. 1996;39(7):723–9. https://doi.org/10.1007/bf02054434.
49. Cheong DM, Nogueras JJ, Wexner SD, Jagelman DG. Anal endosonography for recurrent anal fistulas: image enhancement with hydrogen peroxide. Dis Colon Rectum. 1993;36(12):1158–60. https://doi.org/10.1007/bf02052266.
50. Navarro-Luna A, García-Domingo MI, Rius-Macías J, Marco-Molina C. Ultrasound study of anal fistulas with hydrogen peroxide enhancement. Dis Colon Rectum. 2004;47(1):108–14. https://doi.org/10.1007/s10350-003-0015-8.
51. Buchanan GN, Bartram CI, Williams AB, Halligan S, Cohen CRG. Value of hydrogen peroxide enhancement of three-dimensional endoanal ultrasound in fistula-in-ano. Dis Colon Rectum. 2005;48(1):141–7. https://doi.org/10.1007/s10350-004-0752-3.
52. Abou-Zeid AA. Anal fistula: intraoperative difficulties and unexpected findings. World J Gastroenterol WJG. 2011;17(28):3272–6. https://doi.org/10.3748/wjg.v17.i28.3272.
53. Whiteford MH, Kilkenny J, Hyman N, et al. Practice parameters for the treatment of perianal abscess and fistula-in-ano (revised). Dis Colon Rectum. 2005;48(7):1337–42. https://doi.org/10.1007/s10350-005-0055-3.
54. van Tets WF, Kuijpers HC. Continence disorders after anal fistulotomy. Dis Colon Rectum. 1994;37(12):1194–7. https://doi.org/10.1007/bf02257781.
55. Ho Y-H, Tan M, Leong AFPK, Seow-Choen F. Marsupialization of fistulotomy wounds improves healing: a randomized controlled trial. BJS Br J Surg. 1998;85(1):105–7. https://doi.org/10.1046/j.1365-2168.1998.00529.x.
56. Pescatori M, Ayabaca SM, Cafaro D, Iannello A, Magrini S. Marsupialization of fistulotomy and fistulectomy wounds improves healing and decreases bleeding: a randomized controlled trial. Colorectal Dis. 2006;8(1):11–4. https://doi.org/10.1111/j.1463-1318.2005.00835.x.
57. Kronborg O. To lay open or excise a fistula-in-ano: a randomized trial. Br J Surg. 1985;72(12):970. https://doi.org/10.1002/bjs.1800721211.
58. Belmonte Montes C, Ruiz Galindo GH, Montes Villalobos JL, Decanini TC. Fistulotomy vs fistulectomy. Ultrasonographic evaluation of lesion of the anal sphincter function. Rev Gastroenterol Mex. 1999;64(4):167–70.
59. Browder LK, Sweet S, Kaiser AM. Modified Hanley procedure for management of complex horseshoe fistulae. Tech Coloproctol. 2009;13(4):301–6. https://doi.org/10.1007/s10151-009-0539-6.
60. Raslan SM, Aladwani M, Alsanea N. Evaluation of the cutting seton as a method of treatment for perianal fistula. Ann Saudi Med. 2016;36(3):210–5. https://doi.org/10.5144/0256-4947.2016.210.
61. Kamrava A, Collins JC. A decade of selective use of adjustable cutting seton combined with fistulotomy for anal fistula. Am Surg. 2011;77(10):1377–80.
62. Memon AA, Murtaza G, Azami R, Zafar H, Chawla T, Laghari AA. Treatment of complex fistula in ano with cable-tie seton: a prospective case series. ISRN Surg. 2011;2011. https://doi.org/10.5402/2011/636952.
63. Hammond TM, Knowles CH, Porrett T, Lunniss PJ. The Snug Seton: short and medium term results of slow fistulotomy for idiopathic anal fistulae. Colorectal Dis. 2006;8(4):328–37. https://doi.org/10.1111/j.1463-1318.2005.00926.x.
64. Izadpanah A, Rezazadehkermani M, Hosseiniasl SM, et al. Pulling seton: combination of mechanisms. Adv Biomed Res. 2016;5. https://doi.org/10.4103/2277-9175.180637.
65. Ritchie RD, Sackier JM, Hodde JP. Incontinence rates after cutting seton treatment for anal fistula. Colorectal Dis. 2009;11(6):564–71. https://doi.org/10.1111/j.1463-1318.2008.01713.x.
66. Vial M, Parés D, Pera M, Grande L. Faecal incontinence after seton treatment for anal fistulae with and without surgical division of internal anal sphincter: a systematic review. Colorectal Dis. 2010;12(3):172–8. https://doi.org/10.1111/j.1463-1318.2009.01810.x.
67. Daodu OO, O'Keefe J, Heine JA. Draining setons as definitive management of fistula-in-ano. Dis Colon Rectum. 2018;61(4):499–503. https://doi.org/10.1097/DCR.0000000000001045.
68. Emile SH, Elfeki H, Thabet W, et al. Predictive factors for recurrence of high trans sphincteric anal fistula after placement of seton. J Surg Res. 2017;213:261–8. https://doi.org/10.1016/j.jss.2017.02.053.
69. Kelly ME, Heneghan HM, McDermott FD, et al. The role of loose seton in the management of anal fistula: a multicenter study of 200 patients. Tech Coloproctol. 2014;18(10):915–9. https://doi.org/10.1007/s10151-014-1186-0.
70. Omar W, Alqasaby A, Abdelnaby M, et al. Drainage seton versus external anal sphincter-sparing seton after rerouting of the fistula tract in the treatment of complex anal fistula: a randomized controlled trial. Dis Colon Rectum. 2019;62(8):980–7. https://doi.org/10.1097/DCR.0000000000001416.

71. Hjortrup A, Moesgaard F, Kjaergård J. Fibrin adhesive in the treatment of perineal fistulas. Dis Colon Rectum. 1991;34(9):752–4. https://doi.org/10.1007/bf02051064.
72. Singer M, Cintron J, Nelson R, et al. Treatment of fistulas-in-ano with fibrin sealant in combination with intra-adhesive antibiotics and/or surgical closure of the internal fistula opening. Dis Colon Rectum. 2005;48(4):799–808. https://doi.org/10.1007/s10350-004-0898-z.
73. Buchanan GN, Bartram CI, Phillips RKS, et al. Efficacy of fibrin sealant in the management of complex anal fistula: a prospective trial. Dis Colon Rectum. 2003;46(9):1167–74. https://doi.org/10.1007/s10350-004-6708-9.
74. Adams T, Yang J, Kondylis LA, Kondylis PD. Long-term outlook after successful fibrin glue ablation of cryptoglandular trans sphincteric fistula-in-ano. Dis Colon Rectum. 2008;51(10):1488–90. https://doi.org/10.1007/s10350-008-9405-2.
75. Loungnarath R, Dietz DW, Mutch MG, Birnbaum EH, Kodner IJ, Fleshman JW. Fibrin glue treatment of complex anal fistulas has low success rate. Dis Colon Rectum. 2004;47(4):432–6. https://doi.org/10.1007/s10350-003-0076-8.
76. Cintron JR, Park JJ, Orsay CP, et al. Repair of fistulas-in-ano using fibrin adhesive: long-term follow-up. Dis Colon Rectum. 2000;43(7):944–9; discussion 949–950. https://doi.org/10.1007/bf02237355.
77. Swinscoe MT, Ventakasubramaniam AK, Jayne DG. Fibrin glue for fistula-in-ano: the evidence reviewed. Tech Coloproctol. 2005;9(2):89–94. https://doi.org/10.1007/s10151-005-0204-7.
78. Johnson EK, Gaw JU, Armstrong DN. Efficacy of anal fistula plug vs. fibrin glue in closure of anorectal fistulas. Dis Colon Rectum. 2006;49(3):371–6. https://doi.org/10.1007/s10350-005-0288-1.
79. Limura E, Giordano P. Modern management of anal fistula. World J Gastroenterol WJG. 2015;21(1):12–20. https://doi.org/10.3748/wjg.v21.i1.12.
80. Kleif J, Hagen K, Wille-Jørgensen P. Acceptable results using plug for the treatment of complex anal fistulas. Dan Med Bull. 2011;58(3):A4254.
81. Champagne BJ, O'Connor LM, Ferguson M, Orangio GR, Schertzer ME, Armstrong DN. Efficacy of anal fistula plug in closure of cryptoglandular fistulas: long-term follow-up. Dis Colon Rectum. 2006;49(12):1817–21. https://doi.org/10.1007/s10350-006-0755-3.
82. El-Gazzaz G, Zutshi M, Hull T. A retrospective review of chronic anal fistulae treated by anal fistulae plug. Colorectal Dis. 2010;12(5):442–7. https://doi.org/10.1111/j.1463-1318.2009.01802.x.
83. Kodner IJ, Mazor A, Shemesh EI, Fry RD, Fleshman JW, Birnbaum EH. Endorectal advancement flap repair of rectovaginal and other complicated anorectal fistulas. Surgery. 1993;114(4):682–9; discussion 689–690.
84. Jones IT, Fazio VW, Jagelman DG. The use of transanal rectal advancement flaps in the management of fistulas involving the anorectum. Dis Colon Rectum. 1987;30(12):919–23. https://doi.org/10.1007/bf02554276.
85. Uribe N, Millán M, Minguez M, et al. Clinical and manometric results of endorectal advancement flaps for complex anal fistula. Int J Colorectal Dis. 2007;22(3):259–64. https://doi.org/10.1007/s00384-006-0172-z.
86. Uribe N, Balciscueta Z, Mínguez M, et al. "Core out" or "curettage" in rectal advancement flap for cryptoglandular anal fistula. Int J Colorectal Dis. 2015;30(5):613–9. https://doi.org/10.1007/s00384-015-2133-x.
87. Jarrar A, Church J. Advancement flap repair: a good option for complex anorectal fistulas. Dis Colon Rectum. 2011;54(12):1537–41. https://doi.org/10.1097/DCR.0b013e31822d7ddd.
88. Hall JF, Bordeianou L, Hyman N, et al. Outcomes after operations for anal fistula: results of a prospective, multicenter, regional study. Dis Colon Rectum. 2014;57(11):1304–8. https://doi.org/10.1097/DCR.0000000000000216.
89. Lee C-L, Lu J, Lim T-Z, et al. Long-term outcome following advancement flaps for high anal fistulas in an Asian population: a single institution's experience. Int J Colorectal Dis. 2015;30(3):409–12. https://doi.org/10.1007/s00384-014-2100-y.
90. Mitalas LE, Gosselink MP, Oom DMJ, Zimmerman DDE, Schouten WR. Required length of follow-up after transanal advancement flap repair of high trans sphincteric fistulas. Colorectal Dis. 2009;11(7):726–8. https://doi.org/10.1111/j.1463-1318.2008.01666.x.
91. van Koperen PJ, Wind J, Bemelman WA, Bakx R, Reitsma JB, Slors JFM. Long-term functional outcome and risk factors for recurrence after surgical treatment for low and high perianal fistulas of cryptoglandular origin. Dis Colon Rectum. 2008;51(10):1475–81. https://doi.org/10.1007/s10350-008-9354-9.
92. Balciscueta Z, Uribe N, Balciscueta I, Andreu-Ballester JC, García-Granero E. Rectal advancement flap for the treatment of complex cryptoglandular anal fistulas: a systematic review and meta-analysis. Int J Colorectal Dis. 2017;32(5):599–609. https://doi.org/10.1007/s00384-017-2779-7.
93. Ellis CN, Clark S. Effect of tobacco smoking on advancement flap repair of complex anal fistulas. Dis Colon Rectum. 2007;50(4):459–63. https://doi.org/10.1007/s10350-006-0829-2.
94. Zimmerman DDE, Delemarre JBVM, Gosselink MP, Hop WCJ, Briel JW, Schouten WR. Smoking affects the outcome of transanal mucosal advancement flap repair of trans-sphincteric fistulas. Br J Surg. 2003;90(3):351–4. https://doi.org/10.1002/bjs.4044.
95. Mizrahi N, Wexner SD, Zmora O, et al. Endorectal advancement flap: are there predictors of failure? Dis Colon Rectum. 2002;45(12):1616–21. https://doi.org/10.1097/01.DCR.0000037654.01119.CD.
96. van Onkelen RS, Gosselink MP, Thijsse S, Schouten WR. Predictors of outcome after transanal advancement flap repair for high trans sphincteric fistulas. Dis Colon Rectum. 2014;57(8):1007–11. https://doi.org/10.1097/DCR.0000000000000154.
97. Boenicke L, Karsten E, Zirngibl H, Ambe P. Advancement flap for treatment of complex cryptoglandular anal fistula: prediction of therapy success or failure using anamnestic and clinical parameters. World J Surg. 2017;41(9):2395–400. https://doi.org/10.1007/s00268-017-4006-7.
98. Ozuner G, Hull TL, Cartmill J, Fazio VW. Long-term analysis of the use of transanal rectal advancement flaps for complicated anorectal/vaginal fistulas. Dis Colon Rectum. 1996;39(1):10–4. https://doi.org/10.1007/bf02048261.
99. Yellinek S, Krizzuk D, Moreno Djadou T, Lavy D, Wexner SD. Endorectal advancement flap for complex anal fistula: does flap configuration matter? Colorectal Dis. 2019;21(5):581–7. https://doi.org/10.1111/codi.14564.
100. Stremitzer S, Riss S, Swoboda P, et al. Repeat endorectal advancement flap after flap breakdown and recurrence of fistula-in-ano--is it an option? Colorectal Dis. 2012;14(11):1389–93. https://doi.org/10.1111/j.1463-1318.2012.02990.x.
101. Mitalas LE, Gosselink MP, Zimmerman DDE, Schouten WR. Repeat transanal advancement flap repair: impact on the overall healing rate of high trans sphincteric fistulas and on fecal continence. Dis Colon Rectum. 2007;50(10):1508–11. https://doi.org/10.1007/s10350-007-9015-4.
102. Soltani A, Kaiser AM. Endorectal advancement flap for cryptoglandular or Crohn's fistula-in-ano. Dis Colon Rectum. 2010;53(4):486–95. https://doi.org/10.1007/DCR.0b013e3181ce8b01.
103. van Koperen PJ, Wind J, Bemelman WA, Slors JFM. Fibrin glue and transanal rectal advancement flap for high trans sphincteric perianal fistulas; is there any advantage? Int J Colorectal Dis. 2008;23(7):697–701. https://doi.org/10.1007/s00384-008-0460-x.

104. Göttgens KW, Vening W, van der Hagen SJ, et al. Long-term results of mucosal advancement flap combined with platelet-rich plasma for high cryptoglandular perianal fistulas. Dis Colon Rectum. 2014;57(2):223–7. https://doi.org/10.1097/DCR.0000000000000023.
105. Dubsky PC, Stift A, Friedl J, Teleky B, Herbst F. Endorectal advancement flaps in the treatment of high anal fistula of cryptoglandular origin: full-thickness vs. mucosal-rectum flaps. Dis Colon Rectum. 2008;51(6):852–7. https://doi.org/10.1007/s10350-008-9242-3.
106. Lewis P, Bartolo DC. Treatment of trans-sphincteric fistulae by full thickness anorectal advancement flaps. Br J Surg. 1990;77(10):1187–9. https://doi.org/10.1002/bjs.1800771033.
107. Jun SH, Choi GS. Anocutaneous advancement flap closure of high anal fistulas. Br J Surg. 1999;86(4):490–2. https://doi.org/10.1046/j.1365-2168.1999.01077.x.
108. Amin SN, Tierney GM, Lund JN, Armitage NC. V-Y advancement flap for treatment of fistula-in-ano. Dis Colon Rectum. 2003;46(4):540–3. https://doi.org/10.1007/s10350-004-6596-z.
109. Del Pino A, Nelson RL, Pearl RK, Abcarian H. Island flap anoplasty for treatment of trans sphincteric fistula-in-ano. Dis Colon Rectum. 1996;39(2):224–6. https://doi.org/10.1007/bf02068080.
110. Rojanasakul A, Pattanaarun J, Sahakitrungruang C, Tantiphlachiva K. Total anal sphincter saving technique for fistula-in-ano; the ligation of intersphincteric fistula tract. J Med Assoc Thail Chotmaihet Thangphaet. 2007;90(3):581–6.
111. Malakorn S, Sammour T, Khomvilai S, et al. Ligation of intersphincteric fistula tract for fistula in ano: lessons learned from a decade of experience. Dis Colon Rectum. 2017;60(10):1065–70. https://doi.org/10.1097/DCR.0000000000000880.
112. Hong KD, Kang S, Kalaskar S, Wexner SD. Ligation of intersphincteric fistula tract (LIFT) to treat anal fistula: systematic review and meta-analysis. Tech Coloproctol. 2014;18(8):685–91. https://doi.org/10.1007/s10151-014-1183-3.
113. Sirany A-ME, Nygaard RM, Morken JJ. The ligation of the intersphincteric fistula tract procedure for anal fistula: a mixed bag of results. Dis Colon Rectum. 2015;58(6):604–12. https://doi.org/10.1097/DCR.0000000000000374.
114. Alasari S, Kim NK. Overview of anal fistula and systematic review of ligation of the intersphincteric fistula tract (LIFT). Tech Coloproctol. 2014;18(1):13–22. https://doi.org/10.1007/s10151-013-1050-7.
115. Vergara-Fernandez O, Espino-Urbina LA. Ligation of intersphincteric fistula tract: what is the evidence in a review? World J Gastroenterol. 2013;19(40):6805–13. https://doi.org/10.3748/wjg.v19.i40.6805.
116. Zirak-Schmidt S, Perdawood SK. Management of anal fistula by ligation of the intersphincteric fistula tract - a systematic review. Dan Med J. 2014;61(12):A4977.
117. Liu WY, Aboulian A, Kaji AH, Kumar RR. Long-term results of ligation of intersphincteric fistula tract (LIFT) for fistula-in-ano. Dis Colon Rectum. 2013;56(3):343–7. https://doi.org/10.1097/DCR.0b013e318278164c.
118. Tan K-K, Tan IJ, Lim FS, Koh DC, Tsang CB. The anatomy of failures following the ligation of intersphincteric tract technique for anal fistula: a review of 93 patients over 4 years. Dis Colon Rectum. 2011;54(11):1368–72. https://doi.org/10.1097/DCR.0b013e31822bb55e.
119. van Onkelen RS, Gosselink MP, Schouten WR. Ligation of the intersphincteric fistula tract in low trans sphincteric fistulae: a new technique to avoid fistulotomy. Colorectal Dis. 2013;15(5):587–91. https://doi.org/10.1111/codi.12030.
120. van Onkelen RS, Gosselink MP, Schouten WR. Is it possible to improve the outcome of transanal advancement flap repair for high trans sphincteric fistulas by additional ligation of the intersphincteric fistula tract? Dis Colon Rectum. 2012;55(2):163–6. https://doi.org/10.1097/DCR.0b013e31823c0f74.
121. Madbouly KM, El Shazly W, Abbas KS, Hussein AM. Ligation of intersphincteric fistula tract versus mucosal advancement flap in patients with high trans sphincteric fistula-in-ano: a prospective randomized trial. Dis Colon Rectum. 2014;57(10):1202–8. https://doi.org/10.1097/DCR.0000000000000194.
122. Stellingwerf ME, van Praag EM, Tozer PJ, Bemelman WA, Buskens CJ. Systematic review and meta-analysis of endorectal advancement flap and ligation of the intersphincteric fistula tract for cryptoglandular and Crohn's high perianal fistulas. BJS Open. 2019;3(3):231–41. https://doi.org/10.1002/bjs5.50129.
123. Lau YC, Brown KGM, Cheong J, Byrne C, Lee PJ. LIFT and BioLIFT: a 10-year single-centre experience of treating complex fistula-in-ano with ligation of intersphincteric fistula tract procedure with or without bio-prosthetic reinforcement (BioLIFT). J Gastrointest Surg. 2019. https://doi.org/10.1007/s11605-019-04305-x.
124. Han JG, Wang ZJ, Zheng Y, et al. Ligation of intersphincteric fistula tract vs ligation of the intersphincteric fistula tract plus a bioprosthetic anal fistula plug procedure in patients with trans-sphincteric anal fistula: early results of a multicenter prospective randomized trial. Ann Surg. 2016;264(6):917–22. https://doi.org/10.1097/SLA.0000000000001562.
125. Sirikurnpiboon S, Awapittaya B, Jivapaisarnpong P. Ligation of intersphincteric fistula tract and its modification: results from treatment of complex fistula. World J Gastrointest Surg. 2013;5(4):123–8. https://doi.org/10.4240/wjgs.v5.i4.123.
126. Wilhelm A. A new technique for sphincter-preserving anal fistula repair using a novel radial emitting laser probe. Tech Coloproctol. 2011;15(4):445–9. https://doi.org/10.1007/s10151-011-0726-0.
127. Giamundo P, Geraci M, Tibaldi L, Valente M. Closure of fistula-in-ano with laser--FiLaC™: an effective novel sphincter-saving procedure for complex disease. Colorectal Dis. 2014;16(2):110–5. https://doi.org/10.1111/codi.12440.
128. Oztürk E, Gülcü B. Laser ablation of fistula tract: a sphincter-preserving method for treating fistula-in-ano. Dis Colon Rectum. 2014;57(3):360–4. https://doi.org/10.1097/DCR.0000000000000067.
129. Lauretta A, Falco N, Stocco E, Bellomo R, Infantino A. Anal fistula laser closure: the length of fistula is the Achilles' heel. Tech Coloproctol. 2018;22(12):933–9. https://doi.org/10.1007/s10151-018-1885-z.
130. Giamundo P, Esercizio L, Geraci M, Tibaldi L, Valente M. Fistula-tract laser closure (FiLaC™): long-term results and new operative strategies. Tech Coloproctol. 2015;19(8):449–53. https://doi.org/10.1007/s10151-015-1282-9.
131. Wilhelm A, Fiebig A, Krawczak M. Five years of experience with the FiLaC™ laser for fistula-in-ano management: long-term follow-up from a single institution. Tech Coloproctol. 2017;21(4):269–76. https://doi.org/10.1007/s10151-017-1599-7.
132. Meinero P, Mori L. Video-assisted anal fistula treatment (VAAFT): a novel sphincter-saving procedure for treating complex anal fistulas. Tech Coloproctol. 2011;15(4):417–22. https://doi.org/10.1007/s10151-011-0769-2.
133. Garg P, Singh P. Video-assisted anal fistula treatment (VAAFT) in cryptoglandular fistula-in-ano: a systematic review and proportional meta-analysis. Int J Surg. 2017;46:85–91. https://doi.org/10.1016/j.ijsu.2017.08.582.
134. Emile SH, Elfeki H, Shalaby M, Sakr A. A systematic review and meta-analysis of the efficacy and safety of video-assisted anal fistula treatment (VAAFT). Surg Endosc. 2018;32(4):2084–93. https://doi.org/10.1007/s00464-017-5905-2.
135. Ratto C, Litta F, Donisi L, Parello A. Fistulotomy or fistulectomy and primary sphincteroplasty for anal fistula (FIPS): a system-

atic review. Tech Coloproctol. 2015;19(7):391–400. https://doi.org/10.1007/s10151-015-1323-4.
136. Litta F, Parello A, De Simone V, Grossi U, Orefice R, Ratto C. Fistulotomy and primary sphincteroplasty for anal fistula: long-term data on continence and patient satisfaction. Tech Coloproctol. 2019;23(10):993–1001. https://doi.org/10.1007/s10151-019-02093-9.
137. Ratto C, Litta F, Parello A, Zaccone G, Donisi L, De Simone V. Fistulotomy with end-to-end primary sphincteroplasty for anal fistula: results from a prospective study. Dis Colon Rectum. 2013;56(2):226–33. https://doi.org/10.1097/DCR.0b013e31827aab72.
138. Farag AFA, Elbarmelgi MY, Mostafa M, Mashhour AN. One stage fistulectomy for high anal fistula with reconstruction of anal sphincter without fecal diversion. Asian J Surg. 2019;42(8):792–6. https://doi.org/10.1016/j.asjsur.2018.12.005.
139. Garcia-Olmo D, Herreros D, Pascual I, et al. Expanded adipose-derived stem cells for the treatment of complex perianal fistula: a phase II clinical trial. Dis Colon Rectum. 2009;52(1):79–86. https://doi.org/10.1007/DCR.0b013e3181973487.
140. Herreros MD, Garcia-Arranz M, Guadalajara H, De-La-Quintana P, Garcia-Olmo D, FATT Collaborative Group. Autologous expanded adipose-derived stem cells for the treatment of complex cryptoglandular perianal fistulas: a phase III randomized clinical trial (FATT 1: fistula advanced therapy trial 1) and long-term evaluation. Dis Colon Rectum. 2012;55(7):762–72. https://doi.org/10.1097/DCR.0b013e318255364a.
141. Amor IB, Lainas P, Kassir R, Chenaitia H, Dagher I, Gugenheim J. Treatment of complex recurrent fistula-in-ano by surgery combined to autologous bone marrow-derived mesenchymal stroma cells and platelet-rich plasma injection. Int J Colorectal Dis. 2019;34(10):1795–9. https://doi.org/10.1007/s00384-019-03367-2.
142. de la Portilla F, Muñoz-Cruzado MVD, Maestre MV, et al. Platelet-rich plasma (PRP) versus fibrin glue in cryptogenic fistula-in-ano: a phase III single-center, randomized, double-blind trial. Int J Colorectal Dis. 2019;34(6):1113–9. https://doi.org/10.1007/s00384-019-03290-6.
143. Dozois EJ, Lightner AL, Mathis KL, et al. Early results of a phase I trial using an adipose-derived mesenchymal stem cell-coated fistula plug for the treatment of transsphincteric cryptoglandular fistulas. Dis Colon Rectum. 2019;62(5):615–22. https://doi.org/10.1097/DCR.0000000000001333.
144. Prosst RL, Ehni W. The OTSC® proctology clip system for anorectal fistula closure: the "anal fistula claw": case report. Minim Invasive Ther Allied Technol. 2012;21(4):307–12. https://doi.org/10.3109/13645706.2012.692690.
145. Prosst RL, Joos AK, Ehni W, Bussen D, Herold A. Prospective pilot study of anorectal fistula closure with the OTSC proctology. Colorectal Dis. 2015;17(1):81–6. https://doi.org/10.1111/codi.12762.
146. Prosst RL, Joos AK. Short-term outcomes of a novel endoscopic clipping device for closure of the internal opening in 100 anorectal fistulas. Tech Coloproctol. 2016;20(11):753–8. https://doi.org/10.1007/s10151-016-1537-0.
147. Mascagni D, Pironi D, Grimaldi G, et al. OTSC® Proctology vs. fistulectomy and primary sphincter reconstruction as a treatment for low trans-sphincteric anal fistula in a randomized controlled pilot trial. Minerva Chir. 2019;74(1):1–6. https://doi.org/10.23736/S0026-4733.18.07617-4.
148. Marinello F, Kraft M, Ridaura N, Vallribera F, Espín E. Treatment of fistula-in-ano with OTSC® proctology clip device: short-term results. Cir Esp. 2018;96(6):369–74. https://doi.org/10.1016/j.ciresp.2018.02.003.

Rectourethral and Complex Fistulas: Evaluation and Management

14

Jan Rakinic and W. Brian Perry

Key Concepts

- Rectourethral fistula (RUF) is an uncommon but potentially devastating condition which may significantly impact a patient's quality of life.
- Treatment of prostate cancer is most common etiology.
- Up to 45% of simple RUF may heal with fecal diversion alone.
- Ultimate repair may be quite complex, involving a multispecialty team approach over the course of several procedures.
- Surgical repair with interposition of well-vascularized tissue has good outcomes, though radiation confers higher risk for permanent fecal or urinary diversion.

Introduction

Rectourethral fistula (RUF) is an uncommon but potentially devastating condition which may significantly impact a patient's quality of life. Ultimate repair may be quite complex, involving a multispecialty team approach over the course of several procedures. This chapter discusses acquired rectourethral fistulas in adults; congenital RUFs which are typically found and treated in the neonatal period are not covered in this chapter.

Etiology

The vast majority of acquired RUF are iatrogenic following treatment of prostate cancer, which is more frequently multimodal than in past years. Inflammatory bowel disease and pelvic infections may also cause primary RUF, though far less frequently. Traumatic pelvic injuries from vehicular trauma, other trauma with pelvic fracture, or battle-related instances may also lead to RUF. Kucera reported three soldiers with complex penetrating perineal injuries who required RUF repair in a staged manner over several months, illustrating the complex nature of these injuries and their management [1].

RUF complicates radical retropubic prostatectomy in 1–6% of cases, regardless of whether the procedure was performed open, laparoscopically, or robotically. The prostatic urethra is separated from the anterior rectal wall only by Denonvilliers' fascia and capsule of the prostate, making it vulnerable to damage and fistulization. Many of these RUFs result from unrecognized rectal injury or failed rectal repair at the index operation and typically occur at the vesicourethral anastomosis. The incidence of rectal injury at prostatectomy has been reported from 0.1% to 9% [2, 3]. In one review, 54% of patients who developed an RUF had an overt rectal injury. Other non-ablative risk factors for RUF include age, prior transurethral resection of the prostate, bacterial prostatitis, previous hormonal therapy, and a perineal operative approach [4].

The addition of radiation to the treatment of prostate cancer contributes significantly to RUF formation. Ionizing radiation leads to microvascular injury, mucosal ischemia, and tissue fibrosis. Prior to 1997, less than 4% of RUF had received radiation; from 1998 to 2012, more than 50% involved some form of radiotherapy [5]. When used as stand-alone primary therapy, the rate of RUF for external beam radiotherapy (EBRT) is about 1%, and, for brachytherapy, about 3% [6, 7]. Combining the two modalities increases the risk regardless of the order or isotopes employed. The rate of RUF after newer modalities such as cryosurgery and high-intensity focused ultrasound (HIFU) is around 2% currently [8].

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The incidence and complexity of RUF increase markedly during salvage therapy for a biologically or histologically confirmed prostate cancer recurrence after EBRT. Regardless of the salvage method employed – prostatectomy, cryosurgery, HIFU, or BT – rates of RUF range from 3% to 6% to as high as 60% [9–11]. These RUFs are among the most complex, with large fibrotic connections in a field of poor-quality tissue. Concomitant urethral and rectal strictures as well as sexual and urinary dysfunction are common [5].

Iatrogenic RUF may also occur following low rectal resections for rectal cancer or salvage resections for anal cancer; these patients have often also received pelvic radiation. Secondary rectal cancer following EBRT is a concern, occurring 5–15 years posttreatment [12]. Rectal biopsies, especially anteriorly, may be the final precipitating event in the formation of RUF and should be performed with great care in this situation [13]. Other elective rectal and anal surgeries can rarely lead to RUF, including fistulotomy and stapled hemorrhoidopexy. [14]

Clinical Presentation

RUFs due to a complication of prostatectomy typically present with the first 2–4 weeks after surgery [15]. Radiation-associated RUF can present up to 14 years after the last radiotherapy dose, supporting the role of long-standing tissue damage in these patients. Patients with RUF may present with fecaluria, pneumaturia, and pelvic or bladder pain. The passage of urine per rectum on attempted urination is often reported. Recurrent urinary tract infections are common. In one series, over 80% had preexisting erectile dysfunction [16].

Diagnostic Evaluation

Physical examination will often reveal a defect in the anterior rectal wall 5 to 6 cm from the anal verge. Direct visualization of the tract with cystoscopy and colonoscopy will help establish the location and size of the fistula and the quality of the surrounding tissues and allows for biopsy of any areas suspicious for recurrent malignancy. Voiding cystourethrography or gastrograffin enema may yield additional information. Axial imaging and computed tomography or magnetic resonance imaging are useful adjuncts, especially when other modalities are equivocal [4]. If possible, the functional status of the urinary system should be assessed with a urodynamic evaluation. Those with severe underlying incontinence or voiding dysfunction are unlikely to see significant improvement after RUF repair and may be better served by permanent urinary diversion [17].

Classification

Rivera et al. have proposed this classification system for RUF, based on location, size, and patient history, to help guide treatment decisions and standardize reporting [18]. Not all authors have adopted this schema.

- Stage 1 – <4 cm from the anal verge, nonirradiated
- Stage 2 – >4 cm from the anal verge, nonirradiated
- Stage 3 – <2-cm-diameter fistula regardless of distance in a patient with prior radiation
- Stage 4 – >2-cm-diameter fistula regardless of distance in a patient with prior radiation
- Stage 5 – ischial decubitus fistula

Most other authors separate RUF into simple and complex fistulas. Simple RUFs are small (<1 cm), nonirradiated, with minimal symptoms, no associated sepsis, and no previous repair attempt. Complex RUFs are larger (>1 cm), with other complicating factors that may include previous radiation or cryotherapy, urethral stricture, sepsis, or previous failed repair.

Management of Rectourethral Fistula

Management of rectourethral fistula (RUF) depends on the fistula size and etiology, as well as the familiarity of the managing team with a particular approach. If a neoplasm is the cause of the RUF, management of the neoplasm must take precedence. Similarly, in the setting of Crohn's disease, medical management must be optimized before any attempt is made to intervene on the fistula. Readers are directed to the chapters on these entities for further information.

RUF is best managed with a multidisciplinary team including a colorectal surgeon, a urologist, and often a reconstructive/plastic surgeon. When the initial assessment has been completed, patients fall into one of two groups: simple or complex RUF. It is important to remember that a significant number of patients with RUF may heal without surgical intervention. A spontaneous closure rate of 14–46% was reported after fecal diversion alone [19], and some patients with a small RUF will heal with urethral catheter drainage alone [2]. Figure 14.1 shows an algorithm for assessment and management of RUF [19].

Many RUFs identified following laparoscopic or robotic prostatectomy are classified as simple [2]. Initial manage-

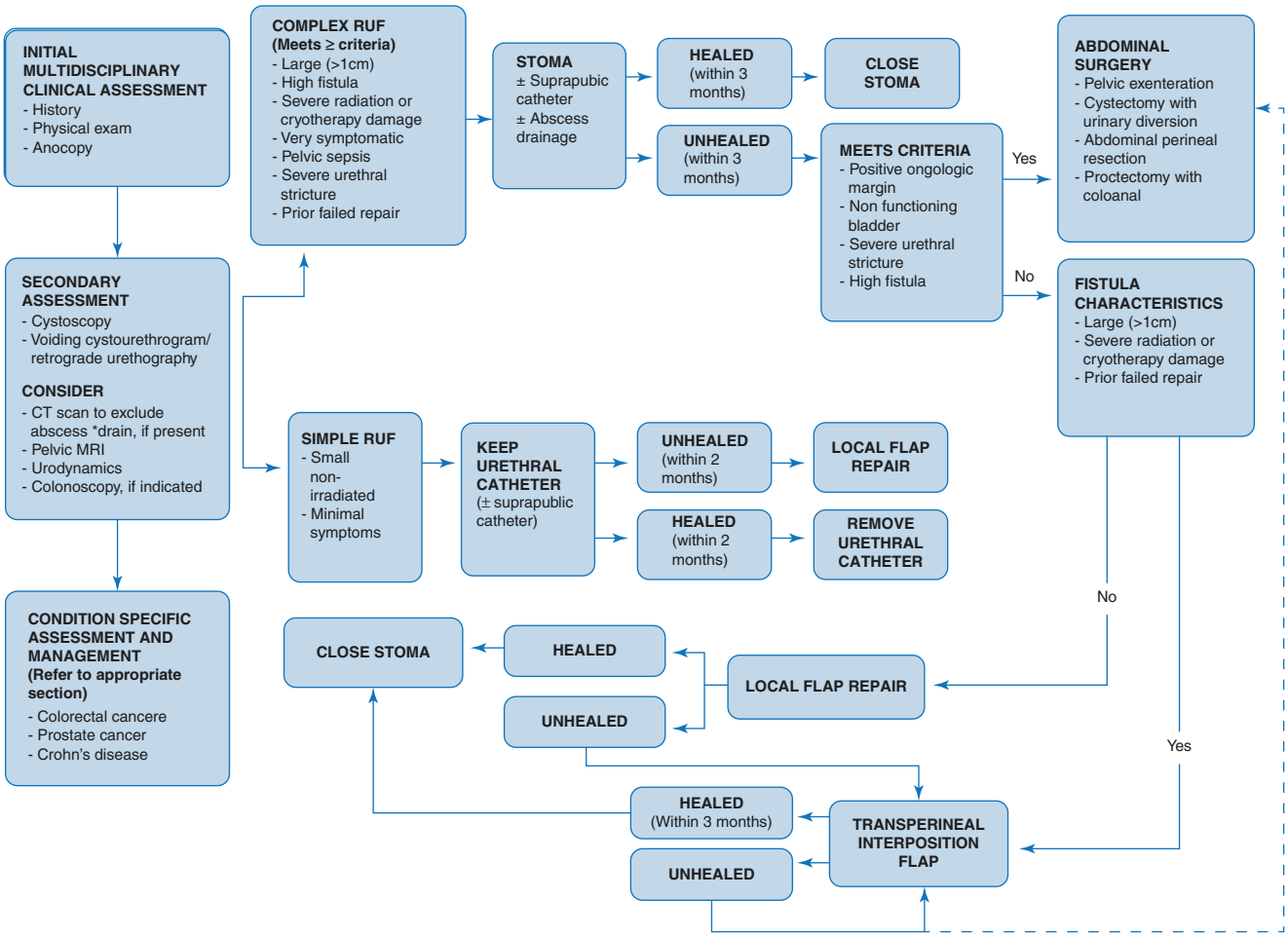

Fig. 14.1 RUF management algorithm. (Reproduced with permission from ASCRS Textbook of Colon and Rectal Surgery, third edition)

ment consists of urinary catheter drainage for 2–3 months. If the fistula heals, the catheter is simply removed. If the fistula has not healed, a local flap repair is indicated. A transanal flap is a good option in this situation, and fecal diversion is not required. If the local flap repair fails to heal, fecal diversion should be done. If the fistula remains unhealed after 2–3 months of fecal diversion, repair should be accomplished by either repeat local flap repair or transperineal repair approach with an interposition flap of gracilis or dartos muscle.

RUFs following external traumatic injury are most often complex [1]. These situations are managed initially with fecal diversion and often suprapubic bladder drainage to minimize fistula symptoms. Abdominopelvic imaging should be obtained to assess for pelvic abscess; if present, drainage is indicated. Most algorithms call for reassessment of the fistula after 3 months of fecal diversion/bladder drainage. Both endoscopic and imaging assessment is recommended, with evaluation of healing from both the rectal and urinary sides. If healing has occurred, the stoma is closed.

If the RUF remains unhealed after fecal diversion, and the patient is a poor operative candidate or refuses further surgery, permanent diversion is an option to manage symptoms. For those patients desiring definitive management, several options exist. For patients with positive oncologic margins after prostatectomy, a nonfunctioning bladder, or other intrapelvic complications, an abdominal approach should be considered. Rectal salvage may be possible in some cases. Otherwise, a transperineal or transanal approach is most commonly employed. A posterior (parasacral or transsphincteric) approach may also be utilized, though this is used less commonly now for reasons that will be discussed. Other techniques, such as puborectalis flap or large endoscopic clip closure, have been described in the literature with small numbers of patients and short follow-up.

Transanal Approach

Transanal repair with an endorectal advancement flap is a good option for a simple RUF. Absence of anal or rectal

stricture is a prerequisite; fecal diversion is not required. The technical details of the flap itself have been aptly described in the chapter on anal fistula (see Chap. 15); TEM platform can also be used to perform the procedure. The flap is outlined and mobilized as usual. The fistula is identified and divided, and the rectal wall is dissected away from the urethra sufficiently to provide exposure. The opening into the urethra is debrided of any granulation tissue. Small fistulas rarely require augmentation of the urethra. Pliable normal tissue such as pararectal fat, if available, can be approximated over the urethral opening of the fistula with interrupted 3–0 absorbable suture; polyglactin (Vicryl) is ideal. Some authors advocate introduction of a biologic mesh into the space between the rectal wall and the urethra; if used, this is parachuted in and secured with further 3–0 absorbable sutures (Fig. 14.2). The endorectal advancement flap is then brought into place and secured with interrupted 3–0 polyglactin sutures. The urethral catheter is maintained for 4–6 weeks before assessing fistula healing.

Transperineal Approach

Transperineal is the preferred approach for RUFs that require interposition of healthy, well-vascularized tissue. Successful closure rates are approximately 90% regardless of radiation or ablative therapy history. This technique allows good exposure for low and mid-rectal RUFs. For low, small RUFs, a

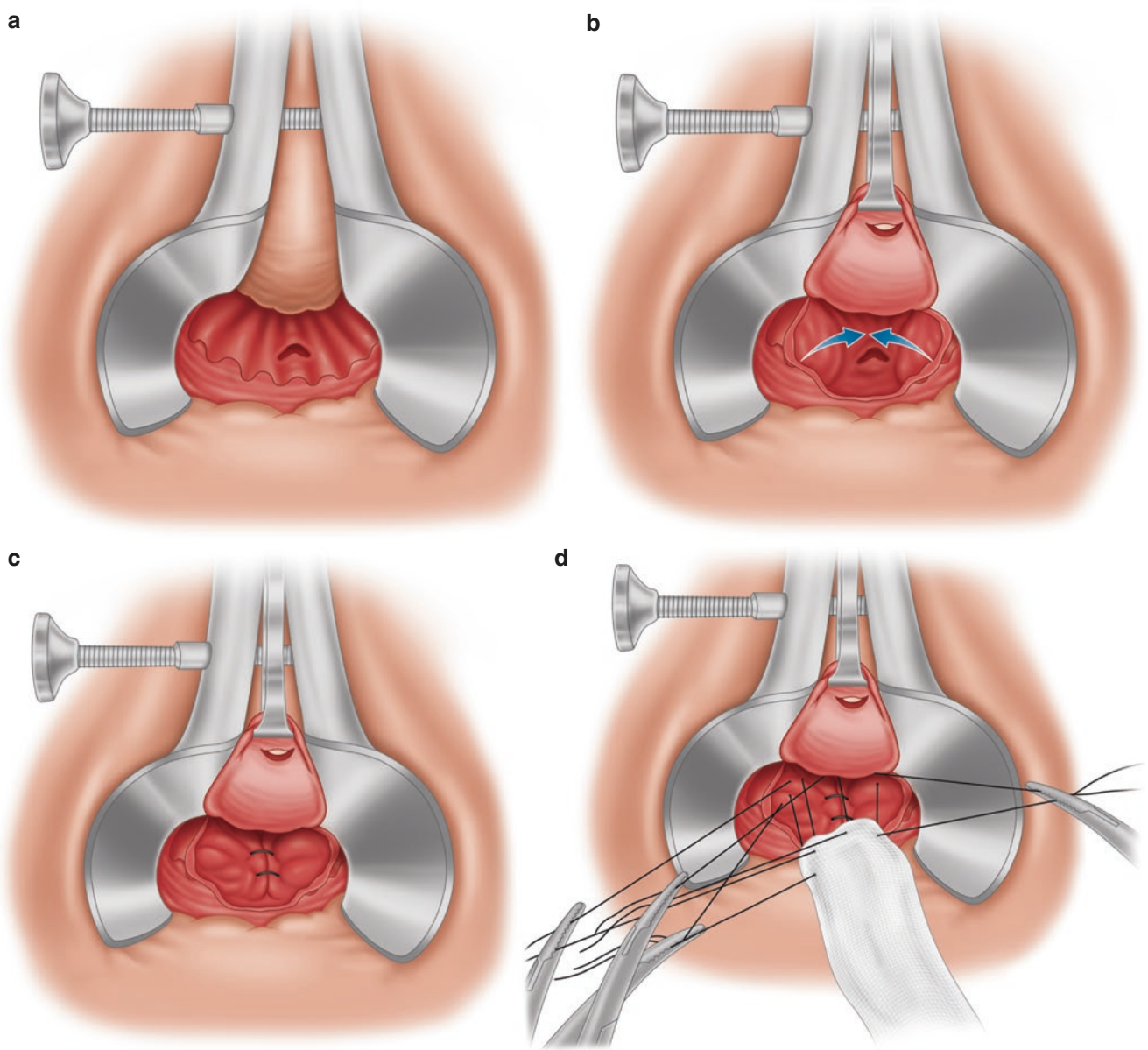

Fig. 14.2 Transanal endorectal advancement flap buttressed with biologic mesh interposition. (Reproduced with permission from ASCRS Textbook of Colon and Rectal Surgery, third edition)

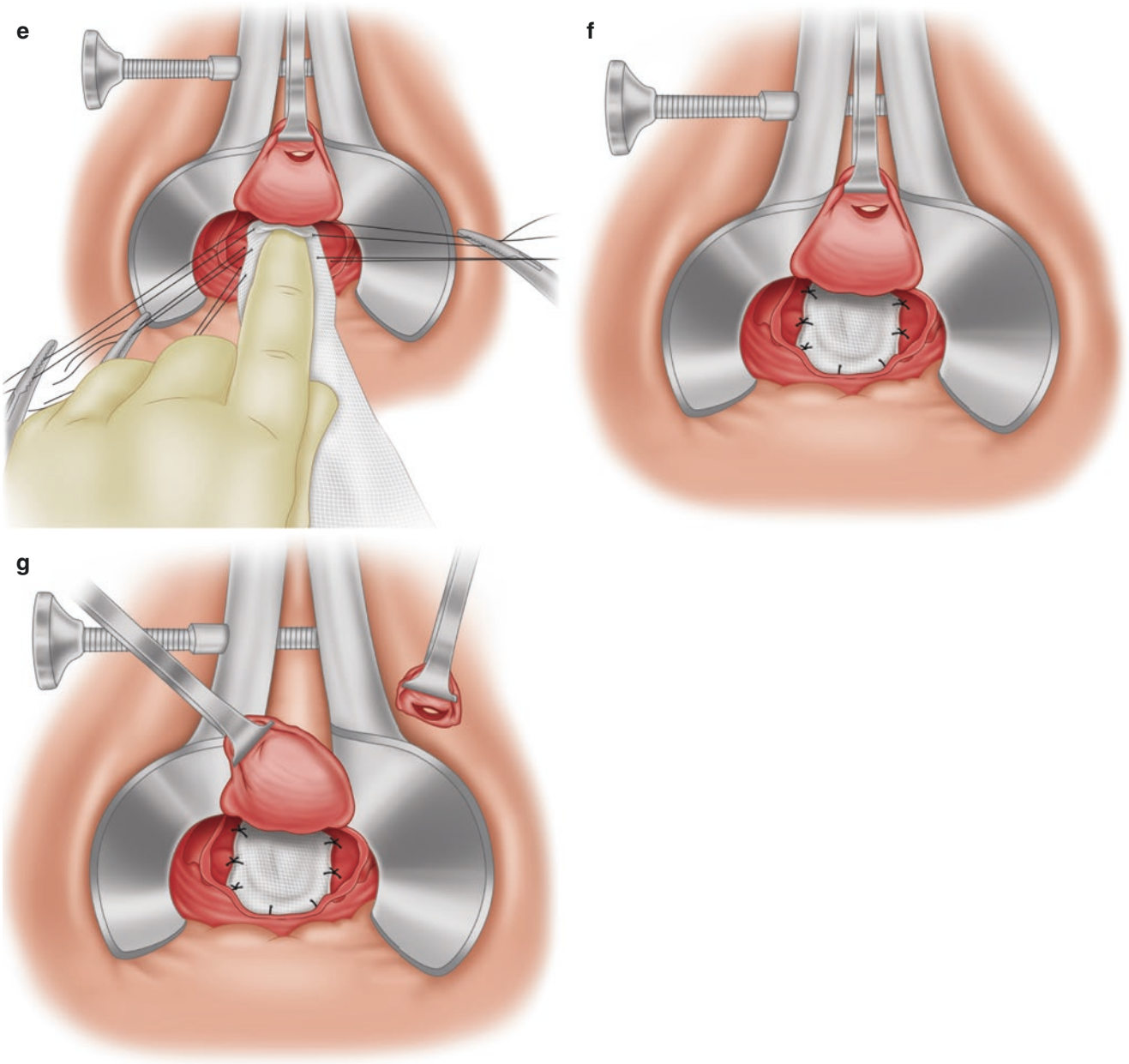

Fig. 14.2 (continued)

dartos muscle flap provides adequate tissue bulk with good reach. The entire operation is performed with the patient in prone jackknife position with excellent exposure. A U-shaped incision is made starting laterally on the perineum, extending onto the posterior scrotum and back up to the opposite side of the perineum (Fig. 14.3). The incision is carried down through the dermis and dartos muscle. This flap is dissected off the testicular tissue, progressively freeing the flap posteriorly to the transperineal edges of the skin incision. Dissection now proceeds into the rectoprostatic plane, anterior to the anal sphincters. The fistula is identified and separated; dissection proceeds another 3–4 cm cephalad. Adequacy of the urethral tissue is assessed; the urethra may be augmented with buccal mucosa [20] or biologic mesh at this point if indicated. Urethral closure is accomplished with 3–0 absorbable suture. Bladder may be imbricated over the closure if possible. Closure of the rectal defect is then performed with 3–0 absorbable suture; horizontal closure is preferred to minimize possible narrowing of the rectal lumen.

The skin is removed from the Dartos flap up to the transperineal incision. The flap is rotated upward into the dissected space. Sutures are placed into the flap edges, and the flap is parachuted into the dissected space with guidance to cover the entire dissection bed. Additional sutures are used to secure the

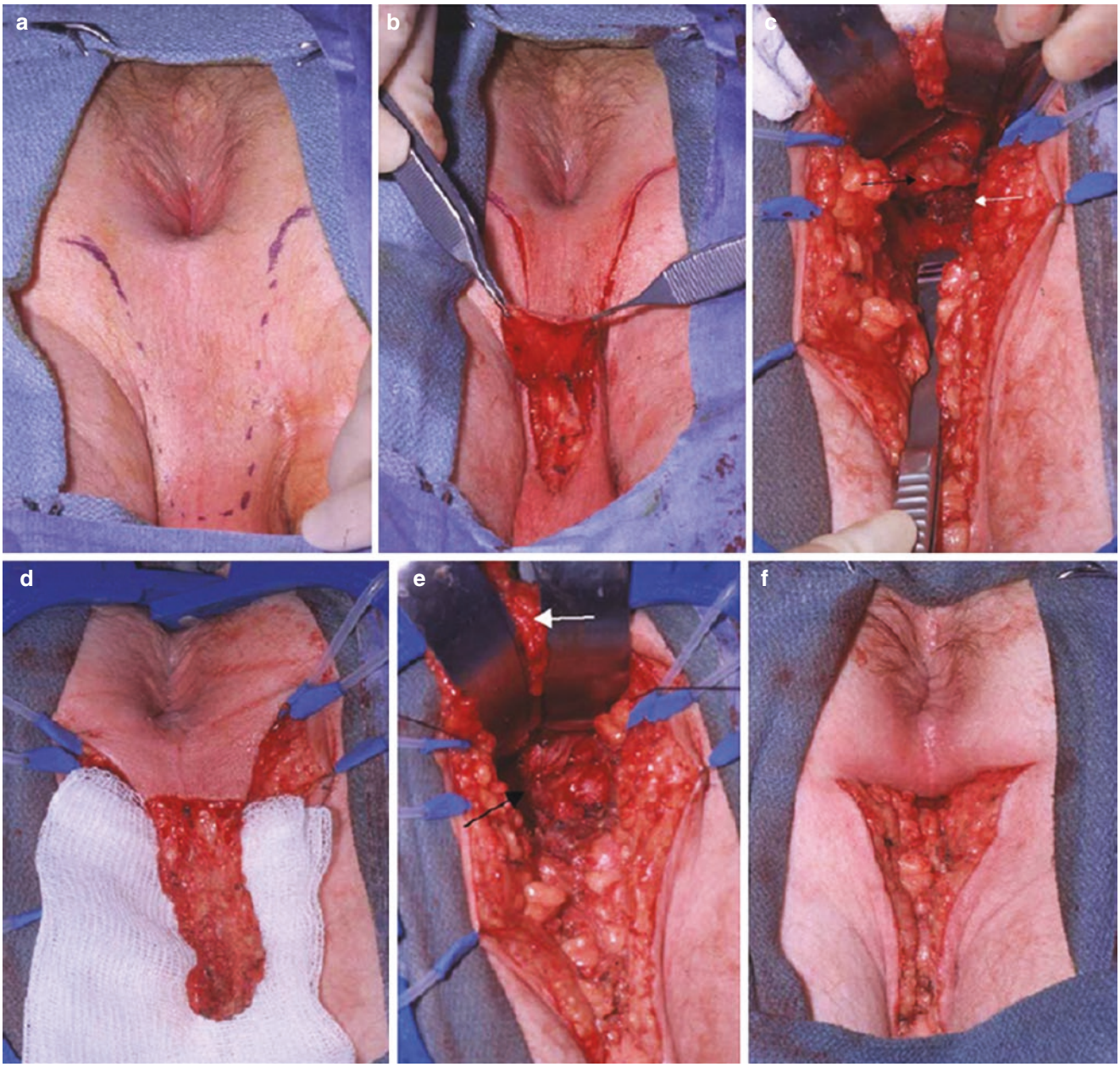

Fig. 14.3 Dartos flap repair. (**a**) Marking of proposed flap. (**b**) Incision has been made; Dartos flap with skin intact is being lifted. (**c**) View of completed repair of fistula openings in rectum and urethra. Solid black arrow points to rectal mucosa. Solid white arrow points to urethral repair. (**d**) Dartos flap denuded of skin in preparation for placement between the fistula repair sites. (**e**) Tacking sutures are placed adjacent to the rectal and urethral repairs; these will be used to parachute the flap deep into the space between the rectum and urethra and secure the flap. (**f**) Completed dartos repair with soft tissue of perineum coapted. (Reproduced with permission from Varma et al. [21]. Copyright © 2007 Wolters Kluwer)

flap as needed. The wound is then closed in layers over a small drain. Varma et al. reported on eight patients managed with a dartos flap. Half had undergone a previous repair attempt; all had fecal diversion and either urethral or suprapubic urinary diversion as well. Six healed without complication. Of the two failed repairs, one had previous radiation for prostate cancer, and the other had a history of HIV [21].

A gracilis flap is preferable for larger, higher, or radiated RUFs. The harvest of the gracilis flap may be performed in lithotomy or prone position, depending on surgeon preference. The gracilis muscle is traced externally about 4 cm posterior to the adductor muscle (Fig. 14.4a). Three small longitudinal incisions are made over the muscle's course; Penrose drains are placed around the muscle at each of these

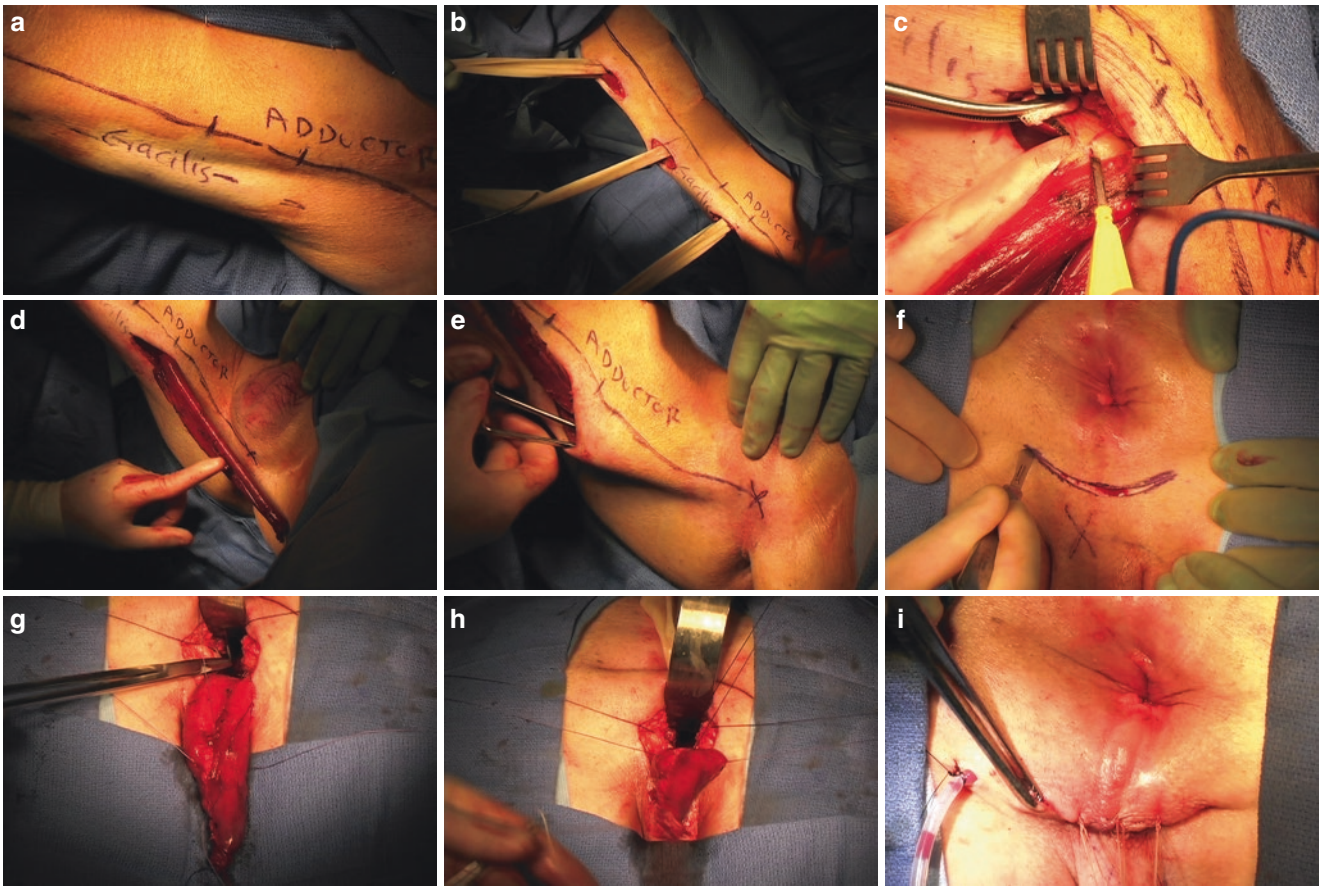

Fig. 14.4 Intraoperative pictures of gracilis muscle interposition flap for transperineal repair of rectourethral fistula. (Special thanks to G.A. Santoro and M.A. Abbas)

sites (Fig. 14.4b). The distal insertion at the medial aspect of the knee is disconnected, and the gracilis muscle is dissected off of surrounding tissue from distal to proximal. Small perforators from the superficial femoral vessels are clipped and divided. Care is taken to preserve the major neurovascular bundle which is typically located within 10 cm of the pubic symphysis (Fig. 14.4c). The freed portion of the muscle is exteriorized through the most proximal skin incision and rotated to ensure adequate length for perineal coverage (Fig. 14.4d). A large clamp is used to create a subcutaneous passage to tunnel the flap from the medial thigh into the *perineum* (Fig. 14.4e). The thigh incisions are closed over a small drain. If performed in lithotomy, the patient is then turned to prone jackknife position. The perineal dissection proceeds as outlined above (Fig. 14.4f). The gracilis flap is parachuted into the dissected perineal space as described above (Fig, 14.4g, h). If the muscle bulk is excessive, it may be carefully tailored. Additional sutures are placed to secure the flap as needed; the incision is closed in layers over a drain (Fig. 14.4i).

Posterior Approach

Posterior approaches have been used for years to manage RUFs. The overall success rate, about 88%, is similar to that of the transperineal approach, but most of the data on posterior approaches has come from nonirradiated patients. The use of these approach has decreased significantly over that last 15 years, in part because fistulas are now generally more complex and due to other issues such as limited exposure, inability to manage urethral stricture or bladder neck issues concurrently, and limited use of interposition flap. The York-Mason technique proceeds by posterior sagittal division of the anal sphincters, levators, and posterior rectal wall, exposing the anterior rectal wall and the fistula. The fistula is divided; urethral and then rectal walls are repaired. The incision is then closed in layers, reapproximating the rectal wall and each muscle layer meticulously. Major complications include rectocutaneous fistula and sphincter compromise. The Kraske technique uses a parasacral incision, coccygeal resection, and division of the anococcygeal ligament to

expose the posterior rectal wall. The posterior rectal wall is opened to provide exposure of the anterior rectal wall and the fistula. Fistula repair proceeds as outlined above. The proctotomy is closed, and the remainder of the incision is closed in layers over a drain.

Posterior approaches are used much less frequently today. Currently, transperineal approach with tissue interposition is favored for most complex RUFs. Patients with RUFs considered too high to approach transperineally, or with other intrapelvic issues, are best managed with a transabdominal or combined approach.

Transabdominal Approach

This approach is best suited for RUF patients with concomitant complex intrapelvic problems which cannot be adequately addressed with a perineal or posterior approach. Patients with positive oncologic margins after prostatectomy require a transabdominal approach for definitive management. Other complex situations such as nonfunctional bladder, strictured urethra, and previous failed repair attempt may also fall into this category. The approach and planned operation are tailored to patient and disease factors. Options include cystectomy and urinary diversion with rectal repair, proctectomy with coloanal anastomosis, abdominoperineal resection, and pelvic exenteration.

Rectal preservation vs. need for proctectomy must be carefully considered; a second attempt at low pelvic dissection and repair carries a much higher risk for failure than the initial attempt. If the rectal tissue is healthy, the fistula is not overly large, and healthy tissue can be obtained for interposition, then repair with omentum or rectus interposition may be a good choice. The urinary procedure should be accomplished first. Primary repair of the rectal wall follows. Omentum is mobilized, preserving the left gastroepiploic artery as a main blood supply. Sutures are placed to parachute the flap into position anterior to the rectal repair. Additional sutures are placed as needed to secure the flap into place. Rectus abdominis flap may also be used, with reconstructive surgery colleagues as co-surgeons.

If the rectal defect is too large for primary closure and tissue quality is poor, proctectomy with or without coloanal anastomosis is indicated. Dissection is carried down to the levator muscles to reach below the fistula. The rectum can be divided with a stapler, and a stapled coloanal anastomosis can be performed. For a very low fistula, mucosectomy or intersphincteric dissection from below may be needed to complete the dissection, with a handsewn anastomosis performed for intestinal continuity. If sphincter preservation is not indicated, the stump of rectum or anal canal can be left in place and an end colostomy performed, avoiding the morbidity of a perineal incision. If, however, there is an indication for a formal abdominoperineal resection, that can be performed.

Other Approaches

Reports of other approaches with small patient numbers appear with some regularity in the surgical literature. Solomon et al. reported on four RUF patients (one with history of radiation, one with Crohn's) in whom a bilateral puborectalis interposition was used via a transperineal repair approach. The puborectalis muscle is exposed bilaterally, mobilized as a 1-cm-wide strip, and released posteriorly at the level of the anorectal junction. The muscle strips are rotated medially and superiorly and overlapped to cover the closed fistula openings. Each muscle flap is stitched into place with absorbable suture; the wound is closed over a drain. All fistulas were healed at median 8 months' follow-up [22]. The smaller size of the available muscle limits this approach somewhat. Anecdotal reports of fibrin glue abound, usually as a low-risk attempt in a poor surgical candidate. Similarly, case reports of fistula cauterization and large over-the-scope-clips also appear; reported follow-up is short. These approaches have not entered the mainstream of RUF management.

Outcomes of RUF Repair

The outcome of RUF repair is variable. There is wide variation in patient populations and techniques, and patient selection clearly plays a role. Nearly all reports are series, with no randomized controlled trials due to the rarity of this problem. The reported overall fistula closure rate after repair is 68–100%. However, closure of intestinal or urinary diversion is significantly less likely in radiated patients.

The transanal approach is safe and effective in small, low (by definition nonradiated) RUFs. Garofalo et al. reported on 12 patients with RUF who underwent rectal advancement flap closure. Primary healing was accomplished in 67% (8/12 patients). Two of the four recurrences underwent a second successful repair for a final success rate of 83% [23].

The transperineal approach with muscle interposition is currently the procedure of choice for complex RUFs which do not have concomitant intrapelvic complications. While good results have been reported using a dartos flap with 75% healing [21], the flap used most commonly is the gracilis muscle. A large systematic review reported postoperative RUF healing in nonradiated and radiated patients at essentially the same rate (89% vs. 90%). However, permanent fecal diversion in radiated patients was 25% compared to 4% in nonradiated patients. Similarly, permanent urinary diversion was 42% in radiated vs. 4% in nonradiated patients. The

initial closure rate with a transperineal approach was 90%; the flap most commonly used was the gracilis [24].

Kaufman et al. reported on a series of 98 patients with RUF who underwent transperineal repair with interposition muscle flap; 49 were nonradiation induced and 49 were radiation or ablation induced. At median follow-up of 14.5 months (range 3–144), 98% of nonradiated RUF were healed after one procedure, compared to 86% of radiated RUF. Gastrointestinal continuity was restored in 94% of nonradiated RUF and 65% of radiated RUF [25].

Tran reported on seven patients, six with radiation history, treated with transperineal fistula repair and gracilis flap interposition (three patients had been previously excluded due to large fistula size). All seven had fecal diversion while five had urinary diversion as well. At 11 months' mean follow-up, all had healed; three had fecal continuity restored, one was awaiting stoma closure, and three had permanent fecal diversion. Five had stress urinary incontinence and two were awaiting artificial urinary sphincter insertion. There was no morbidity related to the gracilis harvest [26]. Hampson et al. reported on 21 patients with RUF; all underwent transperineal repair and all but 1 had a muscle interposition (19 gracilis, 1 of which was bilateral; and 1 rectus flap). Initial success was 95% with mean follow-up of 2.6 years. Thirty-day morbidity was 19%. Fifteen patients were evaluable for long-term telephone follow-up; 53% reported perineal pain, and 43% reported residual problems related to the gracilis harvest [16].

A series from Cleveland Clinic of gracilis flaps employed in a variety of complex fistula repairs included 36 men with RUF, mainly secondary to treatment of prostate cancer. Thirteen of these had undergone previous failed repair attempts. Initial fistula closure rate was 78%, but postoperative complication rate was 47%. Eight patients who failed underwent a subsequent repair attempt which raised the overall healing rate to 97% in this series [27].

It is clear that patient selection leads to improved outcomes. In a series of nine patients with nonradiated RUF, all with a previous failed repair attempt, all were successfully managed with transperineal fistula division and gracilis interposition graft [28]. All but one had fecal continuity restored; none reported fecal dysfunction or difficulty walking related to the gracilis harvest. A small series from India reported outcomes of six patients with RUF resulting from trauma (2), prostatectomy for benign hypertrophy (2), and open radical prostatectomy (2), none with history of radiation. All were managed with transperineal fistula division, buccal augmentation of urethra, rectal repair, and gracilis interposition flap with 100% healing after mean 27 months' follow-up [29].

Outcomes after York-Mason approach for RUF reflect much the same: Adding a muscle interposition improves healing and radiation is associated with poorer outcome [30]. An Italian series of 14 nonradiated patients with RUF managed over 20 years with York-Mason approach reported that all healed successfully with the exception of the single patient with Crohn's who suffered RUF recurrence after 11 years. Eleven (79%) had diverting stomas closed [15].

Dafnis reported on 20 consecutive patients with RUF managed by York-Mason approach between 2002 and 2016. Initial repair was successful in 90% (18 patients), 1 with a dartos interposition; diabetes, smoking, and irradiation history were associated with failure [31]. Van der Doelen et al. reported results of 28 patients who underwent York-Mason repair for RUF between 2008 and 2018. Initial overall success rate was 64%; ultimate overall success rate was 75%. The ultimate success rate in nonirradiated patients was 89%, vs. 50% in radiated. Outcomes after radiation were much improved by use of a gracilis interposition: 100% healing (3/3 patients) with graciloplasty vs. 29% (2/7) without [32].

Conclusion

Adult-acquired RUF is a complex and relatively rare condition. The most common etiology is multimodality management of prostate cancer, though management of rectal cancer and traumatic injury can also result in complex RUF. Population data studies will be required to assess whether the use of multimodality treatment for prostate cancer is related to an increase in the incidence of RUF. Simple RUFs have good outcomes with diversion alone or local flap management without fecal diversion. More complex RUFs require a multidisciplinary approach. Repair of the fistula is most often managed with a transperineal approach utilizing a muscle interposition flap for best outcome. Other complex and recurrent fistulas may also be managed with an algorithm similar to the one proposed here: fistula definition, fecal and urinary diversion as deemed necessary, and repair with interposition of normal, well-vascularized tissue. There are no data to support higher closure rate with fecal diversion; performance is based on surgeon preference and clinical reasoning. Fecal diversion should be considered in large complex RUF with persistent symptoms affecting quality of life and individuals with medical comorbidities that increase risk of infectious complications and the sequelae thereof. Some authors have suggested performance of a diverting loop ileostomy at the time of RUF closure due to its relative ease of performance and closure. Ileostomy also leaves the colon fallow should a more extensive procedure such as proctectomy with low anastomosis be required. Patients who have had radiation continue to experience higher risk of repair failure, as well as higher risk that fecal and urinary diversion will be permanent. It is also important to note that complications related to gracilis harvest, the most common flap used, are not inconsequential.

References

1. Kucera WB, Jezior JR, Duncan JE. Management of post-traumatic rectovesical/rectourethral fistulas: case series of complicated injuries in wounded warriors and review of the literature. Mil Med. 2017;182:e1835–9.
2. Chun L, Abbas MA. Rectourethral fistula following laparoscopic radical prostatectomy. Tech Coloproctol. 2011;15:297–300.
3. Blumberg JM, Lesser T, Tran VQ, Aboseif SR, Bellman GC, Abbas MA. Management of rectal injuries sustained during laparoscopic radical prostatectomy. Urology. 2009;73(1):163–6.
4. Thomas C, Jones J, Jäger W, Hampel C, Thüroff JW, Gillitzer R. Incidence, clinical symptoms and management of rectourethral fistulas after radical prostatectomy. J Urol. 2010;183(2):608–12.
5. Hanna JM, Peterson AC, Mantyh C. Rectourethral fistulas in the cancer survivor. Curr Opin Urol. 2014;24:382–8.
6. Moreira SG Jr, Seigne JD, Ordorica RC, Marcet J, Pow-Sang JM, Lockhart JL. Devastating complications after brachytherapy in the treatment of prostate adenocarcinoma. BJU Int. 2004;93(1):31–5.
7. Huang EH, Pollack A, Levy L, Starkschall G, Dong L, Rosen I, Kuban DA. Late rectal toxicity: dose-volume effects of conformal radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys. 2002;54(5):1314–21.
8. Archer PL, Hodgson DJ, Murphy DG, Cahill DJ. High-intensity focused ultrasound for treating prostate cancer. BJU Int. 2007;99(1):28–32.
9. Ahmed HU, Ishaq A, Zacharakis E, Shaw G, Illing R, Allen C, Kirkham A, Emberton M. Rectal fistulae after salvage high-intensity focused ultrasound for recurrent prostate cancer after combined brachytherapy and external beam radiotherapy. BJU Int. 2009;103(3):321–3.
10. Theodorescu D, Gillenwater JY, Koutrouvelis PG. Prostatourethral-rectal fistula after prostate brachytherapy. Cancer. 2000;89(10):2085–91.
11. Tran A, Wallner K, Merrick G, Seeberger J, Armstrong J, Mueller A, Cavanagh W, Lin D, Butler W. Rectal fistulas after prostate brachytherapy. Int J Radiat Oncol Biol Phys. 2005;63(1):150–4.
12. Baxter NN, Tepper JE, Durham SB, Rothenberger DA, Virnig BA. Increased risk of rectal cancer after prostate radiation: a population-based study. Gastroenterology. 2005;128(4):819–24.
13. Abadir R, Ross G Jr, Weinstein SH. Carcinoma of the prostate treated by pelvic node dissection, iodine-125 seed implant and external irradiation: a study of rectal complications. Clin Radiol. 1984;35(5):359–61.
14. Feo CF, Trompetto M, Chioso PC, Fancellu A, Ginesu GC, Porcu A. Stapled hemorrhoidopexy complicated by rectourethral fistula. Tech Coloproctol. 2016;20(6):425–6.
15. Dal Moro F, Mancini M, Pinto F, Zanovello N, Bassi PF, Pagano F. Successful repair of iatrogenic rectourinary fistulas using the posterior sagittal transrectal approach (York-Mason): 15-year experience. World J Surg. 2006;30(1):107–13.
16. Hampson LA, Muncey W, Sinanan MN, Voelzke BB. Outcomes and quality of life among men after anal sphincter-sparing transperineal rectourethral fistula repair. Urology. 2018;121:175–81.
17. Ghoniem G, Elmissiry M, Weiss E, Langford C, Abdelwahab H, Wexner S. Transperineal repair of complex rectourethral fistula using gracilis muscle flap interposition–can urinary and bowel functions be preserved? J Urol. 2008;179(5):1882–6.
18. Rivera R, Barboglio PG, Hellinger M, Gousse AE. Staging rectourinary fistulas to guide surgical treatment. J Urol. 2007;177(2):586–8.
19. Keller DS, Aboseif SR, Lesser T, Abbas MA, Tsay AT, Abbas MA. Algorithm-based multidisciplinary treatment approach for rectourethral fistula. Int J Color Dis. 2015;30(5):631–8.
20. Vanni AJ, Buckley JC, Zinman LN. Management of surgical and radiation induced rectourethral fistulas with an interposition muscle flap and selective buccal mucosal onlay graft. J Urol. 2010;184(6):2400–4.
21. Varma MG, Wang JY, Garcia-Aguilar J, Shelton AA, McAninch JW, Goldberg SM. Dartos muscle interposition flap for the treatment of rectourethral fistulas. Dis Colon Rectum. 2007;50:1849–55. https://doi.org/10.1007/s10350-007-9032-3.
22. Solomon MJ, Tan K, Bromilow RG, Wong JCH. Bilateral puborectalis interposition repair of rectourethral fistula. Dis Colon Rectum. 2014;57:133–9.
23. Garofalo TE, Delaney CP, Jones SM, Remzi FH, Fazio VW. Rectal acdancement flap repair of rectourethral fistula; a 20-year experience. Dis Colon Rectum. 2003;46(6):762–9. PMID 12794578. https://doi.org/10.1007/s10350-00406654-6.
24. Hechenbleikner EM, Buckley JC, Wick EC. Acquired rectourethral fistula in adults: a systematic review of surgical repair techniques and outcomes. Dis Colon Rectum. 2013;56:374–83.
25. Kaufman DA, Zinman LN, Buckley JC, Marcello P, Browne BM, Vanni AJ. Short and long term complications and outcomes of radiation and surgically induced rectourethral fistula repair with buccal mucosa graft and muscle interposition flap. Urology. 2016;98:170–5.
26. Tran H, Flannigan R, Rapoport D. Transperineal approach to complex rectourinary fistulae. Can Urol Assoc J. 2015;9(11–12):E916–20.
27. Wexner SD, Ruiz DE, Genua J, Nogueras JJ, Weiss EG, Zmora O. Gracilis muscle interposition for the treatment of recto-urethral, rectovaginal, and pouch-vaginal fistulas. Ann Surg. 2008;248(1):39–43.
28. Munoz-Duyos A, Navarro-Luna A, Pardo-Aranda F, Caballero JM, Borrat P, Maristany C, Pando JA, Veloso E. Gracilis muscle interposition for rectourethral fistula after laparoscopic prostatectomy: a prospective evaluation and long-term follow-up. Dis Colon Rectum. 2017;60:393–8.
29. Prabha V, Kadeli V. Repair of recto-urethral fistula with urethral augmentation by buccal mucosal graft and gracilis muscle flap interposition – our experience. Cent European J Urol. 2018;71:121–8.
30. Hanna JM, Turley R, Castleberry A, Hopkins T, Peterson AC, Mantyh C, Migaly J. Surgical management of complex rectourethral fistulas in irradiated and nonirradated patients. Dis Colon Rectum. 2014;57:1105–12.
31. Dafnis G. Transsphincteric repair of rectourethral fistulas: 15 years of experience with the York Mason approach. Int J Urol. 2018;25:290–6.
32. Van der Doelen MJ, van de Putte EE F, Horenblas S, JPFA H. Results of the York Mason procedure with and without concomitant graciloplasty to treat iatrogenic rectourethral fistulas. Eur Urol Focus. 2020;6:762–9. https://doi.org/10.1016/j.euf.2019.07.005.

Rectovaginal Fistula

15

Brooke H. Gurland and Jon D. Vogel

Key Concepts

- Rectovaginal fistula (RVF) may result from benign or malignant disease or iatrogenic causes.
- Diagnostic evaluation of RVF is based on history and examination and may be enhanced by radiological studies.
- Anal sphincter function is a key component in the evaluation and treatment of RVF.
- When infection complicates RVF, it must be resolved prior to definitive treatment of the fistula.
- Asymptomatic or minimally symptomatic RVF may not require intervention.
- RVF due to Crohn's disease may, in some cases, be effectively managed with medical therapy alone.
- Surgical treatment of RVF is influenced by the etiology of the fistula, its location, the integrity of the anal sphincter, and if it is a primary or recurrent fistula.
- In some cases, the use of a well-vascularized soft-tissue flap and/or fecal diversion may be required to effectively manage the RVF.

Rectovaginal fistula is an abnormal connection between the anal canal or rectum and the vagina and most often results from obstetrical injuries or Crohn's disease but may also be due to a variety of other conditions including infection, surgical complications, radiation, or malignancy [1–8].

Rectovaginal fistulas may be classified as "low," with a tract between the distal anal canal (dentate line or below) and the inside of the vaginal fourchette, "high" with a tract connecting the upper vagina (at the level of the cervix) with the rectum, or "middle" for those that lie somewhere between [9]. The terms "anovaginal fistula" and "low rectovaginal fistula" may be used interchangeably. Rectovaginal fistulas may also be classified as "simple" or "complex." Simple rectovaginal fistulas have a low, small-diameter (<2.5 cm) communication between the anal canal and vagina and result from obstetrical injury or infection [10]. "Complex" fistulas involve a higher communication between the rectum and vagina, or a larger opening, or result from radiation, cancer, or complications of pelvic surgical procedures [8, 10, 11].

Flatus and/or stool per vagina, pain, dyspareunia, and local skin and mucosal irritation are the typical symptoms of RVF and range in severity from minimal to severely debilitating. Evaluation of RVF is centered on the history of present illness, past medical and surgical history, and physical examination. Bowel movement frequency, consistency, and the patients' ability to defer defecation and flatus should be assessed. The amount of fistula drainage should also be estimated. In some cases, the use of diagnostic imaging, manometric studies, endoscopy, or examination under anesthesia may be required to adequately define the anatomy of the fistula and the integrity of the anal sphincter complex. When infection complicates a RVF, it should be addressed urgently and prior to attempts to repair the fistula. The definitive treatments of RVF cover a range of interventions from as simple as diet modification to as complex as rectal resection with staged coloanal anastomosis. Between these extremes are other surgical treatments that include endorectal and vaginal advancement flap, anterior overlapping sphincteroplasty, vascularized soft-tissue flaps, low anterior resection of the rectum with colorectal or coloanal anastomosis, and episioproctotomy with reconstruction of the anal sphincter. When choosing the type of surgery to repair a RVF, a variety of factors should be considered and include the severity of symptoms, the general health of the patient, fistula etiology, the integrity of the anal sphincter, the condition of the rectum (e.g., proctitis, stricture), the pliability of the vaginal epithe-

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lium and vaginal length, and if there were previous unsuccessful attempts to repair the fistula [12]. The success of surgical repair is also dependent on these factors, and in many cases, multiple attempts at repair are required [7, 13]. For example, in a retrospective analysis of 125 patients with RVF, who underwent 184 various surgical procedures, only 57% were healed after the initial repair but this increased to 87% after multiple operations [7]. In a more recent review of 79 patients who had surgical treatment(s) of their RVF, 72% were eventually ultimately healed, but this required a mean of 3.6 ± 2.4 (range 1–10) surgical procedures [6]. Aside from surgery, in patients with Crohn's disease-related RVF, Infliximab alone may be sufficient for fistula healing [14].

Etiology of Rectovaginal Fistula

Rectovaginal fistulas may be the result of obstetric injury, Crohn's disease, cryptoglandular infection, a complication of colorectal anastomosis or anorectal surgery, malignancy, or radiation therapy (Table 15.1).

Obstetrical

Obstetrical RVF results from pressure necrosis of the rectovaginal septum that occurs during labor, laceration of the sphincter complex during delivery, or episiotomy [15, 16]. Injuries can be identified at the time of delivery at which point immediate repair should be performed under optimal conditions by a dedicated experienced surgical team [17]. While obstetrical causes have been reported as the most common cause of RVF, the actual contribution of this etiology may be hard to determine [12, 18–20]. For example, in single-center recent studies from the Mayo Clinic [21] and the Cleveland Clinic Florida [7], only 23% and 24% of RVF were caused by obstetrical injury. In a Norwegian population-based study, that included 182 females with enterogenital fistula, 42 (23%) were due to obstetrical injury, and of these, only 24 (13%) were classified as RVF [16].

Crohn's Disease

A 2019 systematic literature review and population-based data analysis indicated a 1% prevalence of rectovaginal fistula among females with Crohn's disease [22]. Similarly, in a longitudinal study of population-based cohort from the Netherlands, including 728 females with CD, the overall cumulative probability of being diagnosed with an RVF at 10 years was 3% [23]. Recent studies indicate that the incidence of RVF has decreased in the biologic era. In the IBD-South Limburg cohort, the cumulative 5-year rectovaginal rate declined from 5.7% in the period 1991–2005 to 1.7% in

Table 15.1 Etiologies and repair options for rectal vaginal fistula

Broad category	Detailed category	Specific etiology	Location	Anal sphincter injury	Procedure options
Childbirth	Prolonged labor	Pressure necrosis of RV septum	Lower third of rectum	No	Transvaginal repair ERAF Transperineal repair
	Obstetric injury	3rd/4th perineal tears Episiotomy		No	Transvaginal repair ERAF
				Yes	Episioproctotomy Transverse perineal repair
Infection	Abscess	Cryptoglandular or Bartholin's cyst abscess	Distal	No	Transvaginal repair ERAF Perineal repair
	Diverticular	Penetrating inflammation	Proximal	No	Sigmoid resection, vaginal repair
Malignancy	Locall advanced Rectal, cervical, or vaginal cancer or radiation induced	Direct extension of tumor into vagina or rectum or chronic tissue damage from radiation		No	Fecal Diversion
					en-bloc resection
					Repair with tissue flap (for radiation-relate fistula only)
Iatrogenic RVF	Low anterior resection Ileoanal pouch anal anastomosis Hysterectomy	Anastomotic complication	Distal	No	Fecal Diversion Redo of anastomosis Flap
			Proximal	No	Redo of anastomosis with tissue interposition
Crohn's disease	Fistulizing perianal Crohn's Disease	Penetrating inflammation	Distal	No	Transvaginal Transperineal
				Yes	Seton Drainage, ERAF, Episioproctotomy, fecal diversion, proctectomy

Key: *ERAF* endorectal advancement flap

the years 2006–2011 [23]. Anal fistula may be the initial manifestation of Crohn's disease or may occur years before or after the diagnosis of proximal luminal disease [24]. The incidence of anal fistula increases with both disease duration and as the luminal disease distribution extends more distally in the GI tract, with the highest incidence in patients with Crohn's proctitis [25, 26]. As with other etiologies of RVF, a first step in their management is to control associated infection ("sepsis") if it is present. In general, this involves some combination of antibiotics, abscess drainage, draining seton(s), and patient-directed self-care with frequent irrigation of the healing wounds. The extent of disease should be assessed via examination of the anus and rectum, with anoproctoscopy, and often requires sedation or general anesthesia to achieve the dual goals of thorough assessment and minimal patient discomfort. The presence of proctitis, anal or rectal stricture, and associated ano-perineal fistula will influence both the course of treatment and prognosis of rectovaginal fistula in this setting. In terms of diagnostic imaging, MRI may be the most useful modality and should be used selectively in cases in which the clinical examination is insufficient [27]. Once any associated infection has been controlled, the next step is to consider if medical and/or surgical treatments are needed. Not all patients with Crohn's RVF require treatment [28]. Like other manifestations of Crohn's disease, the goal of RVF treatment is to control the symptoms of the disease. If the patient is asymptomatic or minimally symptomatic, it may be best to avoid medical and surgical interventions. Alternatively, patients with symptomatic RVF must be offered treatment to alleviate their symptoms.

Infliximab is an anti-TNF antibody that has been proven effective in the treatment of fistulizing perianal Crohn's disease [14]. In a subset analysis of the ACCENT-2, a randomized prospective trial of infliximab versus placebo for the treatment of fistulizing perianal Crohn's disease, among 25 women with RVF who were induced with infliximab, 16 (64%) responded to treatment with at least 50% closure of their RVF tracts. These responders were then randomized to maintenance infliximab or placebo and were assessed every 8 weeks until week 52, at which point 45% and 43% of RVF were closed in the infliximab and placebo groups, respectively [14]. While this study did not show a long-term benefit of infliximab in terms of fistula healing, there was a short-term benefit as the mean duration of RVF closure was longer in the infliximab-treated patients (45 weeks vs. 25 weeks). In a 2016, a systematic review of 16 studies and 137 Crohn's RVF demonstrated that 63% of patients had some response to infliximab and that 38% had a complete response, but did not include data on the long-term results of infliximab treatment in these patients [29]. Thus, with the data available, it may be fair to conclude that infliximab is "worth a try" in patients with Crohn's RVF and that it helps some patients, but it is far from a panacea.

In the not so distant future, fistula healing may be augmented by stem cell injections. There are reports of early promising results with injections of stem cells into rectal vaginal fistula in ten patients with Crohn's disease demonstrating a 60% healing rate [30].

The surgical treatments for Crohn's RVF are the same as those that are used for other causes of RVF and cover a spectrum of complexity that ranges from draining seton insertion to proctectomy with permanent ostomy. Between these extremes lay procedures including endorectal advancement flap, gracilis or bulbocavernosus (Martius) flap, rectal resection with coloanal anastomosis, and others. In comparison with non-Crohn's RVF, the success of surgical treatment is often lower for patients with Crohn's and varies with the specific type of intervention [7, 31]. For example, in a study by Pinto and colleagues from Cleveland Clinic Florida, the overall per-procedure success of surgical interventions for RVF was 78% and 44% for patients with non-Crohn's and Crohn's RVF, respectively [7]. As with non-Crohn's RVF, while the initial attempt at repair is not always successful, the majority will be healed after multiple attempts [7, 13]. A special consideration in the surgical treatment of Crohn's RVF is whether the use of Crohn's medical therapy positively or negatively impacts the success of surgical interventions. This question was evaluated by Narang and colleagues at the Cleveland Clinics, who concluded that recent use of anti-TNF, steroids, or immunomodulatory drugs did not negatively impact RVF healing after surgical repair [32]. Another consideration in patients with Crohn's RVF is the value of a temporary diverting ostomy. As stated by Pinto and colleagues, "The influence of a protective stoma on RVF repair remains controversial" [7]. There is no randomized trial of fecal diversion in RVF repair, and while retrospective studies have had variable results in terms of the benefit of diversion, these studies are limited by selection bias [6, 7, 31]. Therefore, the Cleveland Clinic approach to temporary fecal diversion in RVF repair, with its use in "redo repairs, technically challenging repairs, and suboptimal tissue conditions," seems reasonable [28]. In patients with Crohn's RVF in whom all else fails, the construction of a permanent ostomy may be required for symptom and disease control. Risk factors for permanent fecal diversion in patients with perianal Crohn's disease include complex fistula, anal stenosis, history of rectal resection, fecal incontinence, and the use of a temporary fecal diversion [33–35].

Cryptoglandular

In retrospective studies of the surgical treatment of RVF, anywhere from 2% to 40% of cases are classified as cryptoglandular in origin [8, 10, 21, 36]. Initial treatment in these cases is focused on eradication of sepsis. The use of subse-

quent surgical procedures is determined on an individualized basis with consideration of symptoms, anal sphincter integrity, and the condition of the surrounding soft tissues.

Anastomotic and Other Surgical Complications

Fistulization of a colorectal anastomosis to the vagina has been reported to occur in as many as 10% of women who undergo low anterior resection [3, 37, 38]. When this occurs, fecal diversion is generally recommended as the initial step to facilitate resolution of the acute inflammation and associated infection. In some cases, diversion alone may result in healing. In 2005, Kosugi reported that 6 of 16 (37%) colorectal anastomotic-vaginal fistulas treated with diversion alone healed within a period of 6 months [37]. Persistent fistulas were treated with neo-colorectal anastomosis, endorectal advancement flap, or gluteal-fold flap interposition. Other iatrogenic causes of RVF include rare occurrences after stapled hemorrhoidopexy or stapled transanal rectal resection (STARR) [4].

Radiation Injury

Radiation-related RVF occur after the use of radiation to treat cervical cancer and other pelvic malignancies. In a recent review by Zelga and colleagues, RVF developed anywhere from 5 months to 20 years after radiation treatment with a median interval of 20 months [39]. While in their series, the majority of patients with long-term follow-up were maintained with fecal diversion; other studies have demonstrated high rates of fistula resolution with the use of a bulbocavernosus flap [40, 41] or rectal resection with coloanal anastomosis [42].

Evaluation of Patient with RVF

RVF clinical evaluation begins with a thorough history of the illness: information about the duration of symptoms, the nature and volume of vaginal discharge, number and consistency of day and night bowel movements, the patient's ability to defer defecation and flatus, and if they have experience fecal incontinence. The use of pads to control drainage and the number of pad changes per day may be helpful in quantifying the amount of drainage from the fistula. Inquiries about the presence of urinary symptoms such as pneumaturia or fecaluria are also important and may help uncover the presence of an associated enterovaginal fistula. The patient's past medical, surgical, and childbirth history should be assessed to find clues of the etiology of the fistula and if prior attempts were made to repair the fistula. Awake examination in the surgery clinic is an important step in evaluation of the fistula. Inspection of the anoperineum includes an evaluation of the integrity of the perineal body and if there are scars in this area that resulted from an episiotomy or sphincter laceration repair. Inspection and digital examination of the anorectum and vagina are useful to assess the internal and external anal sphincter and the location and size of the RVF. Vaginoscopy and anoproctoscopy may also be useful to obtain information about the location and size of the fistula and if there is a stricture, proctitis, or other mucosal abnormalities of concern. If sufficient information about the anatomy of the fistula cannot be obtained during awake examination, an exam under sedation or general anesthesia should be considered. The "tampon test," in which the patient inserts a tampon or gauze pad into her vagina, leaves it in place for several hours, and then removes and inspects it for fecal staining, is an occasionally useful test to confirm the presence or absence of a RVF [18]. This test may also be modified and used during awake or sedated examination for the same purpose. This is done by carefully inserting a clean gauze or lap pad into the vagina and then by instilling a dilute Betadine solution into the rectum with a 60 cc syringe or similar instrument. The pad in the vagina is then removed and inspected to see if there is Betadine staining.

Diagnostic imaging is used selectively in the evaluation of RVF to define the trajectory and number of tracts and to determine if there are undrained fluid collections or local pathology. To obtain this information, magnetic resonance imaging (MRI) is the preferred imaging modality [43, 44]. CT imaging may also be used, but limitations in its ability to provide sharp contrasts between pelvic soft tissues make this modality relatively inferior to MRI. Fluoroscopic studies, including rectal contrast enema, are useful to evaluate a colorectal anastomosis for patency or fistula, while vaginography has been shown to have high sensitivity for detection of RVF [45]. Endoluminal ultrasound may also have a role in the evaluation of RVF, particularly for examination of the anal sphincter, but has limits in terms of its readability and limited view of the surrounding anatomy [44, 46]. Endoscopic evaluation of the rectum and colon may be considered in cases in which Crohn's disease or radiation injury is the suspected etiology of the fistula. Consultation with urologist and/or gynecologist may be needed in patients with suspected coexistent rectourethral or enterovesical fistula or in cases in which gynecological interventions are needed. In patients in whom surgery is planned and an ostomy is considered, preoperative site marking and education is advised [47].

Surgical Techniques

There are excellent review articles which describe the surgical techniques for RVF [18, 48]. A distal anovaginal or rectovaginal fistula can be surgically approached through the perineum, vagina, or rectum. For patient with anal sphincter injuries, deficient perineal tissue, or gaping introitus, a perineal approach is preferred (Figs. 15.1 and 15.2). However, if the perineum and sphincters are intact, the fistula can be repaired through the rectum or vagina avoiding the trauma associated with a perineal incision. Traditionally, colorectal surgeons prefer a transanal approach both based on their experience and comfort level with operating in the rectum and the philosophy that focusing the repair on the high-pressure zone of the rectum would lead to better fistula healing. However, no one specific surgical technique has been found to be superior, and fistula healing rates range from 50% to 85% depending on the case series and patient characteristics [1, 49, 50]. There are situations where avoiding anal sphincter stretching with retractors is advantageous, and we recommend that the colorectal surgeon consider transvaginal approaches in appropriate cases.

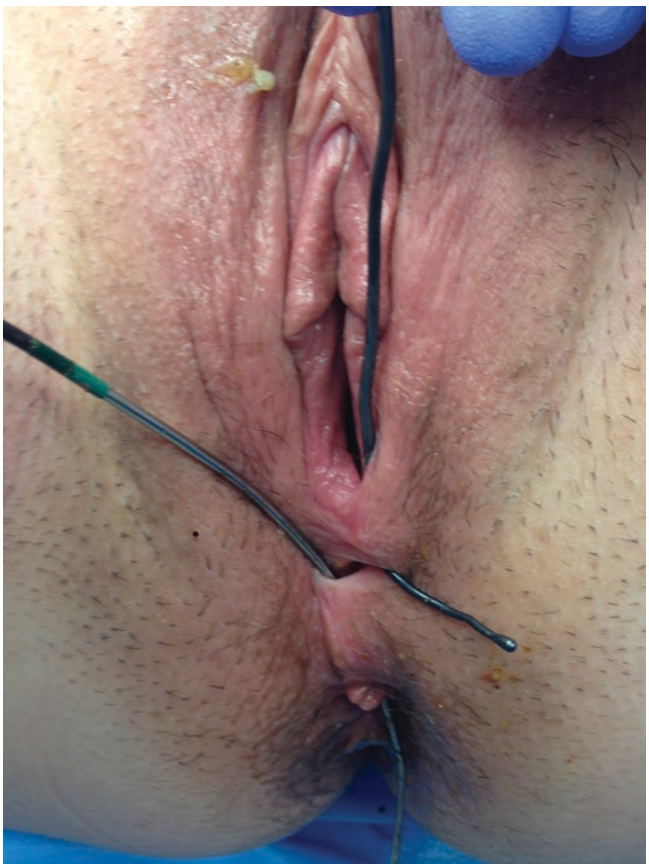

Fig. 15.1 This woman suffered from an obstetric injury several years prior. A probe is placed from the vagina through the perineum and from the perineum to the anus. This woman will benefit from a perineal approach to reconstruct her perineum. Her underlying sphincter injury will be addressed with an overlapping sphincter repair

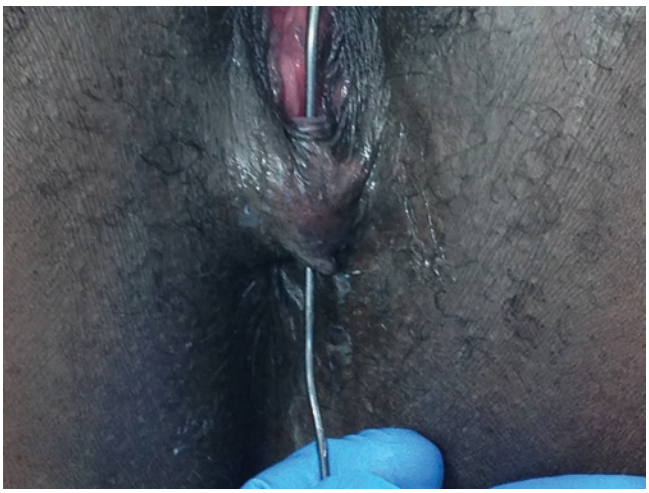

Fig. 15.2 A fistula probe is in place through the vagina and rectum in this very distal fistula. Endoanal ultrasound confirms an anterior anal sphincter defect. A perineal approach with episioproctotomy is performed to repair the fistula and sphincter defect

Preoperative considerations include smoking cessation, weight loss, diabetes control, and improving bowel consistency and frequency. We recommend mechanical bowel preparation, but many authors prefer only an enema clean out and a single dose of perioperative antibiotics. It is important to discuss the possibility of postoperative dyspareunia and changes in bowel function associated with the repair. Postoperative complications may include infection, bleeding, and perineal sepsis. Breakdown of the perineal skin is common, and some surgeons leave the perineal skin loose to heal by secondary intention. The use of drains is surgeon dependent. Vaginal packing at the end of the procedure is selectively inserted as a pressure dressing to help with hemostasis. A short course of oral postoperative antibiotic is used by some surgeons but is not in our practice. Women undergoing local repairs are usually discharged the following morning with no dietary restrictions and on a stool softener or mineral oil to lubricate the stool. Perineal wound care involves a peri-bottle and handheld shower but tub soaking is avoided. Patients are restricted from sexual activity, tampon use, excessive leg stretches, and strenuous activities until their 6-week postsurgical visit.

Perineal Approach

Episioproctotomy

Episioproctotomy is our preferred approach for women with sphincter or perineal injuries (Fig. 15.3) [51]. This technique involves opening the fistula tract and creating a defect similar to a fourth degree perineal laceration. The

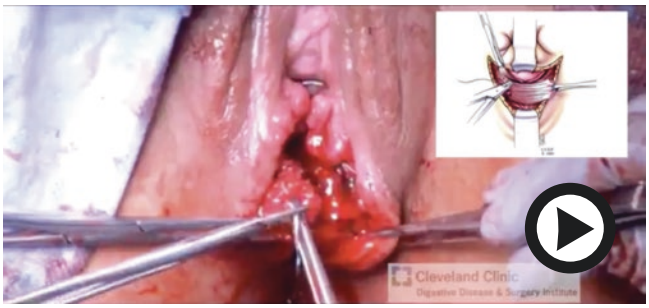

Fig. 15.3 Episioproctotomy. (https://doi.org/10.1007/000-339)

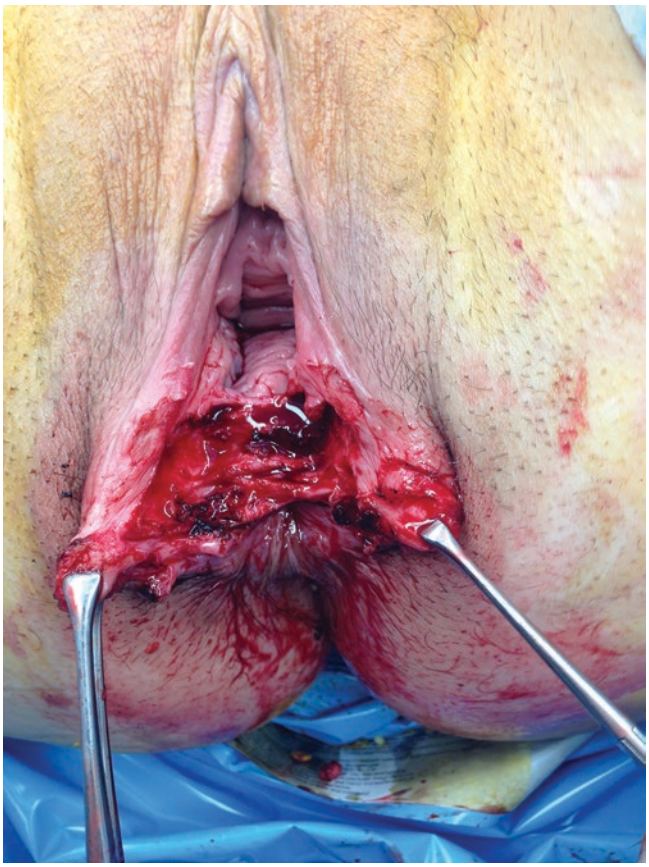

Fig. 15.4 The patient is in lithotomy position and the fistula tract was opened over the probe. Allis clamps hold the edges of the perineal skin. Anterior sphincter scar is visualized in the midline, and the sphincter complex will be mobilized laterally to perform overlapping sphincter repair

patient is positioned in either lithotomy or prone position. A longitudinal incision is made over the probe to create a cloacal defect (Fig. 15.4). Skin flaps are created on either side to mobilize the external sphincter laterally. The fistula tract edges are excised, and complete debridement of the fistula tract or granulation tissue is performed. The plane between the rectum and vagina is mobilized in the rectal vaginal septum until healthy pliable tissue is appreciated. Meticulous hemostasis is obtained throughout the procedure. The rectal mucosa is approximated with running 3-0 absorbable sutures. The levators and rectovaginal septum are approximated, but deep suture bites and unnecessary tension are avoided which can lead to levator spasm and dyspareunia. The sphincter muscles are overlapped and secured with mattress sutures. The vaginal mucosa is approximate with a running locking 3-0 absorbable suture. The hymenal edges are identified and aligned. The transverse perineal muscles are repaired and the perineal skin is loosely approximated. Success rates are reported from 64% to 100% [50].

Transverse Perineal Repair

An incision is made transversely through the perineal body, and dissection is carried out proximal to the fistula tract. The vaginal and rectal wall are mobilized and the fistula tract edges are excised. Closure of the rectal wall is performed in two layers. The rectovaginal septum and levators are approximated in the midline, and the vaginal epithelium is closed (Fig. 15.5).

Transrectal Approaches

Endorectal advancement flap (ERAF) technique has been well described in the literature, and this is by far the most common approach in the colorectal literature. A curvilinear incision is made nearly 180 degrees just distal to the fistula opening in the anal canal. The flap of mucosa, submucosa, and rectal wall is dissected off the rectovaginal septum. Mobilization of the rectal wall is performed proximal to the fistula to avoid tension on the repair. The fistula tract is excised and the opening is closed with absorbable suture. The flap is trimmed and approximated to the distal cut end (Fig. 15.6). The vaginal or perineal openings are left open to heal by secondary intention. Overall success rates are reported at 43–93% [1, 31, 50, 52, 53].

Rectal Sleeve Advancement

Rectal sleeve advancement can be used in select situations when the distal rectum is diseased but the proximal rectum is normal such as with Crohn's disease, radiation, or prior surgical procedure. Starting at the dentate line, a mucosectomy of the mucosa and submucosa is performed, and dissection is taken cephalad proximal until healthy tissue is encountered. Mobilization of the rectum is 90–100%. The healthy proximal rectum is brought down without tension and sutured to the neodentate line. This repair is typically considered in patients where the only other option is total proctocolectomy or permanent fecal diversion [54].

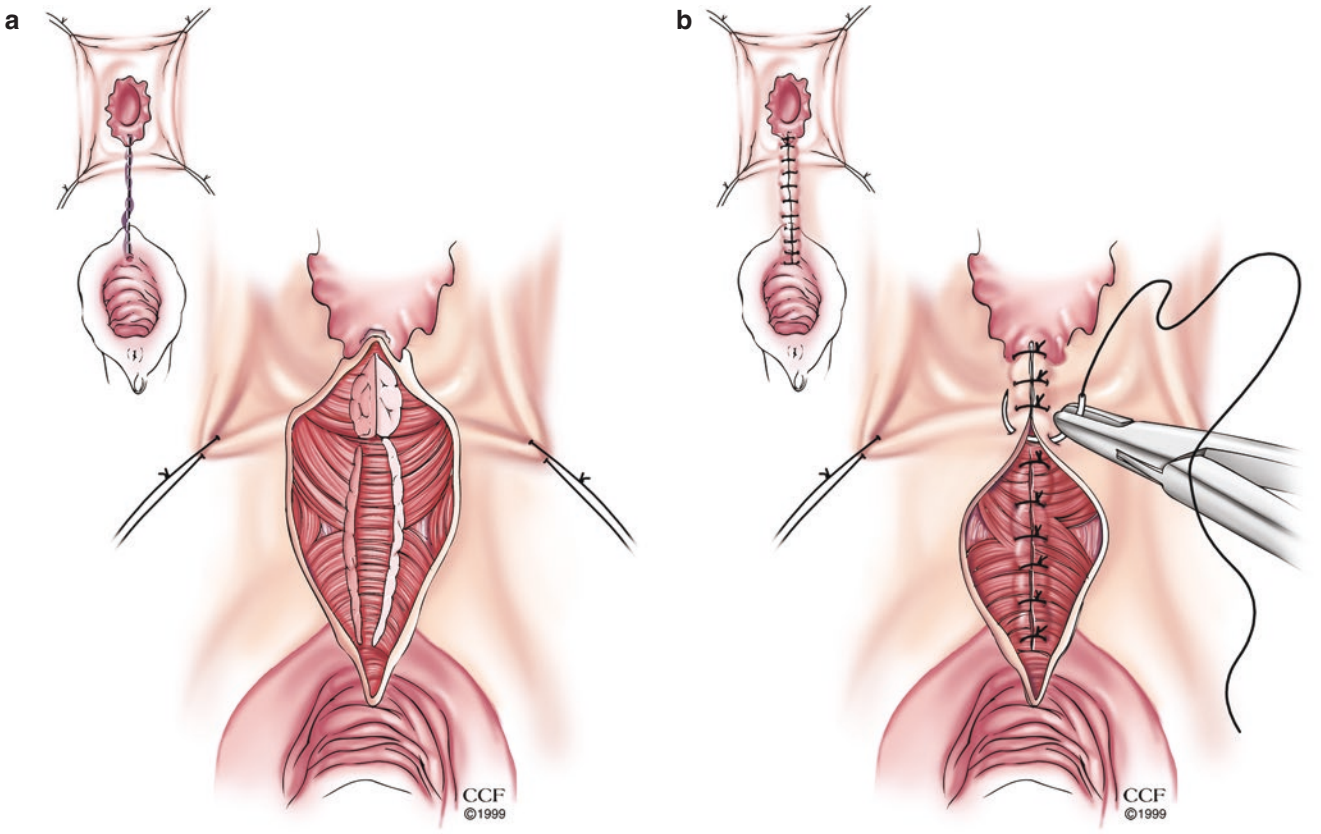

Fig. 15.5 Episioproctotomy. (**a**) flap of mucosa and submucosa is raised. A longitudinal incision is made along the perineum opening the skin, transverse perineal muscles, sphincter complex or midline scar, and rectovaginal septum and vaginal epithelium so that the fistula is completely opened. (**b**) The fistula tract and granulation tissue have been excised and the muscle layers identified and mobilized. A layered repair is performed. (Reprinted with permission, The Cleveland Clinic Center for Medical Art & Photography © 1999–2020. All Rights Reserved)

Vaginal Approach

Transvaginal repair is least commonly reported in the colorectal literature (Fig. 15.7). Advantages of vaginal approach are avoiding extensive mobilization of diseased rectum and avoiding sphincter stretch associated with anal retractors and tissue trauma associated with rectal flaps. Transvaginal approach is favored in patients with active Crohn's disease in the rectum, and studies have shown that endovaginal flaps produce similar outcomes to endorectal flaps [55]. The vaginal advancement flap consists of raising a posterior flap of vagina over the fistula. The rectal and vaginal orifices of the fistula are identified and repaired with absorbable sutures. The levator ani muscles are approximated in the midline. The vaginal flap is advanced over the repair. Alternative techniques are described in the literature involving coring out the fistula tract, freshening up the edges, and creating a flapless transvaginal RVF repair with healing rates of 67% in 15 patients [56].

Tissue Transposition Repairs

For more complicated repairs (such as prior failed attempts, Crohn's, and radiation-induced fistula), tissue transposition with muscle or pedicled adipose has been shown to be effective. The interposition of healthy well-vascularized tissue between the fistula layers increases bulk and obliterates dead space.

The Martius flap is harvested from the labia and includes fat and bulbocavernosus muscle. The posterolateral vascular pedicle which originates from a branch off the internal pudendal artery is preserved, and the flap is rotated and interposed between the cut and closed edges of the RVF (Fig. 15.8). Success rates for this procedure range from 60% to 100% [57, 58].

The gracilis muscle interposition offers a greater bulk of healthy vascularized tissue. The muscle is harvested from the thigh and then passed through a tunnel from the proximal aspects of the thigh toward the perineum and then positioned between the rectum and vagina. Overall success rates are reported from 53% to 92% [59, 60].

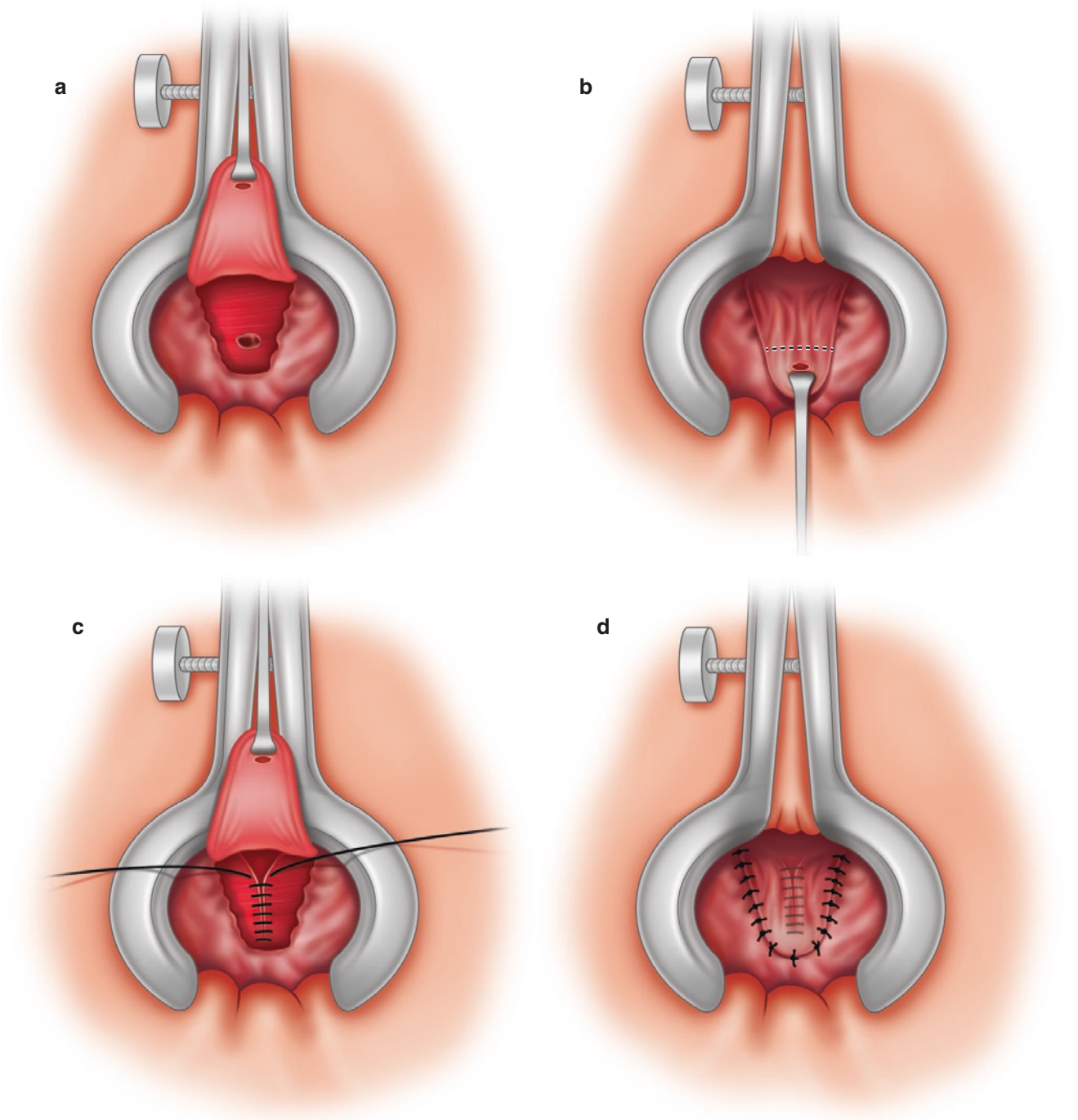

Fig. 15.6 Endorectal advancement flap. (**a**) flap of mucosa and submucosa is raised. (**b**) Adequate mobilization of the flap is performed to avoid tension. (**c**) Approximation of the lateral edges of the muscular layer over the fistula as an additional layer for reinforcement. (**d**) The flap is sutured in place

Bioprosthetic Products

There have been several biosynthetic products developed for fistula tract closure. The biological matrix is thought to promote inflammatory response and scar formation while minimizing dissection and trauma. Success rates are low ranging from 20% to 35%, and the initial enthusiasm for bioprosthetic material has diminished [6].

Abdominal Approaches

For RVF originating in the middle third of the rectum or upper portion of the vaginal or in patients with severely damaged tissue following surgery or radiation, an abdominal approach is warranted. When the patient has a high fistula with healthy tissue anterior dissection between the rectum and vagina, excision of the fistula tract and interposition of omentum have been reported with satisfactory success rates [61]. In most cases, resection of the diseased rectum with anastomosis at a lower level is necessary [62, 63]. This can be performed with two main techniques: an immediate anastomosis or delayed coloanal anastomosis (Turnbull-Cutait). When the distal rectal tissue is normal, an immediate anastomosis is performed. However, the Turnbull-Cutait is reserved for situations when there are other fistulous connections or an internal opening close to the suture line [64]. Circumferential sutures are placed at the neodentate line. The proximal bowel is prolapsed out of the anus and wrapped in gauze for 5–7 days at which point the patient returns to the operating room for amputation of the prolapsed rectum and suture fixation to the neodentate line [65, 66]. Temporary fecal diversion is highly recommended in the setting of abdominal procedures and radiation. Permanent colostomy should be considered in patients with severe radiation injury.

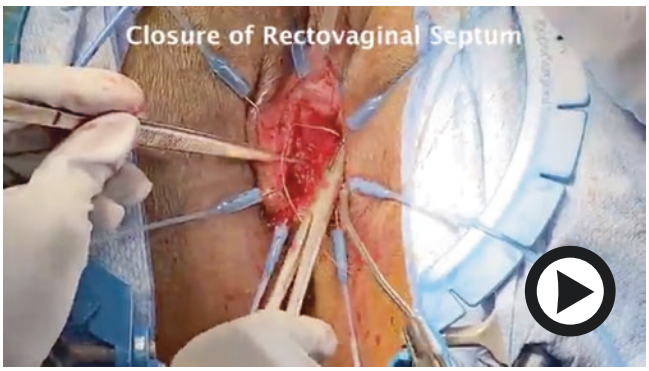

Fig. 15.7 Vaginal approach. (https://doi.org/10.1007/000-338)

Conclusion

RVF are uncommon but can pose a very challenging problem. The colorectal surgeon is likely to encounter the most complicated cases. A thorough understanding of the disease process and surgical options are imperative to provide the patient with the best opportunities for fistula healing.

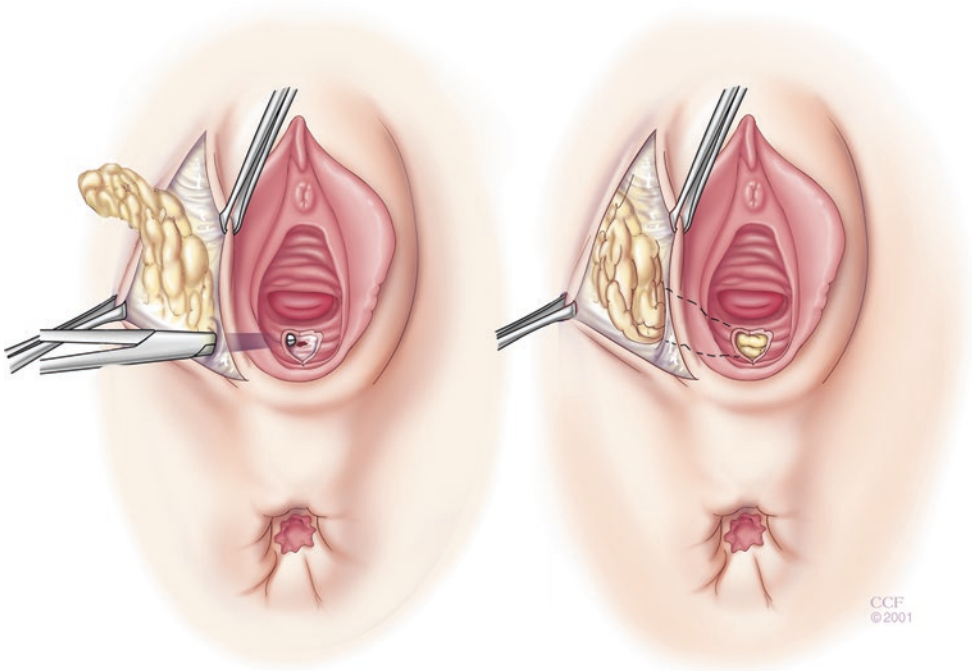

Fig. 15.8 Martius flap. The fat pad is dissected from the labia and then the flap is rotated and interposed between the rectal and vaginal fistula. (Reprinted with permission, The Cleveland Clinic Center for Medical Art & Photography © 1999–2020. All Rights Reserved)

References

1. Ommer A, Herold A, Berg E, Furst A, Schiedeck T, Sailer M. German S3-Guideline: rectovaginal fistula. Ger Med Sci. 2012;10:Doc15.
2. Radcliffe AG, Ritchie JK, Hawley PR, Lennard-Jones JE, Northover JM. Anovaginal and rectovaginal fistulas in Crohn's disease. Dis Colon Rectum. 1988;31(2):94–9.
3. Matthiessen P, Hansson L, Sjodahl R, Rutegard J. Anastomotic-vaginal fistula (AVF) after anterior resection of the rectum for cancer--occurrence and risk factors. Colorectal Dis. 2010;12(4):351–7.
4. Naldini G. Serious unconventional complications of surgery with stapler for haemorrhoidal prolapse and obstructed defaecation because of rectocoele and rectal intussusception. Colorectal Dis. 2011;13(3):323–7.
5. Kasibhatla M, Clough RW, Montana GS, Oleson JR, Light K, Steffey BA, et al. Predictors of severe gastrointestinal toxicity after external beam radiotherapy and interstitial brachytherapy for advanced or recurrent gynecologic malignancies. Int J Radiat Oncol Biol Phys. 2006;65(2):398–403.
6. Corte H, Maggiori L, Treton X, Lefevre JH, Ferron M, Panis Y. Rectovaginal fistula: what is the optimal strategy?: an analysis of 79 patients undergoing 286 procedures. Ann Surg. 2015;262(5):855–60; discussion 60–1.
7. Pinto RA, Peterson TV, Shawki S, Davila GW, Wexner SD. Are there predictors of outcome following rectovaginal fistula repair? Dis Colon Rectum. 2010;53(9):1240–7.
8. Mazier WP, Senagore AJ, Schiesel EC. Operative repair of anovaginal and rectovaginal fistulas. Dis Colon Rectum. 1995;38(1):4–6.
9. Lowry AC. In: Wolf BG, Fleshman FJ, Beck DE, Pemberton JH, Wexner SD, editors. The ASCRS textbook of colon and rectal surgery benign anorectal: rectovaginal fistulas. New York: Springer; 2007.
10. Lowry AC, Thorson AG, Rothenberger DA, Goldberg SM. Repair of simple rectovaginal fistulas. Influence of previous repairs. Dis Colon Rectum. 1988;31(9):676–8.
11. Rahbour G, Gabe SM, Ullah MR, Thomas GP, Al-Hassi HO, Yassin NA, et al. Seven-year experience of enterocutaneous fistula with univariate and multivariate analysis of factors associated with healing: development of a validated scoring system. Colorectal Dis. 2013;15(9):1162–70.
12. Kniery KR, Johnson EK, Steele SR. Operative considerations for rectovaginal fistulas. World J Gastrointest Surg. 2015;7(8):133–7.
13. Halverson AL, Hull TL, Fazio VW, Church J, Hammel J, Floruta C. Repair of recurrent rectovaginal fistulas. Surgery. 2001;130(4):753–7; discussion 7–8.
14. Sands BE, Blank MA, Patel K, van Deventer SJ, Study AI. Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II study. Clin Gastroenterol Hepatol. 2004;2(10):912–20.
15. Brown HW, Wang L, Bunker CH, Lowder JL. Lower reproductive tract fistula repairs in inpatient US women, 1979–2006. Int Urogynecol J. 2012;23(4):403–10.
16. Trovik J, Thornhill HF, Kiserud T. Incidence of obstetric fistula in Norway: a population-based prospective cohort study. Acta Obstet Gynecol Scand. 2016;95(4):405–10.
17. Meister MR, Rosenbloom JI, Lowder JL, Cahill AG. Techniques for repair of obstetric anal sphincter injuries. Obstet Gynecol Surv. 2018;73(1):33–9.
18. Abu Gazala M, Wexner SD. Management of rectovaginal fistulas and patient outcome. Expert Rev Gastroenterol Hepatol. 2017;11(5):461–71.
19. Das B, Snyder M. Rectovaginal fistulae. Clin Colon Rectal Surg. 2016;29(1):50–6.
20. Senatore PJ Jr. Anovaginal fistulae. Surg Clin North Am. 1994;74(6):1361–75.
21. Byrnes JN, Schmitt JJ, Faustich BM, Mara KC, Weaver AL, Chua HK, et al. Outcomes of rectovaginal fistula repair. Female Pelvic Med Reconstr Surg. 2017;23(2):124–30.
22. Schwartz DA, Tagarro I, Carmen Diez M, Sandborn WJ. Prevalence of fistulizing Crohn's disease in the United States: estimate from a systematic literature review attempt and population-based database analysis. Inflamm Bowel Dis. 2019;25(11):1773–9.
23. Gottgens KW, Jeuring SF, Sturkenboom R, Romberg-Camps MJ, Oostenbrug LE, Jonkers DM, et al. Time trends in the epidemiology and outcome of perianal fistulizing Crohn's disease in a population-based cohort. Eur J Gastroenterol Hepatol. 2017;29(5):595–601.
24. Eglinton TW, Barclay ML, Gearry RB, Frizelle FA. The spectrum of perianal Crohn's disease in a population-based cohort. Dis Colon Rectum. 2012;55(7):773–7.
25. Hellers G, Bergstrand O, Ewerth S, Holmstrom B. Occurrence and outcome after primary treatment of anal fistulae in Crohn's disease. Gut. 1980;21(6):525–7.
26. Halme L, Sainio AP. Factors related to frequency, type, and outcome of anal fistulas in Crohn's disease. Dis Colon Rectum. 1995;38(1):55–9.
27. Panes J, Rimola J. Perianal fistulizing Crohn's disease: pathogenesis, diagnosis and therapy. Nat Rev Gastroenterol Hepatol. 2017;14(11):652–64.
28. DeLeon MF, Hull TL. Treatment strategies in Crohn's-associated rectovaginal fistula. Clin Colon Rectal Surg. 2019;32(4):261–7.
29. Kaimakliotis P, Simillis C, Harbord M, Kontovounisios C, Rasheed S, Tekkis PP. A systematic review assessing medical treatment for rectovaginal and enterovesical fistulae in Crohn's disease. J Clin Gastroenterol. 2016;50(9):714–21.
30. Garcia-Arranz M, Herreros MD, Gonzalez-Gomez C, de la Quintana P, Guadalajara H, Georgiev-Hristov T, et al. Treatment of Crohn's-related rectovaginal fistula with allogeneic expanded-adipose derived stem cells: a phase I–IIa clinical trial. Stem Cells Transl Med. 2016;5(11):1441–6.
31. Sonoda T, Hull T, Piedmonte MR, Fazio VW. Outcomes of primary repair of anorectal and rectovaginal fistulas using the endorectal advancement flap. Dis Colon Rectum. 2002;45(12):1622–8.
32. Narang R, Hull T, Perrins S, Garcia JS, Wexner SD. Should immunomodulation therapy alter the surgical management in patients with rectovaginal fistula and Crohn's disease? Dis Colon Rectum. 2016;59(7):670–6.
33. Mueller MH, Geis M, Glatzle J, Kasparek M, Meile T, Jehle EC, et al. Risk of fecal diversion in complicated perianal Crohn's disease. J Gastrointest Surg. 2007;11(4):529–37.
34. Marti-Gallostra M, Myrelid P, Mortensen N, Keshav S, Travis SP, George B. The role of a defunctioning stoma for colonic and perianal Crohn's disease in the biological era. Scand J Gastroenterol. 2017;52(3):251–6.
35. Galandiuk S, Kimberling J, Al-Mishlab TG, Stromberg AJ. Perianal Crohn disease: predictors of need for permanent diversion. Ann Surg. 2005;241(5):796–801; discussion -2.
36. El-Gazzaz G, Hull TL, Mignanelli E, Hammel J, Gurland B, Zutshi M. Obstetric and cryptoglandular rectovaginal fistulas: long-term surgical outcome; quality of life; and sexual function. J Gastrointest Surg. 2010;14(11):1758–63.
37. Kosugi C, Saito N, Kimata Y, Ono M, Sugito M, Ito M, et al. Rectovaginal fistulas after rectal cancer surgery: incidence and operative repair by gluteal-fold flap repair. Surgery. 2005;137(3):329–36.
38. Watanabe J, Ota M, Kawaguchi D, Shima H, Kaida S, Osada S, et al. Incidence and risk factors for rectovaginal fistula after low anterior resection for rectal cancer. Int J Colorectal Dis. 2015;30(12):1659–66.

39. Zelga P, Tchorzewski M, Zelga M, Sobotkowski J, Dziki A. Radiation-induced rectovaginal fistulas in locally advanced gynaecological malignancies-new patients, old problem? Langenbecks Arch Surg. 2017;402(7):1079–88.
40. Aartsen EJ, Sindram IS. Repair of the radiation induced rectovaginal fistulas without or with interposition of the bulbocavernosus muscle (Martius procedure). Eur J Surg Oncol. 1988;14(2):171–7.
41. White AJ, Buchsbaum HJ, Blythe JG, Lifshitz S. Use of the bulbocavernosus muscle (Martius procedure) for repair of radiation-induced rectovaginal fistulas. Obstet Gynecol. 1982;60(1):114–8.
42. Karakayali FY, Tezcaner T, Ozcelik U, Moray G. The outcomes of ultralow anterior resection or an abdominoperineal pull-through resection and coloanal anastomosis for radiation-induced rectovaginal fistula patients. J Gastrointest Surg. 2016;20(5):994–1001.
43. Narayanan P, Nobbenhuis M, Reynolds KM, Sahdev A, Reznek RH, Rockall AG. Fistulas in malignant gynecologic disease: etiology, imaging, and management. Radiographics. 2009;29(4):1073–83.
44. VanBuren WM, Lightner AL, Kim ST, Sheedy SP, Woolever MC, Menias CO, et al. Imaging and surgical management of anorectal vaginal fistulas. Radiographics. 2018;38(5):1385–401.
45. Giordano P, Drew PJ, Taylor D, Duthie G, Lee PW, Monson JR. Vaginography--investigation of choice for clinically suspected vaginal fistulas. Dis Colon Rectum. 1996;39(5):568–72.
46. Stoker J, Rociu E, Schouten WR, Lameris JS. Anovaginal and rectovaginal fistulas: endoluminal sonography versus endoluminal MR imaging. AJR Am J Roentgenol. 2002;178(3):737–41.
47. Burch J. Research and expert opinion on siting a stoma: a review of the literature. Br J Nurs. 2018;27(16):S4–S12.
48. Valente MA, Hull TL. Contemporary surgical management of rectovaginal fistula in Crohn's disease. World J Gastrointest Pathophysiol. 2014;5(4):487–95.
49. Athanasiadis S, Yazigi R, Kohler A, Helmes C. Recovery rates and functional results after repair for rectovaginal fistula in Crohn's disease: a comparison of different techniques. Int J Colorectal Dis. 2007;22(9):1051–60.
50. Gottgens KW, Smeets RR, Stassen LP, Beets G, Breukink SO. The disappointing quality of published studies on operative techniques for rectovaginal fistulas: a blueprint for a prospective multi-institutional study. Dis Colon Rectum. 2014;57(7):888–98.
51. Hull TL, El-Gazzaz G, Gurland B, Church J, Zutshi M. Surgeons should not hesitate to perform episioproctotomy for rectovaginal fistula secondary to cryptoglandular or obstetrical origin. Dis Colon Rectum. 2011;54(1):54–9.
52. Jarrar A, Church J. Advancement flap repair: a good option for complex anorectal fistulas. Dis Colon Rectum. 2011;54(12):1537–41.
53. Kodner IJ, Mazor A, Shemesh EI, Fry RD, Fleshman JW, Birnbaum EH. Endorectal advancement flap repair of rectovaginal and other complicated anorectal fistulas. Surgery. 1993;114(4):682–9; discussion 9–90.
54. Marchesa P, Hull TL, Fazio VW. Advancement sleeve flaps for treatment of severe perianal Crohn's disease. Br J Surg. 1998;85(12):1695–8.
55. Ruffolo C, Scarpa M, Bassi N, Angriman I. A systematic review on advancement flaps for rectovaginal fistula in Crohn's disease: transrectal vs transvaginal approach. Colorectal Dis. 2010;12(12):1183–91.
56. Bhome R, Monga A, Nugent KP. A transvaginal approach to rectovaginal fistulae for the colorectal surgeon: technical notes and case series. Tech Coloproctol. 2018;22(4):305–11.
57. Pitel S, Lefevre JH, Parc Y, Chafai N, Shields C, Tiret E. Martius advancement flap for low rectovaginal fistula: short- and long-term results. Colorectal Dis. 2011;13(6):e112–5.
58. Songne K, Scotte M, Lubrano J, Huet E, Lefebure B, Surlemont Y, et al. Treatment of anovaginal or rectovaginal fistulas with modified Martius graft. Colorectal Dis. 2007;9(7):653–6.
59. Wexner SD, Ruiz DE, Genua J, Nogueras JJ, Weiss EG, Zmora O. Gracilis muscle interposition for the treatment of rectourethral, rectovaginal, and pouch-vaginal fistulas: results in 53 patients. Ann Surg. 2008;248(1):39–43.
60. Furst A, Schmidbauer C, Swol-Ben J, Iesalnieks I, Schwandner O, Agha A. Gracilis transposition for repair of recurrent anovaginal and rectovaginal fistulas in Crohn's disease. Int J Colorectal Dis. 2008;23(4):349–53.
61. van der Hagen SJ, Soeters PB, Baeten CG, van Gemert WG. Laparoscopic fistula excision and omentoplasty for high rectovaginal fistulas: a prospective study of 40 patients. Int J Colorectal Dis. 2011;26(11):1463–7.
62. Cooke SA, Wellsted MD. The radiation-damaged rectum: resection with coloanal anastomosis using the endoanal technique. World J Surg. 1986;10(2):220–7.
63. Schouten WR, Oom DM. Rectal sleeve advancement for the treatment of persistent rectovaginal fistulas. Tech Coloproctol. 2009;13(4):289–94.
64. Cutait DE, Figliolini FJ. A new method of colorectal anastomosis in abdominoperineal resection. Dis Colon Rectum. 1961;4:335–42.
65. Cutait DE, Cutait R, Ioshimoto M, Hyppolito da Silva J, Manzione A. Abdominoperineal endoanal pull-through resection. A comparative study between immediate and delayed colorectal anastomosis. Dis Colon Rectum. 1985;28(5):294–9.
66. Kirwan WO, Turnbull RB Jr, Fazio VW, Weakley FL. Pullthrough operation with delayed anastomosis for rectal cancer. Br J Surg. 1978;65(10):695–8.

Pilonidal Disease and Hidradenitis Suppurativa

16

Anuradha R. Bhama and Bradley R. Davis

Key Concepts

- Pilonidal disease is an acquired chronic, infectious disease typically of the natal cleft with an unknown etiology, thought to be due to a combination of environmental and patient-specific factors.
- The treatment for pilonidal disease should not result in worsening of quality of life than the disease itself. Incision and drainage for acute infections is mandatory, but further surgical treatment should be individualized.
- Several operative strategies exist for the treatment of pilonidal disease; surgeons should be familiar with the various options available, though no single option has proven superior.
- Wound care following pilonidal excision can have a major impact on quality of life and several nonoperative treatment strategies exist.
- Hidradenitis suppurativa (HS) is a chronic, relapsing, inflammatory skin condition that typically occurs after puberty. The primary clinical presentation is painful inflamed nodules in the apocrine gland-bearing regions that progress to abscesses, sinus tracts, and scarring.
- The overall disease burden is disproportionate to the estimated prevalence, and patients with HS not seen and evaluated by dermatologists and surgeons may not get timely and appropriate treatment.
- Therapy is initially medical and consists of antibiotics both orally and topically as well as immune modulators to manage the chronic inflammation.
- Surgery is an important treatment for both acute abscess formation and painful scarring and deformity. Excision with primary closure and skin grafting can result in cure for patients with recalcitrant disease.

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Pilonidal Disease

Introduction

Pilonidal disease is a chronic, suppurative condition, typically of the sacrococcygeal natal cleft, that can present from quiescent and asymptomatic disease to an active and purulent infection. Clinical descriptions date as far back as the 1850s, yet this disease process continues to challenge clinicians today. The ideal treatment for this condition remains a dilemma, and classic techniques are still frequently utilized for treatment while newer techniques are explored. Pilonidal disease can result in significant quality of life impairment for the patient, but treatments for the disease can be equally frustrating, not infrequently resulting in chronic open wounds requiring extensive wound care with prolonged healing periods. When caring for patients with pilonidal disease, it is important to remember that the treatment of the disease should not be more debilitating than the disease itself.

The terms "pilonidal cyst," "abscess," "sinus," and "disease" are often used interchangeably. In the setting of an infection of the pilonidal sinus or cyst, the term "abscess" is most appropriate. In general, this spectrum of pilonidal conditions can be referred to as "pilonidal disease." There is a multitude of nonsurgical and surgical treatment options available for pilonidal disease that can be employed at various stages of disease severity. The plethora of literature compares procedures, with variable success and recurrence rates where no single procedure outshines the others. As such, it is important to have an understanding of the assorted options available to patients during any stage of their disease process, from the initial stage of diagnosis to recurrent disease several years after definitive surgical treatment.

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Epidemiology and Etiology

The true incidence of pilonidal disease is unknown, as it relies on patient-reported symptoms and patients may not always seek treatment, especially in the case of relatively quiescent disease. Pilonidal disease can also occur in other anatomic locations besides the natal cleft, such as the interdigital web spaces of hair dressers or dog groomers and even the umbilicus [1–7]. It is estimated that approximately 70,000 cases of natal cleft pilonidal disease occur per year [8]. Traditionally, male sex was associated with higher risk of pilonidal disease; however, data suggests that this disease affects females equally, with up to 55% of female patients in some studies [9–11]. Pilonidal disease was once termed "jeep disease" due to the high incidence during World War II in jeep drivers, with an underlying theory that prolonged sitting in vehicles was the cause in those patients [12]. Other causative risk factors include obesity, hirsutism, poor hygiene, long periods of sitting/driving, excessive sweating, deep natal cleft anatomy, and family history [9, 11, 13–15].

The underlying etiology of pilonidal disease remains unknown, though there are several working theories. While the true underlying etiology may never be elucidated, the main controversy is whether pilonidal disease is inherited or acquired. Previously, pilonidal disease was thought to be due to an inherited, congenital malunion of the dorsal midline and treatment centered around removal of all embryologic remnants [16, 17]. Now, the leading hypothesis is that it is an acquired condition occurring in the natural environment of the natal cleft, which is one of warmth, repeated friction, and moisture. The underlying theory is that this environment, combined with an inciting trauma to the skin and surrounding hair follicles, results in a granulomatous foreign body reaction, leading to the formation of inactive pilonidal sinuses or active infections.

Diagnosis

Patients presenting with pilonidal disease can have a range of symptoms. Those with asymptomatic pilonidal disease may be completely oblivious to the presence of the sinuses. Patients typically become aware of the presence of the disease upon the development of an active infection, typically reporting pain and drainage. Frequently they may mistakenly report rectal bleeding and assume a diagnosis of hemorrhoids; however, these episodes of bleeding do not relate to bowel movements and occur spontaneously. Patients may also be referred with a suspected diagnosis of anal fistula, which rarely track to the natal cleft and can be typically ruled out on physical exam. Making the diagnosis of pilonidal disease is fairly straightforward, and the true diagnosis is evident upon physical exam of the natal cleft.

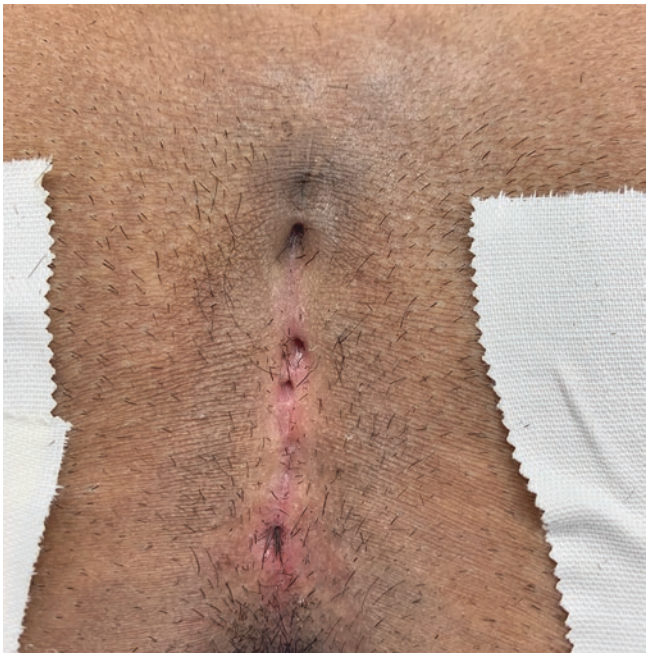

Fig. 16.1 Example of pilonidal disease. Note there are several pits present in the midline of the natal cleft

Physical exam will reveal one or several pits located in the midline of the natal cleft almost always contaminated by debris and hair (Fig. 16.1). The entire natal cleft must be examined after removing the debris and excess free hair. This may demonstrate tufts of hair coming from the pilonidal pits with associated drainage. The hair can be removed from the pits using a hemostat, which may cause some minor bleeding. In the setting of an acute abscess, there will be a raised area of erythema, fluctuance, induration, and tenderness, which is typically located just lateral to the midline. They can also be located quite some distance from the nearest pilonidal pit, but the underlying abscess cavity will communicate with a nearby pit (Fig. 16.2). The pits typically travel in the midline along the natal cleft. In some situations, the pits may be located quite inferiorly in the natal cleft close to the anal verge and may be mistaken for an external opening of an anal fistula.

Despite the prevalence of pilonidal disease and its variants, there is no formal classification system in place. There are no clear guidelines to inform procedure of choice, and typically surgeons perform procedures with which they are most comfortable. The lack of consensus results in an inability to generalize the available data, most of which are small, single-center studies. Generalizability of these single-institution studies is difficult, as procedure of choice is guided by surgeon preference as opposed to validated guidelines. Additionally, there is no true gold standard for comparison, and there is no study comparing all available treatments side by side. There is also heterogeneity in reported outcome measures, including postoperative infec-

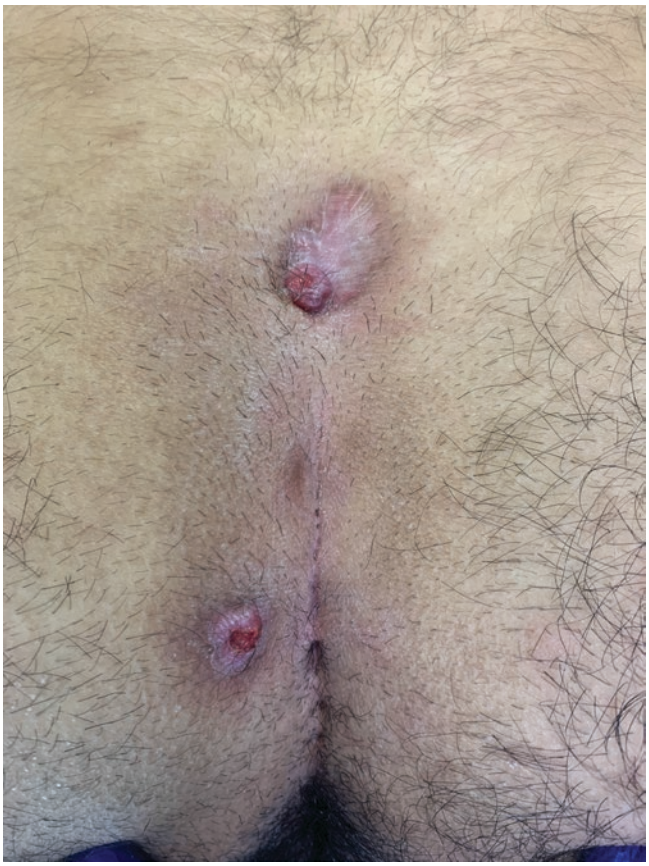

Fig. 16.2 Pilonidal disease with midline pits and two abscesses – one located lateral to the right and one located cephalad in the midline

tion, recurrence rates, postoperative pain, time off work, wound healing time, and quality of life. Despite these challenges, it is important for clinicians to understand the variety of treatments available to treat the disease.

Treatment

Managing Patient Expectations

When caring for patients with pilonidal disease, it is important to establish a baseline set of expectations for their treatment course. Upon initial presentation, a majority of patients may be managed nonoperatively, and it is important for patients to understand the potential for recurrent symptoms that may require future intervention. Additionally, postoperative complication rates are relatively high regardless of which operative strategy is chosen. It is important that the patient has a clear understanding of the potential for these postoperative complications, which largely consist of wound infections and chronic wound complications requiring dressing changes and delayed healing. Additionally, while there are a variety of operative options, the best course of treatment remains controversial.

Nonsurgical Treatment

In patients who have quiescent disease, no invasive treatment is necessary. Risk factor modification may be employed including improved hygiene, weight loss, hair removal, and avoiding prolonged sitting. Cleansing the area with a washcloth or scrub brush may help prevent hairs from becoming trapped within the pits. Hair removal can be very effective as a step towards healing. Hair removal options include shaving, waxing, depilatory creams, or laser hair removal. Patients with light-colored hair may not be candidates for laser hair removal, as it typically works best in those with light-colored skin and dark hair. The available data to support laser hair removal is limited and heterogeneous [18]. Recurrence rates of 0–28% have been reported, which were less than those seen in the non-laser hair removal groups. Additionally, depilatory creams and laser hair removal are not recommended in the setting of an active infection or ulceration. In these cases, patients should be instructed how to shave the area and may even require weekly visits to have the area shaved in the clinic. Even when operative treatment is chosen, postoperative hair removal has been shown to decrease recurrence [19].

Antibiotics

Antibiotics are typically not indicated but should be prescribed in certain circumstances. Antibiotics alone will not treat pilonidal disease but can be used as an adjunct in cases with extensive surrounding erythema/cellulitis and systemic signs of sepsis (fevers, rigors, malaise) or in certain patient populations (diabetes, immunosuppressed, artificial heart valves, or other implanted prostheses). If antibiotics are indicated, a third-generation cephalosporin and metronidazole should be prescribed [20]. If there is an acute abscess, antibiotics should not be used as the sole treatment, and incision and drainage is indicated. Typically, incision and drainage is sufficient treatment.

Phenol

A nonsurgical outpatient option to ablate pilonidal disease is phenol application. This procedure is performed under local anesthesia with overall success rates of 62–95% and low complication rates of 0–2% [21–23]. Phenol causes a caustic burn without causing pain given the anesthetic and analgesic effects of phenol solution. The phenol solution also denatures the hairs thought to cause pilonidal disease. The procedure involves debriding the tract, enlarging the cavity slightly, and then instilling 1–3 mL of crystallized phenol solution into the pilonidal cavity while protecting the surrounding skin with ointment. Typically, one to four sessions are required to achieve good results [24]. Success rates are higher when combined with laser hair removal or depilatory creams [25–27]. The procedure can also be utilized successfully in those with recurrent pilonidal disease [24].

Fibrin Glue

Similar to phenol treatment, fibrin glue (or thrombin gelatin matrix) may be utilized with recurrence rates ranging from 0% to 17%, in the absence of infection [28]. This procedure is performed by first shaving the surrounding hair and preparing the operative field in a sterile fashion. After hair and debris are removed from the sinus using a curette, fibrin glue is instilled into the sinus. The fibrin glue acts as a sealant that allows a clot to form. Efficacy for this procedure demonstrates success rates of 96% with high patient satisfaction (79%) [29, 30]. Those that reported they were dissatisfied required further treatment due to procedure failure [30]. A similar study found a 27% recurrence rate after a median of 4 months, and after second fibrin glue application, the success rates were 96.6% [31]. Fibrin glue may also be used as an adjunct with other more advanced surgical flaps, though the durability of this is unknown [32, 33]. A meta-analysis was performed that comprised four randomized control trials of fibrin glue to treat pilonidal disease which included a total of 253 patients [34]. This study revealed low-quality evidence for the use of fibrin glue as monotherapy or in conjunction with advanced flap-based procedures. Given the lack of high-quality evidence and long-term results, the true utility of fibrin glue remains unclear at this time [35].

Surgical Treatments

Incision and Drainage

Acute pilonidal disease is defined as the presence of an abscess with or without associated cellulitis [36]. Regardless of the chronicity of the disease, if a patient presents with an acute abscess, incision and drainage should be performed. The main overarching concept of performing an incision and drainage in this setting is to place the incision off of the midline over the area of maximum fluctuance. Frequently, incision and drainage with unroofing of the cavity can successfully treat the disease without the need for additional procedures. Incision and drainage is nearly always successful for resolving the immediate infection. Recurrent infections are typically due to failure to address underlying hair, debris, granulation tissue, and epithelization that are present within the cavity [37]. Abscesses that are inadequately drained may also recur if the incision site heals prematurely without true healing by secondary intent. When performing an incision and drainage, it is important to ensure that the abscess is unroofed and the skin edges are no longer opposed to avoid premature healing.

Lay Open Technique Versus Excision with Primary Closure

The lay open technique is one in which an incision is made overlying the sinus tract of the pilonidal cyst and allowed to granulate by secondary intention (Fig. 16.3). A fistula probe can be used to identify the extent of the tract. An incision can be made on top of the probe using electrocautery, unroofing the track. The overlying skin can be excised in order to create a shallow wound and prevent the wound from prematurely healing at the skin surface level. The exposed tract can then be debrided using curettes or cautery. The skin edges can also be marsupialized using absorbable polyglycolic acid or Vicryl suture in a running fashion, making the defect smaller and shallower. The wound may be too shallow for traditional

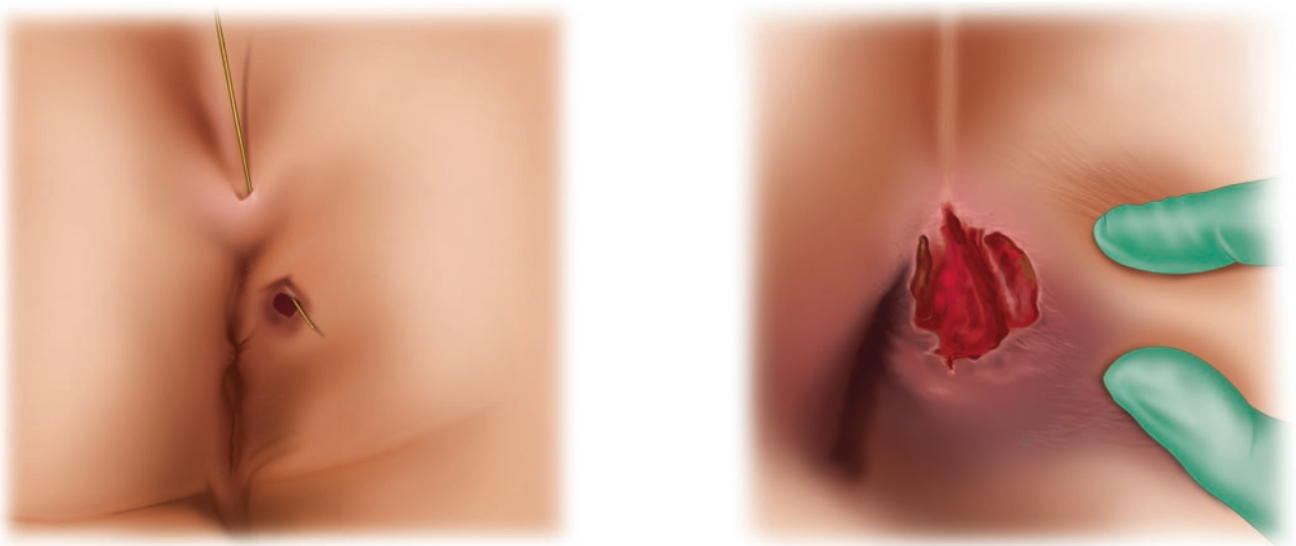

Fig. 16.3 Lay open technique: A fistula probe is used to identify the tract. An incision is made overlying the probe using electrocautery to unroof the tract. The chronic granulation tissue can be debrided and the wound edges marsupialized if desired

packing, but a dressing of gauze can be placed and changed regularly to protect the patient's clothing from drainage.

Success rates for initial operation are reported to be as high as 97% [38]. Patients who undergo the lay open technique have recurrence rates varying between 8.8% if the abscess is incised and left open to 20.8% if they are excised and left open [39]. Postoperative infection rates are similar between lay open and primary closure techniques, but recurrence is significantly less likely with the lay open technique [40]. The lay open technique requires more intense wound care, such as dressing changes done twice daily, often requiring assistance from a family member. Sometimes, wounds can heal with hypertrophic granulation tissue, which can result in drainage and require further cauterization in the office setting to achieve complete healing.

Another option is excision with primary closure. Typically, the entire pilonidal cavity is excised down to the sacral fascia. The wound is then irrigated and closed in layers. The deep tissues are closed using absorbable polyglycolic acid suture. The final skin layer can be closed using a nylon or polypropylene suture in a vertical mattress fashion. The final dressing applied may include buttressing sutures to create a pressure dressing that remains in place for several days postoperatively to prevent the development of a seroma. Primary closure has been shown to result in faster healing and decreased time off from work [41–44]. Avoiding inconvenient and prolonged wound care is one of the attractive benefits of primary closure, but patients should be counselled as to the potential risk of postoperative infection requiring opening of the incision. A Cochrane review comparing 26 trials with 2530 patients identified faster healing times with primary closure but no difference in surgical site infection rates [45]. When comparing midline versus off-midline closure, there were decreased surgical site infection rates with faster healing times with off-midline closure [45]. There are no obvious benefits for open versus closed excision; but if the decisions is made to perform primary closure, then the preferred technique is to keep the closure off of the midline.

Complex Surgical Treatment

There are no formalized guidelines as to when complex surgical treatment is indicated following acute incision and drainage of an abscess. The goal of flap-based surgical treatment is to excise the diseased tissue, cover the defect with healthy tissue, and raise the natal cleft anatomy. In general, surgical excision should be considered for patients with chronic sinuses that harbor extensive, chronic, epithelialized granulation tissue, which will not heal with hygiene and hair removal alone. Surgical excision should also be considered for patients who have undergone multiple abscess drainage procedures. Timing of surgery can be typically arranged in an elective fashion. There are several types of flaps, described below.

Karydakis Flap

A Karydakis flap involves excising the effected tissue in an elliptical fashion, with the inferior and superior corners of the ellipse about 2 cm from the midline (Fig. 16.4). The skin and soft tissue, including all the pilonidal pits, are excised

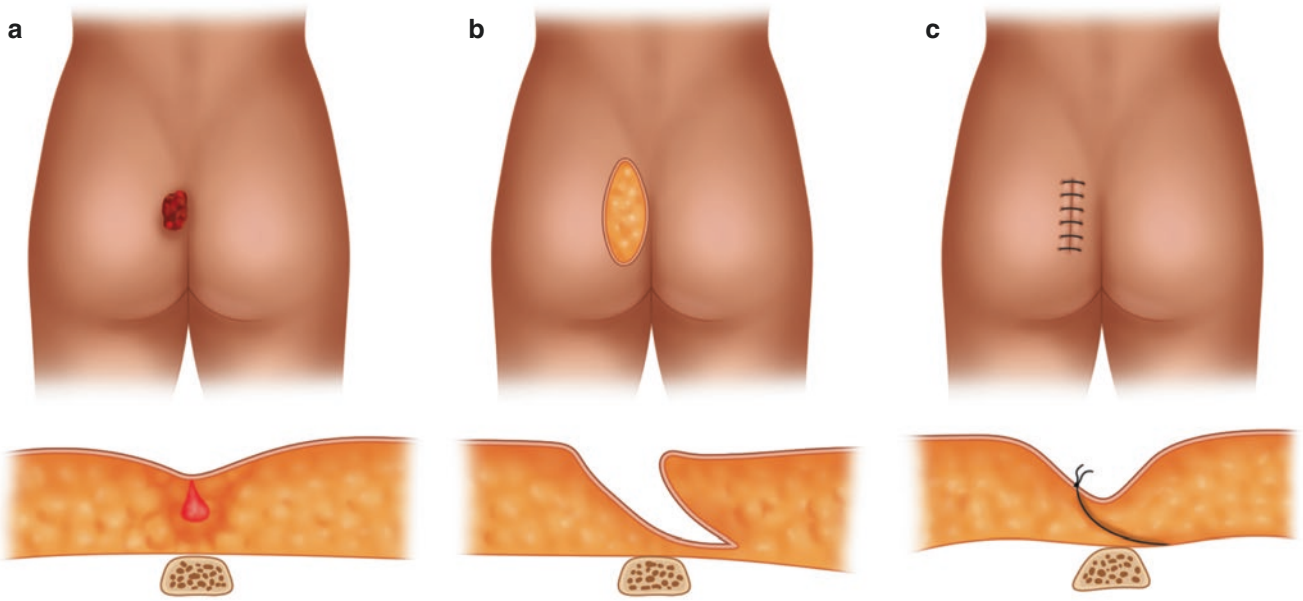

Fig. 16.4 Karydakis flap: (**a**) The affected tissue is excised down to the sacral fascia in an elliptical fashion off of the midline. (**b**) A flap of skin and subcutaneous tissue is raised and advanced over the excision defect. (**c**) This is secured in place by suturing in layers

down to the sacral fascia. After this tissue is excised, a flap of the skin and subcutaneous tissue is raised on the opposite side of the midline. This is then advanced over the resection bed. The wound is closed in layers with the deepest layer of absorbable polyglycolic sutures including the sacral fascia. Additional layers of absorbable polyglycolic sutures are placed to approximate the flap. The skin is finally closed with nonabsorbable suture (either polypropylene or nylon) in a vertical mattress fashion. A pressure dressing is applied and can be secured in place with tie-over sutures [46]. These sutures are typically left in place for 10–12 days [47].

The Karydakis flap generally has good results. Kardyakis reported his results in 6545 subsequent cases with a wound complication rate of 8% and recurrence rate of under 2% [48]. In more recent trials, the Karydakis flap has morbidity rates as high as 21% [49]. A trial comparing Kardyakis flap to excision with healing by secondary intent showed recurrence rates of 1.2% and an 18.7% rate of wound complications [50]. Another study demonstrated a 1-year recurrence rate of 3% and a 10% wound dehiscence rate when performed for recurrent disease [50]. Another trial demonstrated a wound complication rate of 8.1% and recurrence rate of 2.7% [51].

Rhomboid Flap (aka Limberg Flap)

A rhomboid flap, also known as a Limberg flap, is a rotational flap (Fig. 16.5). This involves first mapping the site of excision. This is done by identifying the extent of the pits and marking the shape of a diamond with the superior and inferior apices of the diamond just to the left of the midline. This results in a wound that does not come to a point just above the anus, which is the site with the highest risk of wound failure. The purposed excision site should include any former incision and drainage scars. This excision site will be in the shape of a diamond. The marking of the flap starts from the lateral apex of the diamond, typically on the right side. A horizontal line is drawn from the lateral apex that is approximately 5–6 cm in length. This horizontal mark represents the contralateral lower edge of the flap after rotation, and so it is important to ensure the lengths are congruent. Another line is marked from the lateral end of the horizontal line inferiomedially at an acute angle. Incisions are first made to resect the diamond-shaped tissue down to the sacral fascia. Next, the lipocutaneous flap is raised. Care should be taken to ensure that the flap is undermined appropriately to allow for a tension-free closure without creating ischemia. The flap can be secured into place with absorbable sutures. The final layer of the skin can be closed with vertical mattress sutures, and some may choose to also apply surgical glue. The use of a drain is per surgeon preference.

Results of the Limberg flap are conflicting. Wound infection rates are reported to range from 1.5% to 4% [52, 53]. Recurrence rates have been reported between 0% and 4.9% [51, 52, 54]. Conversely, complications have been reported to be as high as 49%, including a wound dehiscence rate of 45%, infection rate of 4%, and recurrence rate of 13% [53].

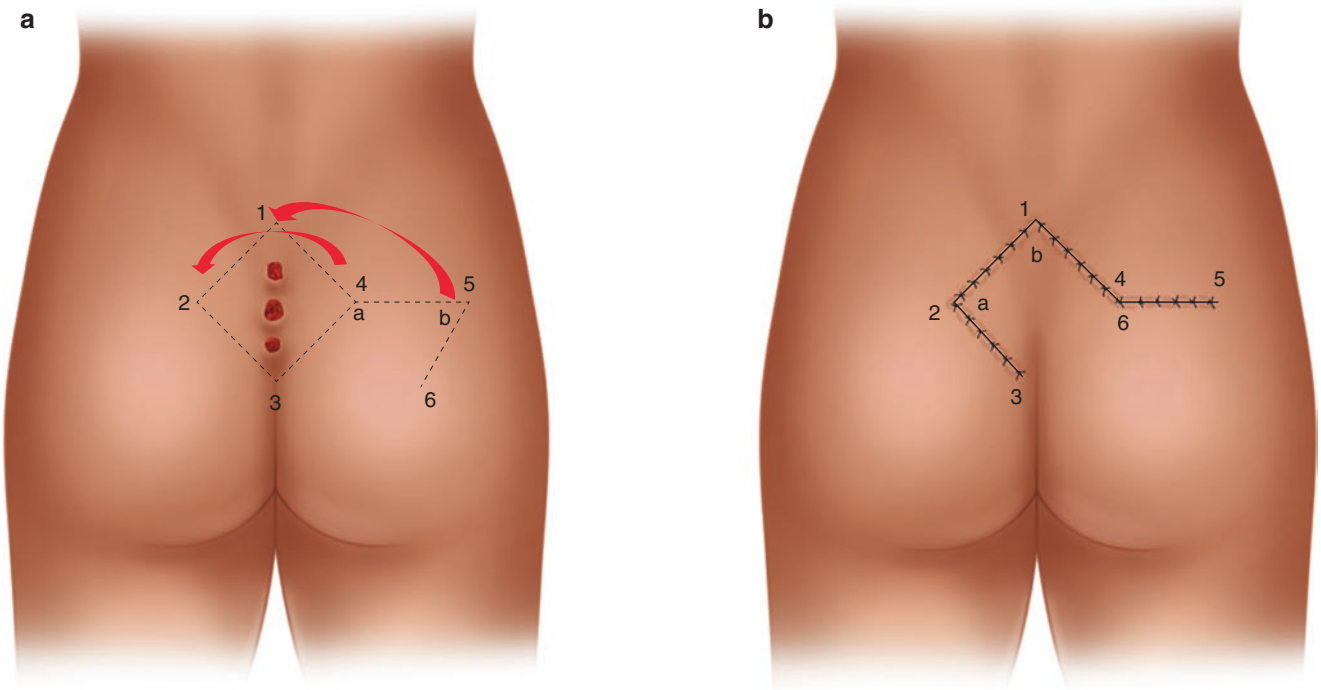

Fig. 16.5 Limberg flap (rhomboid flap). (**a**) The excision site is marked in a rhomboid shape, and the edges of the flap are drawn out. The rhomboid affected area is excised in a rhomboid shape down to the sacral fascia. (**b**) The flaps are raised as marked and then rotated as indicated by the arrows. The flap is secured in place with several layers of absorbable suture over a drain

Another study demonstrated an overall morbidity rate of 19.7% and recurrence rate of 1.6% [55]. One downside of the Limberg flap is the postoperative scarring, as it is not as cosmetically appealing as other flaps.

Cleft Lift Flap (Bascom Procedure)

The cleft lift flap, also known as the Bascom procedure, is designed to "lift" the concavity of the natal cleft and create an incision that is closed off midline (Fig. 16.6). This procedure is performed by first marking the "safety zone" of the gluteal cleft. The patient is placed in a prone position, and the safety zone is defined by the tissues that are able to touch when the gluteal cleft is pulled together – this is marked and represents the most lateral extent of the dissection. The tissue to be excised is also marked out. The area of excision comes across the central pits in the midline and extends in a scimitar shape at the inferior aspect of the excision site. This procedure, unlike the other flaps, does not require excising the entirety of the diseased tissue. After the excision area is marked, create an incision vertically across the midline through the central pits and ensure that the inferior aspect follows the scimitar-shaped marking. Creation of the flap occurs before excision of the diseased tissues. The flap is raised towards the opposite side from the tissue to be excised, which can be performed sharply or with electrocautery. The thickness of the flap should be similar to that of a mastectomy, and care should be taken to preserve subcutaneous tissues towards the anal side. Next, the excision of the skin overlying the area of disease is performed, with a majority of the subcutaneous tissue left in place. Any central scarring

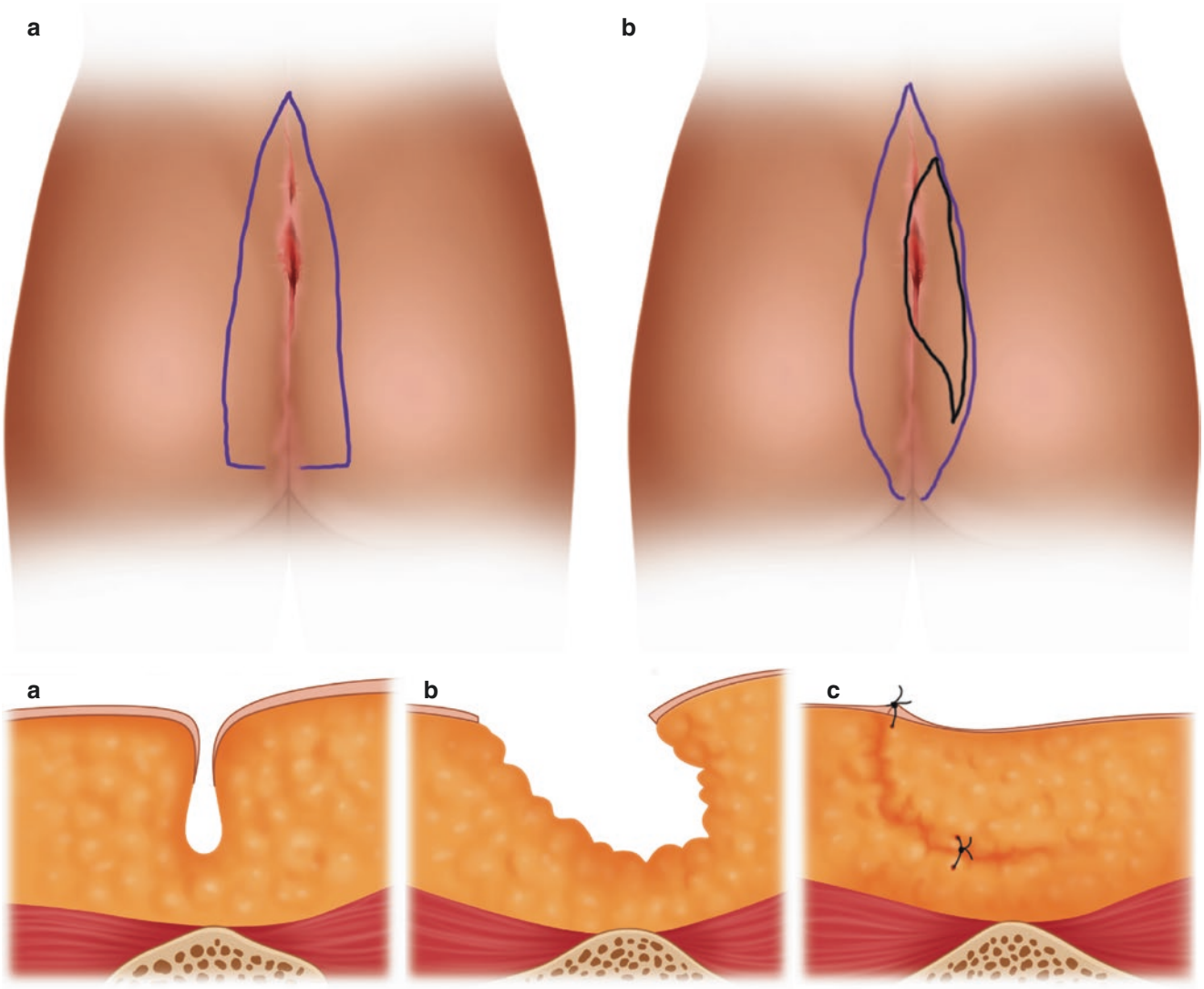

Fig. 16.6 Bascom flap (cleft lift). (**a**) First, a safety zone and a scimitar shaped incision are marked. (**b**) An incision is carried in the vertical midline and a flap is raised towards the opposite side from the tissue to be excised. After the buttock tapes are removed, the flap is checked to see the extent of reach contralaterally. Then the diseased tissue is excised, ensuring the flap will cover this tissue. (**c**) The flap is then secured in layers over a drain

can be lanced to free the contracture. The excision site is then closed with absorbable polyglycolic acid suture to close the deep space. A 7 mm closed suction drain is placed. The skin is then closed over a drain in a subcuticular running fashion using absorbable monofilament suture. This raises the natal cleft and keeps the incision off the midline.

Initially described by Bascom and Bascom, this procedure had initial success rates of 90% with a 100% success rates after the remainder of the patients underwent additional procedures [56]. A follow-up study by the same authors demonstrated healing rates of 96% [57]. Further studies have replicated these good results with healing rates as high as 97% [20, 58]. Patient satisfaction is high with cleft lift procedure, given a decrease in postoperative pain and low recurrence rate, though postoperative morbidity is as high as 20% [55].

Minimally Invasive Treatments

Minimally invasive treatments for pilonidal disease are desirable given the major morbidity that can occur with other operative options. These include endoscopic/video-assisted ablation, laser ablation, and trephination.

Endoscopic/Video-Assisted Ablation of Pilonidal Sinus (VAAPS)

In this procedure, a 4 mm hysteroscope is inserted into the opening of the pilonidal cavity after the opening is saucerized with electrocautery. The sinus and its lateral tracks are identified with the scope, under a continuous infusion of saline, and a mechanical adhesiolysis is performed. Any hair that is visualized is removed with grasping forceps. The cavity is ablated using a 5F bipolar electrode in one centimeter increments. The main sinus tract and any accessory tracts are identified. Finally, the residual cavity is debrided, and an iodine solution is injected into the cavity [59]. This procedure has demonstrated high healing rates and patient satisfaction scores. A prospective study with a median follow-up of 52 weeks demonstrated a success rate of 67% with a delayed healing rate of 77% [60]. Recurrence rates have been reported to be lower than standard excisional operations [61]. Modifications include the injection of phenol in the tract [62, 63]. When compared to the traditional Limberg flap, endoscopic treatment of pilonidal disease may have higher recurrence rates but is associated with fewer postoperative complications [64].

Laser Ablation of Pilonidal Sinus

The diode laser has been used in several other disease processes such as anal fistula and can be applied to pilonidal disease as well. This outpatient procedure depends upon ablation of the epithelium of the pilonidal sinus and promotion of new granulation tissue. The area is injected with local anesthetic, and the subcutaneous tract is located. The tract is debrided to remove hair and debris and then curetted to remove the tissues lining the tract. The tract is irrigated with saline, and a diode laser is introduced into the tract. Laser energy is delivered to the tract to create a homogenous ablation and destruction of the tissues in the tract. Every pit must be treated with the laser. Results of this operation have been promising [65]. Patients are able to return to daily activities and return to work immediately in as many as 92.8% of patients. Patients with less severe disease have better outcomes. Success rates are around 85–90%, and recurrence rates of as low as 2.9% have been reported [66, 67]. Complications include pain, hematoma, abscess, and drainage.

Trephination

Trephination is a procedure that involves the use of skin trephines to excise pilonidal pits and debride the underlying tracts and cavities (Fig. 16.7) [68]. Each pit is individually probed to evaluate the anatomy including the depth of the pit and presence of any associated tracts. Skin trephines sized 2.0–9.0 mm in diameter are used to core out the pits. When a subcutaneous tract is identified, excision is carried down to the cavity with 4.0–5.0 mm trephines. Any acutely infected areas are excised using 6.0–9.50 mm trephines and left open to heal by secondary intent. This technique has been reported to have a healing rate of 89.7% at 4 weeks with a recurrence rate of 16.2%. Postoperative complications occur in <5% of patients with wound infection rate <1% [69]. Postoperative wound care is minimal and includes light packing to allow the wounds to heal by secondary intent. Performing trephination does not exclude future excisional flap procedures in the case of recurrence.

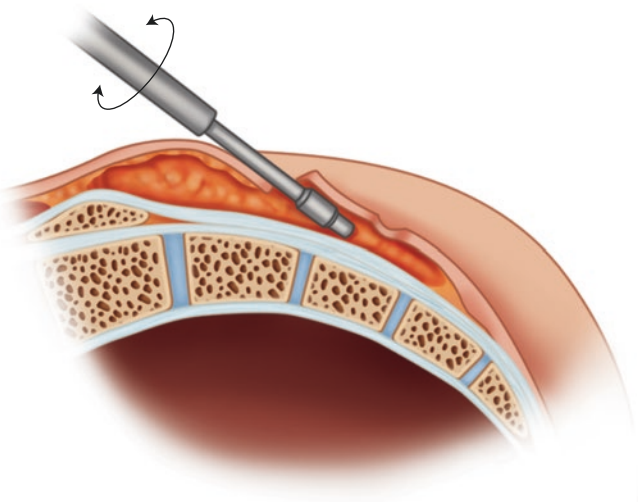

Fig. 16.7 Trephination. A skin biopsy punch is used to core out each symptomatic pit, which are left open to heal by secondary intent

Management of Recurrent Disease

Despite the variety of surgical options available to treat pilonidal disease, recurrent disease remains prevalent with rates as high as 34% after 1 year and 66% after 5 years [70]. There are no formal guidelines for the management of recurrent pilonidal disease with limited data to drive practice guidelines [36]. As described, no single procedure is without recurrence risk, so it is important to recognize the need to manage recurrent disease as well as primary disease. In the setting of an acute abscess, eliminating the immediate infection is necessary with incision and drainage. After resolution of the immediate infectious situation, the wound must be evaluated to assess the extent of the recurrence. Recurrence tends to be higher following treatment with antibiotics and need for incision and drainage, and up to 45% of patients with recurrence are obese [71]. When recurrence occurs, local excision, flap-based procedures, or minimally invasive procedures may be considered.

Wound Healing Adjuncts

Regardless of which type of surgical treatment is chosen, small or large wounds may form and require chronic management. This is most likely the result of the repeated friction that occurs in the natal cleft area with movement. After ruling out recurrent sepsis and prior to embarking on extensive surgical re-excision, local wound care efforts should be utilized to promote healing. Silver nitrate can be applied to any hypertrophic granulation tissue. Warm water soaks and soap cleansing can also encourage the wound to heal by secondary intention. In the case that this does not result in complete wound healing, several products are available that may encourage definitive wound healing. These include silver-impregnated gauze strips, hydrophilic wound dressing cream, and creams with methylene blue and gentian violet. Application of these twice a day, covered with a regular gauze dressing to protect the clothing, can result in successful healing without the need for further surgical intervention (Fig. 16.8).

Hidradenitis Suppurativa

Introduction

Hidradenitis suppurativa (HS) or acne inversa is a chronic, recurrent, inflammatory skin disease, initially presenting as

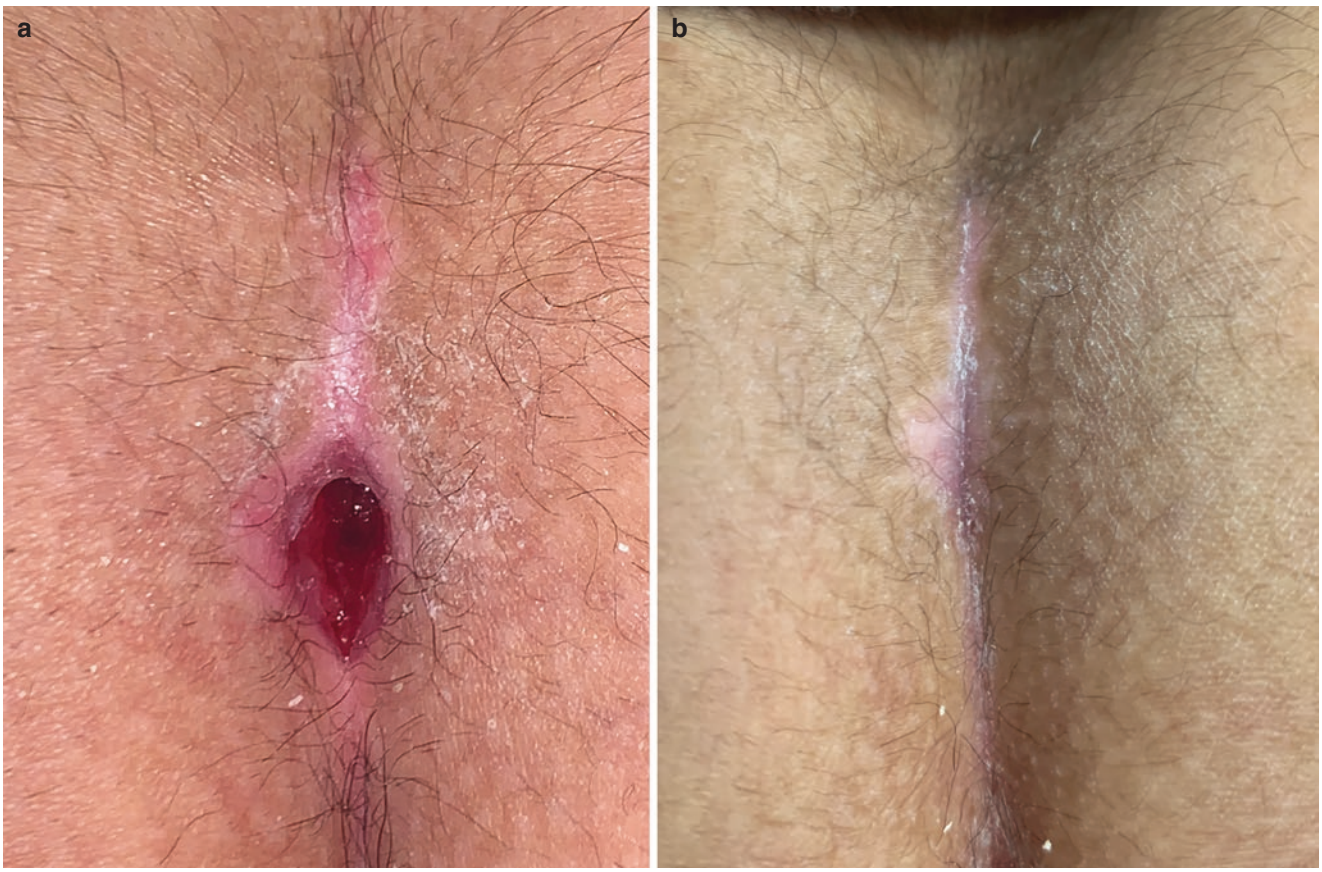

Fig. 16.8 (**a**) This is a nonhealing pilonidal wound after excision with primary closure. Several attempts at sitz baths, dressing changes, and silver nitrate had failed. (**b**) This is the same wound after 2 weeks of twice daily use of hydrophilic wound dressing cream

painful subcutaneous nodules as the characteristic suppurating lesion. These nodules can spontaneously rupture and coalesce which create deep dermal, exquisitely painful abscesses. The inflammatory abscesses can ultimately heal, producing fibrosis, dermal contractures, and induration of the skin as well as chronic sinuses. The severity of the disease is variable as is the clinical presentation with periods of quiescence and active flares. The disease occurs in the apocrine gland-bearing skin folds, typically the perineum, inguinal, inframammary, and axillary regions. The most commonly affected region is the axilla (70%) followed by the perineum and groin [72]. Patients may experience symptoms in more than one location. HS is associated with a marked reduction in quality of life and high incidence of comorbid mental illness [73]. Once believed to be the result of apocrine gland infection, it is now considered a disease of follicular occlusion. Factors implicated in the development of HS include (1) host defenses, (2) genetics, (3) endocrine abnormalities, (4) obesity, (5) smoking, and (6) environmental.

Incidence and Etiology

The exact incidence of HS is not known due to sparse epidemiologic data. In a recent cohort analysis, the overall prevalence in the US population was estimated at 0.1%, or 98 per 100,000 persons [74]. Woman were more than twice as likely to be affected compared to men with the prevalence highest among patients aged 30–39 years compared with all other age groups. HS prevalence among African American patients was more than threefold greater than white patients. Only 2% of cases occur before the age of 11 years [75]. In a retrospective study of 855 patients, 7.7% reported an onset of HS before the age of 13 years [76]. Early onset HS was associated with stronger genetic susceptibility and more widespread disease.

Modifiable risk factors have been identified as smoking and obesity. In a recent cohort analysis of smokers in the United States, the overall adjusted odds of developing HS was 1.9 (95% confidence interval 1.84–1.96) among tobacco smokers, compared with nonsmokers [77]. Tobacco smokers diagnosed with HS were most commonly aged 18–39 years, women, and white and had a body mass index (BMI) ≥30. Although the precise pathophysiologic role of smoking in HS remains uncertain, nicotine has been found to promote colonization of *Staphylococcus aureus* in intertriginous areas, chemotaxis of inflammatory mediators, and hyperplasia of the infundibular epidermis which can lead to the disease process [78]. In a recent meta-analysis of 25 studies (101,977 HS patients and 17,194,921 non-HS controls), a significant association between current smoking status and HS was identified (OR = 4.26 [95% confidence interval 3.68–4.94]) [79]. Both the prevalence and severity of HS are increased in obese patients with one study demonstrating an increased odds ratio of 1.12 for every one unit increase in body mass index [80, 81]. Obesity may aggravate HS via increased skin-skin and skin-clothing friction. Mechanical stress is associated with worsening of HS by increasing follicular occlusion and rupture [72].

Increasingly HS is viewed as an auto-inflammatory skin disorder associated with alterations in the innate immune system although large gaps remain in the understanding of the pathogenesis of HS [82]. There is increasing evidence supporting the role of Th17 cells and enhanced expression of IL-17 and IL-1β, which represent potential targets for therapy. Bacteria and biofilms are likely contributory but secondary drivers of inflammation [83]. This is aggravated by obesity, metabolic syndrome, and smoking [84, 85]. The primary defect in HS pathophysiology rests with the hair follicle. Follicular occlusion, followed by follicular rupture, with discharge of contents including keratin and bacteria into the surrounding dermis resulting in a foreign body-type immune response are necessary conditions for the development of clinical HS [86].

Clinical Presentation and Diagnosis

Diagnostic delay in hidradenitis suppurativa is a significant problem. In one study the average patient delay in seeing a physician (time from onset of symptoms to the first visit with any physician) was 2.3 ± 5.0 years, and the diagnostic delay was 7.2 ± 8.7 years [87]. Patients present with a range of signs and symptoms from a single open comedone (clogged hair follicle) to multiple painful, swollen nodules, generally with little purulent discharge. The inflammatory process may resolve without treatment but often waxes and wanes over many weeks to years. Chronic skin changes and discharge may develop that is both painful and socially limiting including sinus tract formation, contractures, and fibrosis (Fig. 16.1). In a study of 100 patients, 21% reported missing work, and 60% reported loss of work productivity during the preceding week as a result of HS. Seventy-two percent of these patients reported daily activity impairment with moderate to strong correlations between reduction in quality of life and presenteeism, overall work impairment, and activity impairment. Activity impairment was higher among patients with Hurley stage III [88].

The diagnosis of HS is made by lesion morphology (nodules, abscesses, tunnels, and scars), location (axillae, inframammary folds, groin, perigenital, or perineal), and lesion progression (two recurrences within 6 months or chronic or persistent lesions for ≥3 months). The differential diagnosis in the perineal or genital area is primarily between HS and other subcutaneous tunneling diseases, and if uncertain, a biopsy should be considered. The absence of midline pits

over the sacrum helps distinguish HS from pilonidal disease; the absence of involvement of the anal canal helps distinguish HS from Crohn's disease and benign anal fistula.

Given the wide-ranging severity of both disease burden and symptoms, there have been a number of classification systems proposed in an effort to quantify and categorize patients with HS [81, 89–92]. The majority of these scoring systems has not been validated or may be better suited for research purposes than clinical care of patients impacted by the disease. Disease severity can be classified according to the Hurley classification, which defines stage I as transient nonscarring inflammatory lesions; stage II as separate lesions consisting of recurrent abscesses with tunnel formation and scarring and single or multiple lesions separated by normal looking skin; and stage III as coalescent lesions with tunnel formation, scarring, and inflammation [93]. This system has been criticized as its intent was to classify the disease severity in a single anatomic region, and many patients with HS have disease that is multifocal, and a revised system has been proposed. This new classification subdivides Hurley stage I and II into three substages, mild (A), moderate (B), and severe (C) based on the overall extent of the disease and degree of inflammation. Hurley stage III is not subcategorized and is always severe. The refined Hurley classification strongly correlates with HS severity assessed by both patients and clinicians using quality of life scoring tools [20]. Other critics have pointed out that the Hurley score is a static score and not sufficiently responsive to change, particularly relating to the inflammatory component of HS [94]. The Sartorius score is another classification system that is commonly used whereby involved anatomical predetermined regions are counted, classified, and weighted according to type. Additional points are given for the longest distance between two lesions within each affected anatomical region and for any regions containing Hurley III. The points are added for an overall severity score [81]. Another approach for physician assessment is the Hidradenitis Suppurativa Clinical Response (HiSCR) score developed and validated for use as the primary endpoint in randomized control trials studying the use of adalimumab [92]. The primary component of HiSCR evaluation is the objective and uncomplicated counting of HS lesions. The HiSCR is a valid and meaningful endpoint for assessing HS treatment effectiveness in the inflammatory component of HS and is also significantly correlated with improvements in all physician-related measures (Hurley stage, modified Sartorius scores, and HS Physicians Global Assessment) and patient-reported outcomes (visual analogue pain scale, dermatology life quality index, and work productivity and activity impairment questionnaire).

Several comorbid conditions have well-known association with HS given the systemic nature of the disease. The link between hidradenitis suppurativa and systemic associations may be attributed to common genetic or environmental factors or shared inflammatory pathways.

Metabolic disorders including obesity and metabolic syndrome are the most common associated conditions observed in patients with hidradenitis suppurativa [95]. Autoimmune diseases, like inflammatory bowel diseases, autoinflammatory diseases, spondyloarthritis, some genetic keratin disorders, and also the risk of skin tumor, seem to occur more frequently in these patients [82]. There is a well-established link between acne and HS as well as pilonidal disease. In one study evaluating the disease severity of HS, the presence of severe acne was associated with an increased Sartorius score, as was male sex, increasing BMI, atypical locations of HS lesions, and absence of a family history of HS [96]. In a review of 826 patients with HS, overall 45% of the patients had Hurley I, 41% had Hurley II, and 13% had Hurley III. Severity was associated with male sex (OR 2.11; $p < .001$), disease duration (OR 1.03; $p < .001$), body mass index (OR 1.03; $p = .01$), smoking pack-years (OR 1.02; $p = .001$), and axillary (OR 2.24; $p < .001$), perianal (OR 1.92; $p < .001$), and mammary lesions (OR 1.48; $p = .03$). Women had earlier onset, more inguinal and mammary lesions, and more frequent family history for hidradenitis suppurativa. Men more commonly had gluteal, perianal, and atypical lesions and a history of severe acne. Patients with a family history had earlier onset, longer disease duration, a history of severe acne, and more extensive disease and were more often smokers [97].

Treatment

Treatment of HS is multidisciplinary as there are a host of medical and surgical therapies from incision and drainage to infusions with biologic agents. The practicing colorectal surgeon may be the first medical provider to identify these patients especially when their disease is located in the perineal region. Surgery of HS lesions is typically reserved for intractability and acute abscess formation but is one of the most successful treatments available. The persistent and recurring nature of the disease requires an individualized treatment plan. It is imperative to educate the patient about the chronic relapsing nature of the disease and to elicit the goals of therapy prior to making any decisions about treatment options.

Medical Therapy

Topical Therapy

Clindamycin lotion (1%) is the only antibiotic that has been studied as a topical agent. In a placebo-controlled, double-blind, randomized trial in 30 patients with HS, the overall effect of clindamycin treatment based on patients'

assessments, number of abscesses, inflammatory nodules, and pustules was significantly better than placebo at each monthly evaluation over the 3-month study period [98]. It is primarily used in patients with Hurley stage I or mild stage II. The proposed dosing regimen is twice daily, for 3 months. If clinical response is not achieved after that treatment period, other treatment options must be considered.

Other topical agents include resorcinol, a phenol derivate with keratolytic and anti-inflammatory properties. It was evaluated in 32 HS patients, and by days 7 and 30, there was a significant reduction in the clinical size of the lesions and the mean pain score [99].

Systemic Antibiotics

Antibiotics are commonly used to treat HS flares because of secondary bacterial infections, and some, such as tetracycline and rifampicin, also may have immunomodulatory properties. For example, tetracycline suppresses neutrophil migration and chemotaxis and inhibits matrix metalloproteinase [100].

Tetracycline 500 mg b.i.d. has been evaluated and compared with topical clindamycin in a double-blind, randomized, controlled trial of 46 patients with Hurley stage I and II disease [101]. No significant difference was identified between the two treatment arms. Tetracycline can be used as a first-line treatment in patients with more widespread Hurley I and mild Hurley II stage, when topical therapy would not be practical, for up to 4 months. Clindamycin 300 mg b.i.d. in combination with rifampicin 600 mg once daily or 300 mg b.i.d. has been evaluated in several case series [102]. In a study of 116 patients with severe HS, combination therapy decreased the Sartorius scores, while quality of life scores improved significantly. In another prospective study, 26 patients were given combination therapy for 12 weeks with 1-year follow-up with a reported initial clinical response in 19 of 26 patients (73%) immediately following the treatment and then decreasing to 7 of 17 patients (41%) at 1 year. The remaining relapsed a mean of 4.2 months following treatment cessation [103]. This treatment combination can be used as a first-line treatment option in patients with moderate and severe HS for up to 10 weeks.

Biologics

Adalimumab, given subcutaneously at a dose of 40 mg weekly, has been studied in a prospective, randomized, double-blind, placebo controlled trial [104]. One hundred and fifty four patients with moderate to severe HS who had failed antibiotic therapy were treated. There was a significant reduction in the HiSCR, as well as pain scores, while quality of life and work productivity increased. These results have been reproduced in three additional randomized trials [105, 106]. Adalimumab is recommended as a first-line treatment option in patients with moderate to severe HS who were unresponsive or intolerant to oral antibiotics. Infliximab (IFX) 5 mg/kg has been evaluated in a randomized, placebo-controlled, crossover trial. No significant difference was noted in the HiSCR score although more patients receiving IFX achieved a 50% reduction in HS lesions compared to placebo. There was a significant improvement in patients' quality of life scores and VAS pain scores. Infliximab is recommended in patients with moderate to severe HS as a second-line treatment option, only after failure of adalimumab. If clinical response is not achieved after 12 weeks of treatment, other treatment modalities must be considered. Both anakinra (recombinant IL-1 receptor antagonist) and ustekinumab (human IgG1κ monoclonal antibody) have been recently studied in the treatment of moderate to severe HS and have shown to be efficacious as an alternate therapy [107, 108].

There is some evidence to support the use of biologics as an adjunct to surgery as a means to decrease recurrence when compared with surgery alone [109]. In one study, 68 patients with moderate to severe HS were treated with biologics. The mean disease duration was 10 years, and Hurley stage III was seen in 63% of patients. Patients who received biologics had a larger drop in their Sartorius scores and active nodule count than those who never received biologics. The effect of biologics was greater in patients who also underwent surgery. Timing of biologics relative to surgery did not impact efficacy. Patients who received HS surgery with biologic therapy were most likely to achieve a 75% reduction in active nodule count [110]. In another study, 11 patients underwent combined surgical and biologic therapy, whereas radical resection alone was performed in 10 patients. Biologic agents including infliximab ($n = 8$) and ustekinumab ($n = 3$) were initiated 2–3 weeks after closure and were continued for an average of 10.5 months. Recurrence was noted in 19% and 38% of previously treated sites for combined and surgery-only patients, respectively ($p < 0.01$). For the combined cohort, the disease-free interval was approximately 1 year longer on average ($p < 0.001$). New disease developed in 18% and 50% of combined and surgery-only patients, respectively ($p < 001$). No adverse events were noted among patients who received biologic therapy [111].

Other Medical Therapies

Androgens influence HS, as evidenced by the effects of pregnancy and menstrual cycles for many patients, but the recommendations on hormonal therapies are based on limited evidence. The only RCT of hormonal therapy compared ethinyl estradiol/noregestrol with ethinyl estradiol and cyproterone acetate; it was a double-blind, controlled, crossover trial of 24 women. Both therapies resulted in similar improvement, with 12 patients improving or clearing completely [112].

Metformin is a biguanide involved in several processes: it reduces gluconeogenesis of the liver, and it improves the insulin-mediated glucose uptake by skeletal muscles. It also reduces the androgens produced by ovaries and has been shown to have anti-inflammatory properties [113, 114]. Patients with mild to moderate HS have seen improvement in both the clinical course of their disease and quality of life scores when taking metformin over a 24-week period. Most of the patients in the trial were females with features of polycystic ovarian syndrome.

Historically, retinoids were frequently used for HS, because the pathogenesis was considered more similar to that of acne vulgaris. However, results have been disappointing consistent with the current understanding of HS as a follicular disorder. In all, 4 retrospective and 3 prospective uncontrolled cohort studies have been reported for isotretinoin monotherapy, for a total of 207 patients. Therapy ranged from 4 to 10 months, and outcome measures varied markedly, but a total of 85 of 207 (41%) improved, with better responses in milder disease. Isotretinoin should be considered most strongly in patients with concomitant nodulocystic acne [115].

Laser Therapies

Laser and light-based therapies have been used in the management of HS and work to reduce the occurrence of HS flare-ups by decreasing the number of hair follicles, sebaceous glands, and bacteria in affected areas. The best results are seen when treatment is individualized, taking disease severity into consideration when selecting specific energy-based approaches [116]. In a study by Tierney et al., Nd:YAG laser was shown to be an effective treatment for patients with stage II or III HS. The authors completed a prospective randomized controlled study of 22 patients in which 3 monthly laser sessions were performed on half of the body and results were compared with the other control half. Using a modified Sartorius scoring system, percentage decreases in HS severity after 3 months of treatment were 65% for all anatomic sites, 73% for inguinal sites, 62% for axillary sites, and 53% for inframammary sites. This reflected a statistically significant change in HS severity from baseline to month 3 in the treated areas but not at the control sites [117]. Carbon dioxide laser excision may help patients with more extensive involvement and has high patient satisfaction; however, it has been studied only in patients with Hurley stage II disease and has higher recurrence rates compared with wide excision [118]. In a study evaluating the carbon dioxide laser in 24 patients with a mean follow-up of 27 months, 22 patients reported resolution with no recurrence of their HS. Postsurgical results were reported to be cosmetically satisfactory [119]. Vaporization was usually able to reach the deep subcutaneous fat or fascia, and healing occurred over a median of 4 weeks.

Surgery

Patients who fail medical therapy and who are experiencing debility and pain from their HS lesions may opt for surgery which can lead to some excellent outcomes. While the evidence for surgical therapies in HS is limited and mostly based on cohort studies and case series with differing definitions and outcome measures, the main goal is always to excise the pilosebaceous or hair-bearing region of the involved area (axilla, inframammary fold, groins, and perineum). The extent of the excision will depend on the extent of the disease and the goals of the patient, with a range of options from simple incision and drainage to wide local excision and skin grafting. Excision should involve the entire skin down to the subcutaneous fat and even fascia as appropriate to ensure elimination of the pilosebaceous unit. For tense and painful abscesses, no medical therapy should be offered, and surgical drainage is required with the understanding that this is a temporizing measure and recurrence of disease is inevitable [120].

In an effort to avoid the morbidity of a large wound, studies have explored the efficacy of a deroofing technique in which the roof of a lesion is surgically removed and the floor of the lesion is left exposed. Forty-four patients with recurrent Hurley stage I or II HS lesions underwent 73 deroofing techniques with 83% showing no recurrence during a median follow-up period of 34 months. The other 17% of patients showed recurrence after a median follow-up period of 4.6 months. Ninety percent of patients responded that they would recommend the procedure to other individuals with HS [121]. A variation using an electrosurgical loop to excise the overlying skin has been developed and coined the STEEP procedure (skin tissue sparing excision with electrosurgical peeling), with a 4% recurrence rate [122]. The goal is to reduce the collateral injury to surrounding normal tissue and maintaining as much of the subcutaneous fat as possible. This is achieved by performing successive tangential excisions of the affected tissue until the epithelialized bottom of the sinus tracts has been reached. From here, healing occurs by secondary intention. Fibrotic tissue can also be completely removed as this can serve as a source of recurrence. This tissue-sparing technique results in low recurrence rates, high patient satisfaction with relatively short healing times, and favorable cosmetic outcomes without contractures [123]. No controlled, prospective studies exist, but deroofing appears to be effective for acute and chronic lesions, with utility in a variety of outpatient settings [124, 125].

For patients with more extensive disease, wide local excision has been the mainstay of traditional surgery and can result in a disease-free state where the excision is performed. Once the area has been excised, the resulting wound may be approached in different ways. If the wound is small, it can be closed primarily without tension. For larger wounds, the defect may be left open to close by secondary intention.

Perineal and perianal wounds so treated rarely require a colostomy. Large wounds may also be treated by immediate or delayed split-thickness skin graft.

Because surgery alone does not alter disease biology, understanding the trade-offs between extent of excision, surgical morbidity, and reducing the risk of future lesions is an important consideration. In a series of 590 patients treated with excision, deroofing, or drainage, drainage was associated with the highest recurrence, whereas deroofing and wide excision were about equal in effectiveness. Most patients in this series were white (91%), men (57%), and smokers (58%) with Hurley stage III disease (81%). Postoperative complications occurred in 15 patients (2.5%), and 24% suffered postoperative recurrence, which necessitated reoperation in 12% of those patients. Recurrence risk was increased by younger age (hazard ratio [HR], 0.8), multiple surgical sites (HR, 1.6), and drainage-type procedures (HR, 3.5). Operative location, disease severity, gender, and operative extent did not influence the recurrence rate [120]. In a retrospective review of 79 patients who had 220 operative sites evaluated over a 4-year period, a 25% recurrence rate was identified. The median disease-free interval between surgery and recurrence was 8 months. Almost two thirds of recurrences necessitated repeated excisional surgery ($n = 35$, 63%). Patients who achieved remission had a significantly lower number of affected regions than those who experienced a recurrence (2.3 vs 3.6, $p = .0023$). Additionally, recurrence rate differed significantly between body locations ($p = .0440$). Operative sites in the axilla had the lowest rate of recurrence, while operative sites at the groin held the highest recurrence rate. There was no significant difference between the rates of wound complication for each location. Smoking, BMI, Hurley grade, closure method, and excision size did not influence local cure rate. There was no difference in the recurrence or complication rates between operative sites closed with direct sutures, skin grafts, or rotation advancement flaps [126]. In a meta-analysis of 22 articles on surgical treatment of HS, the estimated average recurrences were wide excision, 13.0%; local incision, 22.0%; and deroofing, 27.0%. In the wide excision group, recurrence rates were as follows: 15% for primary closure, 8% for flaps, and 6.0% for grafting. The secondary intention healing option was most commonly chosen after local excision and deroofing [127].

Overall, patients report good outcomes following surgery with one study evaluating patient-reported outcomes included movement, pain, satisfaction with treatment, willingness to undergo surgery again, and appearance. Patients graded each outcome on a 4-point scale. The median score regarding function, aesthetics, and satisfaction after all interventions was 17 out of 20, but the score was lower after fasciocutaneous flaps than primary closure, healing by secondary intent, and split-thickness skin grafting [128]. In a survey of 111 patients with Hurley stage III disease following excision or unroofing, patients were satisfied or very satisfied with their surgical results (85%), were glad they underwent surgery (96%), and would recommend surgery to a friend or relative (83%). Most patients were satisfied or very satisfied with the appearance of their healed wound (62%). Retrospective mean quality of life increased significantly from 5 preoperatively to 8.4 postoperatively ($p < .001$) [125]. Negative pressure wound therapy has been shown to shorten the duration between excision and delayed closure or grafting. It has been suggested that this system improves wound healing by increasing blood flow and granulation tissue formation, reducing bacterial load, and thereby reducing the size and complexity of the wound. Comparisons of various approaches using negative-pressure wound therapy alone versus silver dressings or dermal regeneration templates (Integra, Integra LifeSciences, Plainsboro, NJ) are limited [129–131].

Conclusions

HS is a chronic disease that can result in significant debility and suffering. Most patients present in their prime working years and report a loss of productivity secondary to the waxing and waning nature of the disease. Treatment should be multidisciplinary with a focus on managing the patient's goals and expectations. For smaller areas of mild disease, topical or oral antibiotic therapy can be effective. For more widespread or severe disease, biologic agents have shown to be efficacious with newer treatment options emerging with evolving understanding of the inflammatory targets. Surgery remains an important treatment option and includes controlling infection with incision and drainage to wide local excision of the affected area to remove the hair-bearing skin followed by split-thickness skin grafting or healing by secondary intention.

References

1. Shikowitz-Behr L, Freedman A. Recurrent interdigital pilonidal sinus in a dog groomer. J Hand Microsurg. 2016. https://doi.org/10.1055/s-0036-1585469.
2. Mohanna PN, Flemming AFS, Al-Sam SZ. Subungual pilonidal sinus of the hand in a dog groomer. Br J Plast Surg. 2001. https://doi.org/10.1054/bjps.2000.3457.
3. Papa CA, Ramsey ML, Tyler WB. Interdigital pilonidal sinus in a dog groomer. J Am Acad Dermatol. 2002. https://doi.org/10.1067/mjd.2002.109256.
4. Ito A, Yoshida Y, Yamamoto O. Case of interdigital pilonidal sinus in a dog groomer. J Dermatol. 2013. https://doi.org/10.1111/1346-8138.12343.
5. Mustafa G, Akber G, Lodhi JK, Mutahir M, Malik A. Umbilical pilonidal sinus. J Ayub Med Coll Abbottabad. 2014. https://doi.org/10.1002/bjs.1800640712.

6. Dixit SP. Pilonidal sinus of the umbilicus. Can J Surg. 1976. https://doi.org/10.1016/S0140-6736(58)91196-6.
7. Thorlakson RH. Pilonidal sinus of the umbilicus. Br J Surg. 1966. https://doi.org/10.1002/bjs.1800530119.
8. Søndenaa K, Andersen E, Nesvik I, Søreide JA. Patient characteristics and symptoms in chronic pilonidal sinus disease. Int J Colorectal Dis. 1995. https://doi.org/10.1007/BF00337585.
9. Bolandparvaz S, et al. Evaluation of the risk factors of pilonidal sinus: a single center experience. Turk J Gastroenterol. 2012. https://doi.org/10.4318/tjg.2012.0381.
10. Armed Forces Health Surveillance Center (AFHSC). Pilonidal cysts, active component, U.S. Armed Forces, 2000–2012. MSMR. 2013;20(12):8–11.
11. Yildiz T, Elmas B, Yucak A, Turgut HT, Ilce Z. Risk factors for pilonidal sinus disease in teenagers. Indian J Pediatr. 2017. https://doi.org/10.1007/s12098-016-2180-5.
12. Buie LA. Jeep disease: (pilonidal disease of mechanized warfare). South Med J. 1944. https://doi.org/10.1097/00007611-194402000-00012.
13. Higgins PDR, et al. Computed tomographic enterography adds information to clinical management in small bowel Crohn's disease. Inflamm Bowel Dis. 2007. https://doi.org/10.1002/ibd.20013.
14. Doll D, et al. Family history of pilonidal sinus predisposes to earlier onset of disease and a 50% long-term recurrence rate. Dis Colon Rectum. 2009. https://doi.org/10.1007/DCR.0b013e3181a87607.
15. Harlak A, et al. Sacrococcygeal pilonidal disease: analysis of previously proposed risk factors. Clinics. 2010. https://doi.org/10.1590/S1807-59322010000200002.
16. Hull TL, Wu J. Pilonidal disease. Surg Clin North Am. 2002. https://doi.org/10.1016/S0039-6109(02)00062-2.
17. Khanna A, Rombeau JL. Pilonidal disease. Clin Colon Rectal Surg. 2011. https://doi.org/10.1055/s-0031-1272823.
18. Halleran DR, et al. Laser hair depilation in the treatment of pilonidal disease: a systematic review. Surg Infect. 2018. https://doi.org/10.1089/sur.2018.099.
19. Pronk AA, Eppink L, Smakman N, Furnee EJB. The effect of hair removal after surgery for sacrococcygeal pilonidal sinus disease: a systematic review of the literature. Tech Coloproctol. 2018. https://doi.org/10.1007/s10151-017-1722-9.
20. Ortega PM, et al. Is the cleft lift procedure for non-acute sacrococcygeal pilonidal disease a definitive treatment? Long-term outcomes in 74 patients. Surg Today. 2014. https://doi.org/10.1007/s00595-014-0923-3.
21. Dogru O, Camci C, Aygen E, Girgin M, Topuz Ö. Pilonidal sinus treated with crystallized phenol: an eight-year experience. Dis Colon Rectum. 2004. https://doi.org/10.1007/s10350-004-0720-y.
22. Dag A, Colak T, Turkmenoglu O, Sozutek A, Gundogdu R. Phenol procedure for pilonidal sinus disease and risk factors for treatment failure. Surgery. 2012. https://doi.org/10.1016/j.surg.2011.07.015.
23. Emiroğlu M, Karaali C, Esin H, Akpinar G, Aydin C. Treatment of pilonidal disease by phenol application. Turk J Surg. 2017. https://doi.org/10.5152/UCD.2016.3532.
24. Aygen E, Arslan K, Dogru O, Basbug M, Camci C. Crystallized phenol in nonoperative treatment of previously operated, recurrent pilonidal disease. Dis Colon Rectum. 2010. https://doi.org/10.1007/DCR.0b013e3181d8283b.
25. Girgin M, et al. Minimally invasive treatment of pilonidal disease: crystallized phenol and laser depilation. Int Surg. 2012. https://doi.org/10.9738/CC130.1.
26. Stephens FO, Sloane DR. Conservative management of pilonidal sinus. Surg Gynecol Obstet. 1969;129(4):786–8.
27. Stansby G, Greatorex R. Phenol treatment of pilonidal sinuses of the natal cleft. Br J Surg. 1989. https://doi.org/10.1002/bjs.1800760727.
28. Handmer M. Sticking to the facts: a systematic review of fibrin glue for pilonidal disease. ANZ J Surg. 2012. https://doi.org/10.1111/j.1445-2197.2011.05752.x.
29. Elbanna HG, et al. Novel approach of treatment of pilonidal sinus disease with thrombin gelatin matrix as a sealant. Dis Colon Rectum. 2016. https://doi.org/10.1097/DCR.0000000000000604.
30. Elsey E, Lund JN. Fibrin glue in the treatment for pilonidal sinus: high patient satisfaction and rapid return to normal activities. Tech Coloproctol. 2013. https://doi.org/10.1007/s10151-012-0956-9.
31. Sian TS, Herrod PJJ, Blackwell JEM, Hardy EJO, Lund JN. Fibrin glue is a quick and effective treatment for primary and recurrent pilonidal sinus disease. Tech Coloproctol. 2018. https://doi.org/10.1007/s10151-018-1864-4.
32. Sözen S, Emir S, Güzel K, Özdemir CŞ. Are postoperative drains necessary with the Karydakis flap for treatment of pilonidal sinus? (Can fibrin glue be replaced to drains?) A prospective randomized trial. Ir J Med Sci. 2011. https://doi.org/10.1007/s11845-010-0549-4.
33. Altinli E, Koksal N, Onur E, Celik A, Sumer A. Impact of fibrin sealant on Limberg flap technique: results of a randomized controlled trial. Tech Coloproctol. 2007. https://doi.org/10.1007/s10151-007-0320-7.
34. Lund J, Tou S, Doleman B, Williams JP. Fibrin glue for pilonidal sinus disease. Cochrane Database Syst Rev. 2017. https://doi.org/10.1002/14651858.CD011923.pub2.
35. Lund JN, Leveson SH. Fibrin glue in the treatment of pilonidal sinus: results of a pilot study. Dis Colon Rectum. 2005. https://doi.org/10.1007/s10350-004-0905-4.
36. Johnson EK, Vogel JD, Cowan ML, Feingold DL, Steele SR. The American Society of colon and rectal surgeons' clinical practice guidelines for the management of pilonidal disease. Dis Colon Rectum. 2019. https://doi.org/10.1097/DCR.0000000000001237.
37. Fitzpatrick EB, et al. Pilonidal disease in a military population: how far have we really come? Am J Surg. 2014. https://doi.org/10.1016/j.amjsurg.2013.07.038.
38. Garg P. Laying open (deroofing) and curettage under local anesthesia for pilonidal disease: an outpatient procedure. World J Gastrointest Surg. 2015. https://doi.org/10.4240/wjgs.v7.i9.214.
39. Gidwani AL, Murugan K, Nasir A, Brown R. Incise and lay open: an effective procedure for coccygeal pilonidal sinus disease. Ir J Med Sci. 2010. https://doi.org/10.1007/s11845-009-0450-1.
40. McCallum I, King PM, Bruce J. Healing by primary versus secondary intention after surgical treatment for pilonidal sinus. Cochrane Database Syst Rev. 2007. https://doi.org/10.1002/14651858.CD006213.pub2.
41. Rao MM, Zawislak W, Kennedy R, Gilliland R. A prospective randomised study comparing two treatment modalities for chronic pilonidal sinus with a 5-year follow-up. Int J Colorectal Dis. 2010. https://doi.org/10.1007/s00384-009-0804-1.
42. Khawaja HT, Bryan S, Weaver PC. Treatment of natal cleft sinus: a prospective clinical and economic evaluation. Br Med J. 1992. https://doi.org/10.1136/bmj.304.6837.1282.
43. Füzün M, et al. Which technique for treatment of pilonidal sinus-Open or closed? Dis Colon Rectum. 1994. https://doi.org/10.1007/BF02049819.
44. Søndenaa K, Nesvik I, Andersen E, Søreide JA. Recurrent pilonidal sinus after excision with closed or open treatment: final result of a randomised trial. Eur J Surg. 1996;162(3):237–40.
45. Al-Khamis A, McCallum I, King PM, Bruce J. Healing by primary versus secondary intention after surgical treatment for pilonidal sinus. Cochrane Database Syst Rev. 2010. https://doi.org/10.1002/14651858.cd006213.pub3.
46. Sewefy AM, Hassanen A, Atyia AM, Saleh SK. Karydakis flap with compressing tie-over interrupted sutures without drain versus standard Karydakis for treatment of sacrococcygeal pilonidal

sinus disease. Dis Colon Rectum. 2017. https://doi.org/10.1097/DCR.0000000000000784.
47. Kumar NA, Sutradhar P. Karydakis procedure for sacrococcygeal pilonidal sinus disease: our experience. Indian J Plast Surg. 2014. https://doi.org/10.4103/0970-0358.146615.
48. Karydakis GE. Easy and successful treatment of pilonidal sinus after explanation of its causative process. Aust N Z J Surg. 1992. https://doi.org/10.1111/j.1445-2197.1992.tb07208.x.
49. Petersen S, et al. Short-term results of Karydakis flap for pilonidal sinus disease. Tech Coloproctol. 2007. https://doi.org/10.1007/s10151-007-0357-7.
50. Keshvari A, et al. Karydakis flap versus excision-only technique in pilonidal disease. J Surg Res. 2015. https://doi.org/10.1016/j.jss.2015.05.039.
51. Alvandipour M, Zamani MS, Ghorbani M, Charati JY, Karami MY. Comparison of Limberg flap and Karydakis flap surgery for the treatment of patients with pilonidal sinus disease: a single-blinded parallel randomized study. Ann Coloproctol. 2019. https://doi.org/10.3393/ac.2018.09.27.
52. Topgül K, Özdemir E, Kiliç K, Gökbayir H, Ferahköşe Z. Long-term results of limberg flap procedure for treatment of pilonidal sinus: a report of 200 cases. Dis Colon Rectum. 2003. https://doi.org/10.1007/s10350-004-6811-y.
53. Käser SA, Zengaffinen R, Uhlmann M, Glaser C, Maurer CA. Primary wound closure with a Limberg flap vs. secondary wound healing after excision of a pilonidal sinus: a multicentre randomised controlled study. Int J Colorectal Dis. 2014. https://doi.org/10.1007/s00384-014-2057-x.
54. Urhan MK, Kücükel F, Topgul K, Özer I, Sari S. Rhomboid excision and Limberg flap for managing pilonidal sinus: results of 102 cases. Dis Colon Rectum. 2002. https://doi.org/10.1007/s10350-004-6263-4.
55. Guner A, et al. Limberg flap versus Bascom cleft lift techniques for sacrococcygeal pilonidal sinus: prospective, randomized trial. World J Surg. 2013. https://doi.org/10.1007/s00268-013-2111-9.
56. Bascom J, Bascom T. Failed pilonidal surgery: new paradigm and new operation leading to cures. Arch Surg. 2002. https://doi.org/10.1001/archsurg.137.10.1146.
57. Bascom J, Bascom T. Utility of the cleft lift procedure in refractory pilonidal disease. Am J Surg. 2007. https://doi.org/10.1016/j.amjsurg.2007.01.008.
58. Senapati A, Cripps NPJ, Flashman K, Thompson MR. Cleft closure for the treatment of pilonidal sinus disease. Colorectal Dis. 2011. https://doi.org/10.1111/j.1463-1318.2009.02148.x.
59. Milone M, et al. Video-assisted ablation of pilonidal sinus: a new minimally invasive treatment – a pilot study. Surgery (United States). 2014. https://doi.org/10.1016/j.surg.2013.08.021.
60. Kalaiselvan R, Liyanage A, Rajaganeshan R. Short-term outcomes of endoscopic pilonidal sinus treatment. Ann R Coll Surg Engl. 2019. https://doi.org/10.1308/rcsann.2019.0097.
61. Milone M, et al. Video-assisted ablation of pilonidal sinus (VAAPS) versus sinusectomy for treatment of chronic pilonidal sinus disease: a comparative study. Updates Surg. 2019. https://doi.org/10.1007/s13304-018-00611-2.
62. Gecim IE, Goktug UU, Celasin H. Endoscopic pilonidal sinus treatment combined with crystalized phenol application may prevent recurrence. Dis Colon Rectum. 2017. https://doi.org/10.1097/DCR.0000000000000778.
63. Gecim IE, Goktug UU, Celasin H, Balcl D. Video-assisted treatment of pilonidal disease, using a combination of diathermy ablation and phenol application. BMJ Case Rep. 2016. https://doi.org/10.1136/bcr-2016-214629.
64. Romaniszyn M, Swirta JS, Walega PJ. Long-term results of endoscopic pilonidal sinus treatment vs Limberg flap for treatment of difficult cases of complicated pilonidal disease: a prospective, nonrandomized study. Colorectal Dis. 2019. https://doi.org/10.1111/codi.14857.
65. Pappas AF, Christodoulou DK. A new minimally invasive treatment of pilonidal sinus disease with the use of a diode laser: a prospective large series of patients. Colorectal Dis. 2018. https://doi.org/10.1111/codi.14285.
66. Georgiou GK. Outpatient laser treatment of primary pilonidal disease: the PiLaT technique. Tech Coloproctol. 2018. https://doi.org/10.1007/s10151-018-1863-5.
67. Dessily M, Charara F, Ralea S, Allé JL. Pilonidal sinus destruction with a radial laser probe: technique and first Belgian experience. Acta Chir Belg. 2017. https://doi.org/10.1080/00015458.2016.1272285.
68. Gips M, Melki Y, Salem L, Weil R, Sulkes J. Minimal surgery for pilonidal disease using trephines: description of a new technique and long-term outcomes in 1,358 patients. Dis Colon Rectum. 2008. https://doi.org/10.1007/s10350-008-9329-x.
69. Di Castro A, Guerra F, Levi Sandri GB, Ettorre GM. Minimally invasive surgery for the treatment of pilonidal disease. The Gips procedure on 2347 patients. Int J Surg. 2016. https://doi.org/10.1016/j.ijsu.2016.10.040.
70. Uçar AD, et al. Recurrent pilonidal disease surgery: is it second primary or reoperative surgery? Turk J Surg. 2016. https://doi.org/10.5152/UCD.2015.3112.
71. Halleran DR, et al. Recurrence of pilonidal disease: our best is not good enough. J Surg Res. 2018. https://doi.org/10.1016/j.jss.2018.06.071.
72. Alikhan A, Lynch PJ, Eisen DB. Hidradenitis suppurativa: a comprehensive review. J Am Acad Dermatol. 2009. https://doi.org/10.1016/j.jaad.2008.11.911.
73. Sandhu VK, Shah M, Piguet V, Alavi A. The impact of Hidradenitis suppurativa on work productivity and activity impairment. Br J Dermatol. 2019. https://doi.org/10.1111/bjd.18695.
74. Garg A, Kirby JS, Lavian J, Lin G, Strunk A. Sex- and age-adjusted population analysis of prevalence estimates for hidradenitis suppurativa in the United States. JAMA Dermatol. 2017. https://doi.org/10.1001/jamadermatol.2017.0201.
75. Liy-Wong C, Pope E, Lara-Corrales I. Hidradenitis suppurativa in the pediatric population. J Am Acad Dermatol. 2015. https://doi.org/10.1016/j.jaad.2015.07.051.
76. Deckers IE, Van Der Zee HH, Boer J, Prens EP. Correlation of early-onset hidradenitis suppurativa with stronger genetic susceptibility and more widespread involvement. J Am Acad Dermatol. 2015. https://doi.org/10.1016/j.jaad.2014.11.017.
77. Garg A, Papagermanos V, Midura M, Strunk A. Incidence of hidradenitis suppurativa among tobacco smokers: a population-based retrospective analysis in the U.S.A. Br J Dermatol. 2018. https://doi.org/10.1111/bjd.15939.
78. Kurzen H, et al. What causes hidradenitis suppurativa? Exp Dermatol. 2008. https://doi.org/10.1111/j.1600-0625.2008.00712_1.x.
79. Acharya P, Mathur M. Hidradenitis suppurativa and smoking: a systematic review and meta-analysis. J Am Acad Dermatol. 2019. https://doi.org/10.1016/j.jaad.2019.10.044.
80. Revuz JE, et al. Prevalence and factors associated with hidradenitis suppurativa: results from two case-control studies. J Am Acad Dermatol. 2008. https://doi.org/10.1016/j.jaad.2008.06.020.
81. Sartorius K, Emtestam L, Jemec GBE, Lapins J. Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. Br J Dermatol. 2009. https://doi.org/10.1111/j.1365-2133.2009.09198.x.
82. Vossen ARJV, van der Zee HH, Prens EP. Hidradenitis suppurativa: a systematic review integrating inflammatory pathways into a cohesive pathogenic model. Front Immunol. 2018. https://doi.org/10.3389/fimmu.2018.02965.
83. Negus D, Ahn C, Huang W. An update on the pathogenesis of hidradenitis suppurativa: implications for therapy. Expert

Rev Clin Immunol. 2018. https://doi.org/10.1080/1744666X.2018.1449647.
84. Melnik BC, John SM, Chen W, Plewig G. T helper 17 cell/regulatory T-cell imbalance in hidradenitis suppurativa/acne inversa: the link to hair follicle dissection, obesity, smoking and autoimmune comorbidities. Br J Dermatol. 2018. https://doi.org/10.1111/bjd.16561.
85. Ergun T. Hidradenitis suppurativa and the metabolic syndrome. Clin Dermatol. 2018. https://doi.org/10.1016/j.clindermatol.2017.09.007.
86. Prens E, Deckers I. Pathophysiology of hidradenitis suppurativa: an update. J Am Acad Dermatol. 2015. https://doi.org/10.1016/j.jaad.2015.07.045.
87. Saunte DM, et al. Diagnostic delay in hidradenitis suppurativa is a global problem. Br J Dermatol. 2015. https://doi.org/10.1111/bjd.14038.
88. Yao Y, Jørgensen AHR, Thomsen SF. Work productivity and activity impairment in patients with hidradenitis suppurativa: a cross-sectional study. Int J Dermatol. 2019. https://doi.org/10.1111/ijd.14706.
89. Hessam S, et al. A novel severity assessment scoring system for hidradenitis suppurativa. JAMA Dermatol. 2018. https://doi.org/10.1001/jamadermatol.2017.5890.
90. Prens LM, et al. The refined Hurley classification: the inter-rater and intrarater reliability and face validity. Br J Dermatol. 2019. https://doi.org/10.1111/bjd.18235.
91. Rondags A, et al. Correlation of the refined Hurley classification for hidradenitis suppurativa with patient-reported quality of life and objective disease severity assessment. Br J Dermatol. 2019. https://doi.org/10.1111/bjd.17508.
92. Kimball AB, et al. Assessing the validity, responsiveness and meaningfulness of the Hidradenitis Suppurativa Clinical Response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment. Br J Dermatol. 2014. https://doi.org/10.1111/bjd.13270.
93. Clark D. Roenigk & Roenigk's dermatologic surgery: principles and practice. Mayo Clin Proc. 1996. https://doi.org/10.1016/s0025-6196(11)64852-0.
94. Gulliver W, Zouboulis CC, Prens E, Jemec GBE, Tzellos T. Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa. Rev Endocr Metab Disord. 2016. https://doi.org/10.1007/s11154-016-9328-5.
95. Choi F, Lehmer L, Ekelem C, Mesinkovska NA. Dietary and metabolic factors in the pathogenesis of hidradenitis suppurativa: a systematic review. Int J Dermatol. 2019. https://doi.org/10.1111/ijd.14691.
96. Canoui-Poitrine F, et al. Clinical characteristics of a series of 302 French patients with hidradenitis suppurativa, with an analysis of factors associated with disease severity. J Am Acad Dermatol. 2009. https://doi.org/10.1016/j.jaad.2009.02.013.
97. Schrader AMR, Deckers IE, Van Der Zee HH, Boer J, Prens EP. Hidradenitis suppurativa: a retrospective study of 846 Dutch patients to identify factors associated with disease severity. J Am Acad Dermatol. 2014. https://doi.org/10.1016/j.jaad.2014.04.001.
98. Clemmensen OJ. Topical treatment of hidradenitis suppurativa with clindamycin. Int J Dermatol. 1983. https://doi.org/10.1111/j.1365-4362.1983.tb02150.x.
99. Pascual JC, et al. Topical 15% resorcinol for hidradenitis suppurativa: an uncontrolled prospective trial with clinical and ultrasonographic follow-up. J Am Acad Dermatol. 2017. https://doi.org/10.1016/j.jaad.2017.07.008.
100. Bettoli V, Join-Lambert O, Nassif A. Antibiotic treatment of hidradenitis suppurativa. Dermatol Clin. 2016. https://doi.org/10.1016/j.det.2015.08.013.
101. Jemec GBE, Wendelboe P. Topical clindamycin versus systemic tetracycline in the treatment of hidradenitis suppurativa. J Am Acad Dermatol. 1998. https://doi.org/10.1016/S0190-9622(98)70272-5.
102. Gener G, et al. Combination therapy with clindamycin and rifampicin for hidradenitis suppurativa: a series of 116 consecutive patients. Dermatology. 2009. https://doi.org/10.1159/000228334.
103. Dessinioti C, Zisimou C, Tzanetakou V, Stratigos A, Antoniou C. Oral clindamycin and rifampicin combination therapy for hidradenitis suppurativa: a prospective study and 1-year follow-up. Clin Exp Dermatol. 2016. https://doi.org/10.1111/ced.12933.
104. Kimball AB, et al. Adalimumab for the treatment of moderate to severe hidradenitis suppurativa: a parallel randomized trial. Ann Intern Med. 2012. https://doi.org/10.7326/0003-4819-157-12-201212180-00004.
105. Kimball AB, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. N Engl J Med. 2016. https://doi.org/10.1056/NEJMoa1504370.
106. Miller I, et al. A double-blind placebo-controlled randomized trial of adalimumab in the treatment of hidradenitis suppurativa. Br J Dermatol. 2011. https://doi.org/10.1111/j.1365-2133.2011.10339.x.
107. Tzanetakou V, et al. Safety and efficacy of anakinra in severe hidradenitis suppurativa a randomized clinical trial. JAMA Dermatol. 2016. https://doi.org/10.1001/jamadermatol.2015.3903.
108. Blok JL, et al. Ustekinumab in hidradenitis suppurativa: clinical results and a search for potential biomarkers in serum. Br J Dermatol. 2016. https://doi.org/10.1111/bjd.14338.
109. Van Rappard DC, Mekkes JR. Treatment of severe hidradenitis suppurativa with infliximab in combination with surgical interventions. Br J Dermatol. 2012. https://doi.org/10.1111/j.1365-2133.2012.10807.x.
110. Shanmugam VK, et al. Longitudinal observational study of hidradenitis suppurativa: impact of surgical intervention with adjunctive biologic therapy. Int J Dermatol. 2018. https://doi.org/10.1111/ijd.13798.
111. Defazio MV, et al. Outcomes after combined radical resection and targeted biologic therapy for the management of recalcitrant hidradenitis suppurativa. Ann Plast Surg. 2016. https://doi.org/10.1097/SAP.0000000000000584.
112. Riis PT, Ring HC, Themstrup L, Jemec GB. The role of androgens and estrogens in hidradenitis suppurativa – a systematic review. Acta Dermatovenerol Croat. 2016;24(4):239–49.
113. Saisho Y. Metformin and inflammation: its potential beyond glucose-lowering effect. Endocr Metab Immune Disord Drug Targets. 2015. https://doi.org/10.2174/1871530315666150316124019.
114. Verdolini R, Clayton N, Smith A, Alwash N, Mannello B. Metformin for the treatment of hidradenitis suppurativa: a little help along the way. J Eur Acad Dermatol Venereol. 2013. https://doi.org/10.1111/j.1468-3083.2012.04668.x.
115. Alikhan A, et al. North American clinical management guidelines for hidradenitis suppurativa: a publication from the United States and Canadian Hidradenitis Suppurativa Foundations: part II: topical, intralesional, and systemic medical management. J Am Acad Dermatol. 2019. https://doi.org/10.1016/j.jaad.2019.02.068.
116. Hamzavi IH, Griffith JL, Riyaz F, Hessam S, Bechara FG. Laser and light-based treatment options for hidradenitis suppurativa. J Am Acad Dermatol. 2015. https://doi.org/10.1016/j.jaad.2015.07.050.
117. Mahmoud BH, et al. Prospective controlled clinical and histopathologic study of hidradenitis suppurativa treated with the long-pulsed neodymium:yttrium-aluminium-garnet laser. J Am Acad Dermatol. 2010. https://doi.org/10.1016/j.jaad.2009.07.048.
118. Mikkelsen PR, Dufour DN, Zarchi K, Jemec GBE. Recurrence rate and patient satisfaction of CO2 laser evaporation of lesions

in patients with hidradenitis suppurativa: a retrospective study. Dermatol Surg. 2015. https://doi.org/10.1097/DSS.0000000000000264. LK – http://limo.libis.be/resolver?&sid=EMBASE&issn=15244725&id=doi:10.1097%2FDSS.0000000000000264&atitle=Recurrence+rate+and+patient+satisfaction+of+CO2+laser+evaporation+of+lesions+in+patients+with+hidradenitis+suppurativa%3A+A+retrospective+study&stitle=Dermatol.+Surg.&title=Dermatologic+Surgery&volume=41&issue=2&spage=255&epage=260&aulast=Mikkelsen&aufirst=Peter+Riis&auinit=P.R.&aufull=Mikkelsen+P.R.&coden=DESUF&isbn=&pages=255-260&date=2015&auinit1=P&auinitm=R.

119. Lapins J, Marcusson JA, Emtestam L. Surgical treatment of chronic hidradenitis suppurativa: CO2 laser stripping-secondary intention technique. Br J Dermatol. 1994. https://doi.org/10.1111/j.1365-2133.1994.tb08559.x.
120. Kohorst JJ, et al. Surgical management of hidradenitis suppurativa: outcomes of 590 consecutive patients. Dermatol Surg. 2016. https://doi.org/10.1097/DSS.0000000000000806.
121. Van Der Zee HH, Prens EP, Boer J. Deroofing: a tissue-saving surgical technique for the treatment of mild to moderate hidradenitis suppurativa lesions. J Am Acad Dermatol. 2010. https://doi.org/10.1016/j.jaad.2009.12.018.
122. Van Hattem S, Spoo JR, Horváth B, Jonkman MF, Leeman FWJ. Surgical treatment of sinuses by deroofing in hidradenitis suppurativa. Dermatol Surg. 2012. https://doi.org/10.1111/j.1524-4725.2011.02255.x.
123. Blok JL, Spoo JR, Leeman FWJ, Jonkman MF, Horváth B. Skin-tissue-sparing excision with electrosurgical peeling (STEEP): a surgical treatment option for severe hidradenitis suppurativa Hurley stage II/III. J Eur Acad Dermatol Venereol. 2015. https://doi.org/10.1111/jdv.12376.
124. Lin CH, Chang KP, Huang SH. Deroofing: an effective method for treating chronic diffuse hidradenitis suppurativa. Dermatol Surg. 2016. https://doi.org/10.1097/DSS.0000000000000609.
125. Kohorst JJ, et al. Patient satisfaction and quality of life following surgery for hidradenitis suppurativa. Dermatol Surg. 2017. https://doi.org/10.1097/DSS.0000000000000942.
126. Ngaage LM, et al. Factors influencing the local cure rate of hidradenitis suppurativa following wide local excision. Int Wound J. 2019. https://doi.org/10.1111/iwj.13241.
127. Mehdizadeh A, et al. Recurrence of hidradenitis suppurativa after surgical management: a systematic review and meta-analysis. J Am Acad Dermatol. 2015. https://doi.org/10.1016/j.jaad.2015.07.044.
128. Ovadja ZN, Bartelink SAW, van de Kar AL, van der Horst CMAM, Lapid O. A multicenter comparison of reconstruction strategies after wide excision for severe axillary hidradenitis suppurativa. Plast Reconstr Surg Glob Open. 2019. https://doi.org/10.1097/gox.0000000000002361.
129. Gonzaga TA, Endorf FW, Mohr WJ, Ahrenholz DH. Novel surgical approach for axillary hidradenitis suppurativa using a bilayer dermal regeneration template: a retrospective case study. J Burn Care Res. 2013. https://doi.org/10.1097/BCR.0b013e31826a7be7.
130. Pearce FB, Richardson KA. Negative pressure wound therapy, staged excision and definitive closure with split-thickness skin graft for axillary hidradenitis suppurativa: a retrospective study. J Wound Care. 2017. https://doi.org/10.12968/jowc.2017.26.Sup1.S36. LK – http://limo.libis.be/resolver?&sid=EMBASE&issn=09690700&id=doi:10.12968%2Fjowc.2017.26.Sup1.S36&atitle=Negative+pressure+wound+therapy%2C+staged+excision+and+definitive+closure+with+split-thickness+skin+graft+for+axillary+hidradenitis+suppurativa%3A+a+retrospective+study&stitle=J+Wound+Care&title=Journal+of+wound+care&volume=26&issue=&spage=S36&epage=S42&aulast=Pearce&aufirst=F.B.&auinit=F.B.&aufull=Pearce+F.B.&coden=&isbn=&pages=S36-S42&date=2017&auinit1=F&a.
131. Parrado R, Cadena M, Vergara A, Cadena D, Chalela JG. The role of negative pressure wound therapy in the management of hidradenitis suppurativa: a case report and literature review. Int Wound J. 2017. https://doi.org/10.1111/iwj.12544.

Dermatology and Pruritus Ani

17

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Key Concepts

- Pruritus ani often results in considerable emotional and physical distress and significantly affects the patient's quality of life.
- A detailed and complete history and physical examination can help to identify a specific etiology in 75% of cases.
- Culture swabs and skin biopsy are important adjuncts to physical examination.
- In most cases, initial therapeutic approach is aimed at improvement of anal hygiene, dietary modification, and toileting habits.
- The patient's expectations should be set to anticipate slow improvement of their symptoms.
- Various topical and systemic therapeutic modalities can be offered sequentially with emphasis on incremental improvement rather than complete resolution of symptoms.

Introduction

Pruritus ani is a condition characterized by severe, intense itching around the perianal area. Pruritus ani is the Latin term for "itchy anus" and describes all conditions that result in itching and irritation in the perianal skin. The disease has been first reported in ancient Egypt [1]. Since, it has continued to be a serious disorder usually arising from benign conditions. It may be transient or chronic and difficult to treat. In the 1600s, pruritus (itch) was officially defined by the German physician Samuel Hafenreffer as the "unpleasant sensation that elicits the desire or reflex to scratch" [2]. Anal pruritus is estimated to affect 2–5% of the general population, but most patients will not seek medical attention, unless the symptoms intensify or become chronic [3]. Anal pruritus is more common in the fourth to sixth decades of life and has a higher prevalence in males (4:1 ratio compared to females) [4]. Treating patients with anal pruritus can be frustrating for both the patient and the physician. Having the patient understand the possible cause of the disease, the pathophysiology, and the steps in the treatment of it is critical. This common understanding will help the patient manipulate through a complex treatment plan without losing trust for the treating physician.

The purpose of this chapter is to summarize the presentation and diagnostic approach to pruritus ani, as well as the available treatment strategies and their supporting evidence.

Pathophysiology

The urge to itch in pruritus ani is mediated by the extensive, unmyelinated C fibers that are predominant in the anoderm and perianal skin. Stimulation of these fibers leads to scratching and frequent wiping in order to relieve the urge. This often contributes to excoriation and cutaneous injury, which causes additional stimulation of the C fibers, inciting more itching and scratching (Fig. 17.1). Itch-transmitting polymodal, unmyelinated C fibers enter the dorsal horn of the grey matter of the spinal cord and synapse there with secondary neurons, which cross over to the contralateral spinothalamic tract and ascend to the thalamus [5]. Then tertiary neurons relay itch to the level of conscious perception in the cerebral cortex, anterior cingulate, and insular cortex, while the premotor cortical areas participate in intention to scratch. The most important cytokine mediators of itch sensation include histamine, acetyl choline, substance P, calcitonin gene-related peptide (CGRP), opioid peptides, proteases, bradykinin, serotonin, platelet-activating factor, neurotrophins, prostaglandin E, and other cytokines. Histamine is the most potent pruritogen.

There are two major biochemical pathways for the sensation of itch, one is histamine dependent and one is not. Histamine receptors are coupled with Gq proteins, which upon

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Fig. 17.1 The "vicious cycle" of pruritus ani. Stimulation of C fibers leads to scratching and frequent wiping in order to relieve the urge that contributes to excoriation and cutaneous injury, which causes additional stimulation of the C fibers

binding on histamine activates phospholipase Cβ3 (PLCβ3), which in turn cleaves phosphotidylinositol-4-5-biphosphonate (PIP2) into the second messengers diacylglycerol (DAG) and inositol triphosphate (IP3). DAG activates protein kinase Cε (PKCε) which phosphorylates and thereby opens the TRPV1. Activation of TRPV1 leads to channel opening which allows passage of the positively charged ions sodium, potassium, and calcium resulting in depolarization. Thereby voltage-dependent sodium channels are activated generating action potentials along the nerve fiber which lead to the sensation of itch. Histamine-induced itch is mediated by activation of TRPV1 and requires phosphoinositide-interacting regulator of transient receptor potential channels (PIRT), a membrane protein modulating TRPV1 function [6–11].

In the non-histaminergic pathway of itch, PAR-2 has been shown to play a crucial role [12]. PAR-2 activation has been shown to increase the release of IL-6 and granulocyte-macrophage colony-stimulating factor from keratinocytes in atopic eczema patients. 5-HT is, like histamine, mainly secreted from skin mast cells in the periphery and is able to activate sensory neurons directly. The action of 5-HT may be partly mediated by cutaneous 5-HT2 receptor. It activates PLC 3 elicits, an itching sensation associated with pruritic diseases, such as polycythemia vera and cholestasis.

Etiology

Approximately 75 percent of cases of anal pruritus are secondary to inflammatory, infectious, systemic, neoplastic, and anorectal disorders that contribute to the development of pruritus (Table 17.1). Despite extensive workup, no clear etiology of pruritus ani can be identified in up to 25% of patients.

Table 17.1 Common causes of anal pruritus

Category	Specific inciting factors
Diet	Tomatoes, chocolate, citric fruits, spices, coffee (including both caffeinated and decaffeinated), tea, cola, beer, milk and other dairy products
	Popcorn, figs, prunes, grapes, spicy foods, peanuts
Diarrheal state	Inflammatory bowel diseases, irritable bowel syndrome
Fecal soiling	Encopresis
	Incontinence
	Chronic diarrhea
	Poor hygiene
	Transient relaxation of internal sphincter
	Prolapsed, hemorrhoids, etc.
Local irritation	Soaps and detergents
	Topical creams and medications
	Obesity, excessive hair
	Tight-fit clothing
	Poor hygiene or excessive hygiene
Dermatologic disorders	Psoriasis
	Contact dermatitis
	Atopic dermatitis
	Bowen's disease, Paget's disease
	Hidradenitis
Anorectal disorders	Fissures
	Hemorrhoids
	Proctitis
	Abscess
	Fistula
	Rectal cancer
	Anal cancer (squamous cell carcinoma)
	Adenomatous
Infections	*Candida albicans*
	Dermatophytes (*Malassezia furfur*)
	Staphylococcus aureus
	Beta-hemolytic streptococcus
	Corynebacterium minutissimum (erythrasma)
	Human papilloma virus
	Herpes simplex
	Sarcoptes scabiei (scabies)
	Enterobius vermicularis (pinworms)
Systemic disease	Diabetes mellitus
	Leukemia
	Thyroid disorders
	Liver disease
	Renal failure
Gynecologic	Menopause, vaginitis
Psychological	Depression, anxiety, psychosis

These cases are classified as idiopathic, or primary, pruritus ani and are considered as a diagnosis of exclusion. Cases with no identifiable cause are the most difficult to treat.

Fecal Soilage

It is very common for patients to have perianal fecal contamination that leads to increased wiping that consequently

is associated with trauma and continuous scratching. Fecal soilage can be present because of diarrhea, anal incontinence, pelvic floor dysfunction, or just lack of adequate dietary fiber [13]. In a case-control study that included 23 men with anal pruritus and 16 controls who underwent anorectal electromyography and manometry, patients with anal pruritus had a greater rise in rectal pressure during internal sphincter relaxation (29 versus 18 mmHg) and prolonged internal sphincter relaxation (29 versus 8 seconds) as compared with controls [13]. Others have shown that after doing a saline infusion test, patients with anal pruritus develop early leakage (after 600 mL) as compared to control subjects (after 1300 mL). There is an inverse relationship to the severity of symptoms and the volume of first leakage. Again, leaking and soiling seem to be major factors. Although rare, anal manometry should be considered in cases with negative initial workup and no improvement after intensive therapy. Furthermore, in patients with anal itching and pelvic floor dysfunction, the role of pelvic floor physical therapy is important and should be encouraged in such cases. In patients with chronic diarrhea such as ulcerative colitis, Crohn's disease, or irritable bowel syndrome, the treatment of the primary disease will usually resolve the anal pruritus.

Dietary Factors and Medications

Specific foods such as coffee, tomatoes, beer, cola, tea, peanuts, milk produce, citrus, chocolate, and grapes have been implicated in causing or exacerbating pruritus ani. Some studies have reported that pruritus ani was reduced within 2 weeks after avoiding specific foods, such as chocolate, citric fruits, spices, coffee (including both caffeinated and decaffeinated), tea, cola, beer, milk and other dairy products, and tomatoes and tomato-based products like ketchup [14]. It is not clear whether food-induced pruritus ani is a variation of an allergic reaction to the food or a consequence of direct exposure of the skin to specific ingredients [15]. Several medications such as tetracycline, colchicine, quinidine, peppermint oil, local anesthetics, and neomycin have been associated with anal pruritus. It is unclear if these medications and foods act as direct irritants or indirectly cause irritation by causing diarrhea or fecal seepage. These food and medication can alter the pH of the stool or lower sphincter tone. Relaxed anal sphincter pressure combined with exaggerated anal reflexes lead to liquid stools, quicker transit time, and increased frequency of bowel movements. Ultimately, soiling progresses as does perianal trauma from repetitive cleaning. If a food, beverage, or medication is found to exacerbate symptoms, it should be avoided.

Dermatologic Diseases

Several dermatologic diseases can present with perianal skin lesions or no findings on exam and cause severe anal pruritus [16].

Contact dermatitis is the most common perianal dermatologic condition and is characterized by macular erythema, hyperkeratosis, or radial fissuring. Irritant contact dermatitis results from exposure to substances that cause physical, mechanical, or chemical irritation of the skin [16]. Contact dermatitis can be just from mechanical irritation or from an immune-mediated reaction, which is a result of a mechanical or chemical irritant that may act as an allergen [17]. Irritant contact dermatitis can be caused by common exposures used repeatedly on a daily basis (soaps, cleansers, rubbing alcohol, feces) and, in some cases, with one exposure (bleach, formalin). Treatment involves removing the offending agent, keeping the area dry (cotton ball or folded cotton gauze), and avoiding further trauma to the skin. For cases that first line of treatment is not successful, patch testing by an allergist or dermatologist can be useful to determine if there is an inciting allergen, especially in severe or refractory contact dermatitis.

Atopic dermatitis presents with thickened skin and leathery patches. This commonly hereditary condition presents at a young age (early childhood) and is associated with other lesions in the neck, antecubital, and popliteal fossas. The diagnosis is most of the times clinical based on the type of skin lesions (thickened skin, increased skin markings, lichenification, and excoriated and fibrotic papules), early onset in life (younger than 10 years old), significant family history of severe allergic disease, and the associated skin lesions in flexor areas of the body. Treatment is with a topical barrier like petroleum-based creams, zinc oxide creams, anti-inflammatory drugs, and antihistamines. The concomitant use of topical anesthetics and steroids, while leading to temporary relief, can frustrate attempts at identification of the inciting compound.

Psoriasis presents with erythema and sharply defined boundaries with or without the typical scaling. In most cases of perianal psoriasis, the characteristic scaling is not visible. The psoriasis plaques may look different due to the persistent scratching thereby making the diagnosis difficult. These lesions are sometimes referred to as inverse psoriasis because they are without scales and tend to be paler. Inverse psoriasis, also known as intertriginous or skin-fold psoriasis, is a form of psoriasis that presents itself as erythematous plaques with poor or non-desquamation in skin flexion folds. Patients with anal psoriasis present a cyclical quality to the symptoms, with the majority of pruritus occurring at night. The presence of associated lesions in the groin, genitalia, intergluteal cleft, axilla,

and umbilicus will hint the physician to place the appropriate diagnosis. Furthermore, there are forms of paradoxical psoriasis in the perianal area that can be caused by biologic therapy (anti TNFa agents) for the treatment of patients with inflammatory bowel disease [18]. For perianal psoriasis, the treatment is usually a low- to mid-potency topical steroid. Tacrolimus and dapsone can also be used for more severe cases [19].

Lichen simplex chronicus is a condition that can result from chronic diarrhea. Inflammation in the perianal area results in thickened (lichenified) and cracked, excoriated skin. Treatment is focused on controlling the frequency of bowel movements. Psyllium husk, loperamide, and silver sulfadiazine can be used with addition of low-dose hydrocortisone for more severe cases.

In a similar way, *lichen sclerosus* (*atrophicus*) presents mainly in women with a thinning and wrinkling of the perianal skin, also known as a "cigarette-paper" appearance with associated skin discoloration. This also classically affects the labial skin and perineum. Lichen sclerosis may be associated with squamous cell carcinoma. Thus, the affected area should be examined at least annually, and a biopsy should be considered for any suspicious lesions. Treatment is a topical glucocorticoid like clobetasol propionate 0.05% for 6–8 weeks [20]. Tacrolimus has also been used for this condition.

Seborrheic dermatitis is a rare cause of anal itching. It is caused by a fungus called *Malassezia furfur*, and it is treated with an antidandruff shampoo or any other topical antifungal agent.

Hidradenitis suppurativa is a chronic, suppurative process involving the skin and subcutaneous tissue. The usual initial presentation is of recurrent, painful, and inflamed nodules. The nodules may rupture, discharging purulent, sometimes malodorous material. Persistent disease leads to the formation of sinus tracts, end-stage "tombstone" comedones, and scarring [21]. There are three stages of the disease: stage 1 is abscess formation, single or multiple, without scarring or sinus tracts; stage 2 is recurrent abscesses with tract formation and scarring, single or multiple, and widely separated lesions (Fig. 17.2); and stage 3 is multiple interconnected tracts and abscesses throughout an entire body area. Treatment strategies can be categorized broadly into medical and surgical. Antibiotics, retinoids, hormones, and immunosuppressive agents have been used. All have shown success in reducing symptoms temporarily but none long term. Antibiotics must be chosen to cover both aerobic and anaerobic bacteria. Topical clindamycin and oral clindamycin with rifampin, in addition to tetracycline, erythromycin, and doxycycline, have shown efficacy at reducing symptoms. Long-term treatment up to 12 weeks is required to achieve remission. Evidence is lacking that antibiotics change the natural course of this disease. Isotretinoin, finasteride, prednisone, and cyclosporine have resulted in temporary remission. Infliximab and etanercept (TNF-α inhibitors) are biologics that have shown promise in improving symptoms. Radiation, cryosurgery, and laser therapy have been effective in a small series of patients with early stages. Upon diagnosis of HS, the extent and stage of disease should guide surgical approach. For stages 2–3, surgery is regarded as the most effective treatment.

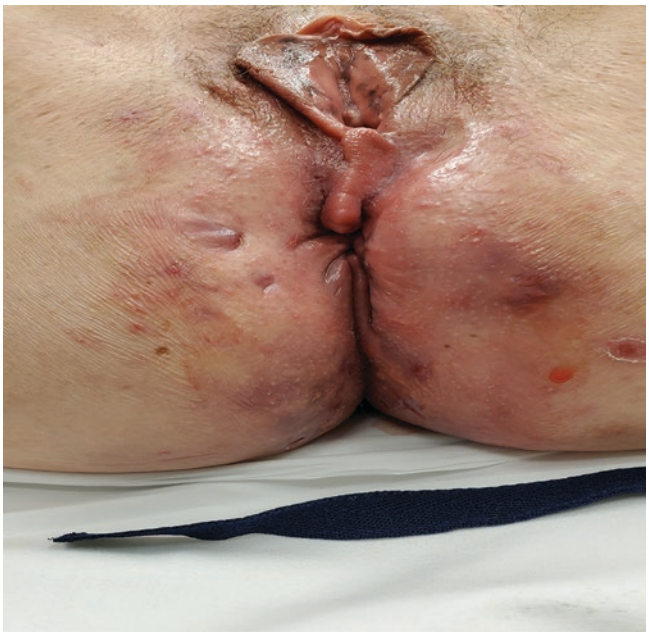

Fig. 17.2 Mild form of hidradenitis suppurativa with several abscesses and sinus tracts

Cutaneous *squamous cell carcinoma* in situ (Bowen's disease) appears as a well-demarcated plaque with crusting and scaling. Perianal *intraepithelial adenocarcinoma* (Paget disease, Fig. 17.3) usually occurs in the seventh decade of life and appears as a slowly expanding, sharply demarcated erythematous plaque that can be eczematous, crusting, scaling, or ulcerated. If discovered, endoscopic evaluation of the colon is needed to rule out an underlying carcinoma. Wide local excision with frozen sections is performed in noninvasive Paget's disease, while more radical surgery may be required for invasive disease [22]. Cloacogenic carcinoma and squamous cell carcinoma of the anal margin can present with refractory pruritus ani (Fig. 17.4) [23]. Thus, for any lesions that do not respond to the first line of treatment, biopsy is mandatory in order to rule out neoplastic disease.

Other skin disorders that may be associated with anal pruritus include scleroderma, erythema multiforme, dermatitis herpetiformis, lichen planus, radiation dermatitis, and Darier disease.

Anorectal diseases associated with anal pruritus include prolapsed internal hemorrhoids, abscesses, fissures, and fistulas. Details about the diagnosis and treatment of these diseases are given in a different chapter.

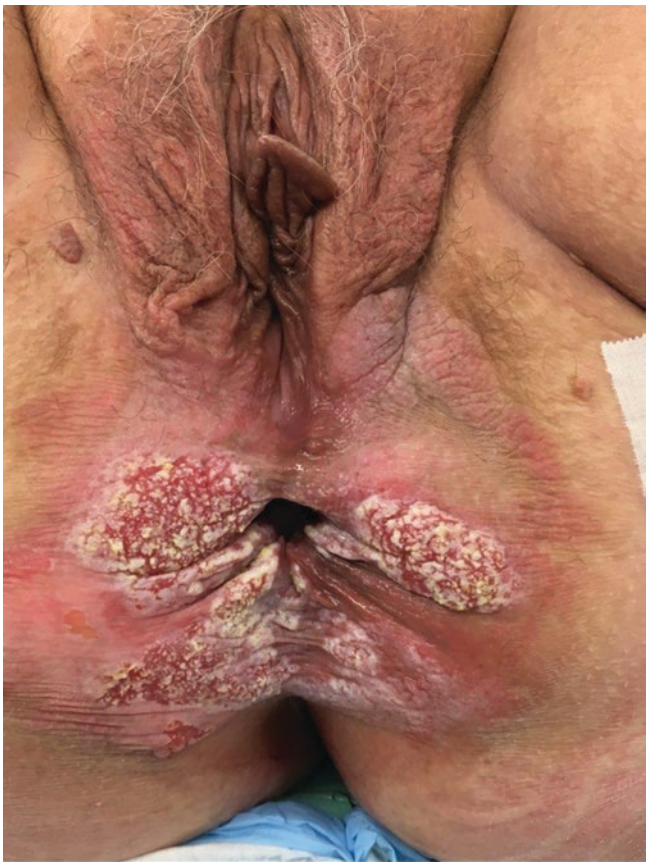

Fig. 17.3 Paget's disease of the perianal skin. (Courtesy of Dr. Dana Fugelso)

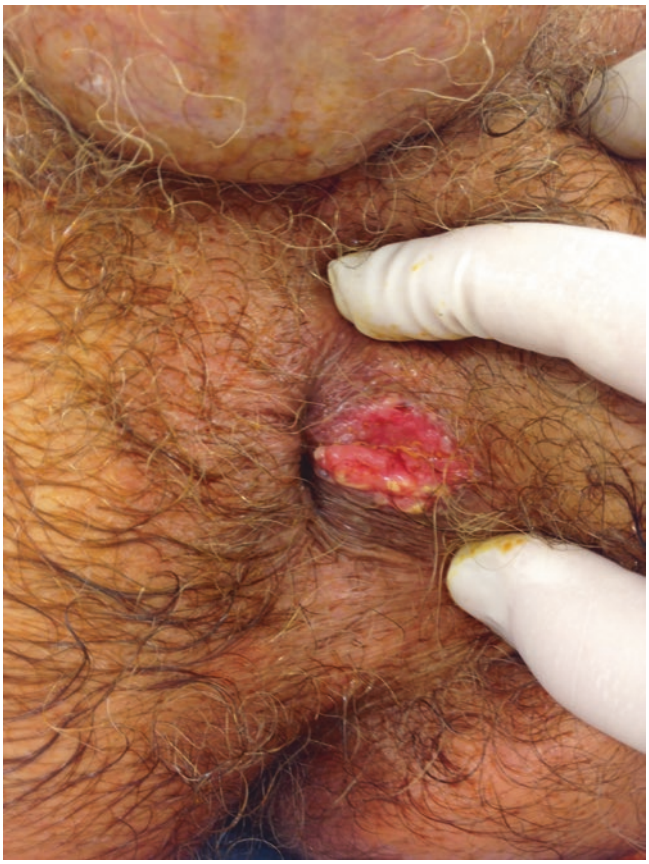

Fig. 17.4 Anal carcinoma presenting as an ulcer. (Courtesy of Dr. Dana Fugelso)

Pruritus ani can have an *infectious* inciting factor. Risk factors for developing an infection that can cause anal symptomatology include diabetes, immunocompromised state, obesity, hyperhidrosis, and living in tropical climates. *Fungal infections* are the most common perianal infections [16]. These include *Candida albicans* and dermatophytes. *Candida albicans*, a saprophytic yeast, is normally present in the gut. The yeast can cause a perianal fungal infection in patients with compromised immune defenses such as patients with uncontrolled diabetes mellitus, on chemotherapy, prolonged antibiotic use, prolonged use of steroids, or other immunosuppressive medications. The infected skin appears moist, red, and macerated. Under microscopic scrutiny, mycelium forms and spores can be identified from scrapings of the lesion, after preparing the scapings with 20% potassium hydroxide. Treatment consists of applying nystatin powder or ointment or imidazole compound several times daily, along with controlling or eliminating the precipitating cause. *Epidermophyton floccosum*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum* are fungal infections that can occur in the perineum. The presence of dermatophytes is always associated with pruritus. Topical and systemic antifungal agents have been successfully used for the eradication of the fungal infections.

Bacterial infections such as *Streptococcus*, *Staphylococcus aureus*, and *Corynebacterium minutissimum* (erythrasma) have all been implicated [24]. *Corynebacterium minutissimum* causes erythrasma which affects the perianal area, axilla, thighs, and toe web spaces. A classic, large pink-reddish patch is seen initially which eventually turns brown. Under an ultraviolet lamp (Wood's lamp), the lesions appear with a coral to salmon fluorescence from the porphyrin production made from the bacteria. It is best diagnosed by a Wood's lamp, which reveals the coral-red fluorescence [25]. *Corynebacterium minutissimum* is susceptible to erythromycin 250 mg q6 hours or tetracycline.

Pruritus ani can also be caused by *parasitic infections*, especially in tropic climates and younger ages. Pinworms (*Enterobius vermicularis*) are often implicated in the pediatric population but can occur in adults. The worms emerge at night, and consequently pruritus worsens in the nighttime. Scratching tends to scatter the eggs in the bed and wherever the patient gets dressed. The diagnosis is made using a cellophane tape test. The adult worms and eggs can be identified on the tape. Lactophenol is used to enhance the slide. Mebendazole is the treatment of choice. Perianal topical application of albendazole as well as a single oral dose 100 mg has been demonstrated to provide immediate relief

[26]. *Pediculosis pubis* is a parasite, visible macroscopically, that can lay its eggs in the pubic and perianal hair. Treatment consists of malathion 0.5% lotion applied to the hair. All sexual partners must be treated, and clothing and bedding need to be sterilized by washing in very hot water. *Scabies* is a mite, *Sarcoptes scabiei*, that creates dark punctate lesions, which are readily identified on the trunk and particularly between the fingers and ventral surface of the wrists. Scabies can infect the perianal area. The diagnosis is established using potassium hydroxide preparation to stain the parasite. Treatment includes topical permethrin with cure rates in randomized trials approximating or exceeding 90%. Alternatively, oral ivermectin is advantageous because of ease of administration and lower cost. Detailed cleansing of all clothing and bedding by washing in hot water is necessary to avoid re-infestation. Individuals with classic scabies can return to work, child care, or school the day after the first treatment.

Sexually transmitted diseases like herpes simplex, gonorrhea, and *condyloma acuminata* can also present with itching. A detailed sexual history is usually the first clue that a sexually transmitted disease needs to be addressed. Patients who present with tenesmus, purulence, and proctitis, in addition to pruritus, should be tested for gonococcal infection. A swab should be done and placed on Thayer-Martin media. Anal gonorrhea is treated with ceftriaxone 250 mg IM plus azithromycin 1 g PO. Syphilis often presents as a painless chancre, starting as a papule that eventually ulcerates. In contrast to syphilis, painful ulcers in the perianal region are usually associated with herpes and chancroid. Syphilis is caused by the spiral-shaped bacterium *Treponema pallidum*. These spirochetes can be seen on dark-field microscopy from scrapings obtained at the base of the lesion. Alternatively, serologic screening can be done with a nontreponemal test. Treatment is a one-time dose of penicillin G 2.4 million units IM.

Viral etiologies of pruritus ani include herpes (HSV) and condyloma (human papilloma virus). HSV infection often presents as painful, scattered lesions including ulcers and vesicles. Perianal presentation of herpes simplex virus (HSV-2) is rare, compared to its frequent presentation as genital infection and even less frequently when compared to herpes simplex virus (HSV-1), which presents as the familiar "cold sore" and "fever blister." The mode of infection is usually sexual, but the virus may be spread by direct contact. A viral culture taken from the base of the ulcer or from vesicular fluid is usually diagnostic. The disease is usually self-limiting in 1–3 weeks if there is no secondary bacterial infection. Supportive treatment is recommended, and medication can limit the symptoms and duration of the attacks. The treatment of an acute episode is acyclovir 800 mg three times a day for 2 days or valacyclovir 500 mg PO three times a day. For patients with frequent recurrences, acyclovir 400 mg twice daily or valacyclovir 500 mg daily have been advocated. Large anal condylomata can cause pruritus and usually requires excision and/or fulguration in the operating room (Fig. 17.5).

Anal pruritus has been associated with *several systemic diseases* such as diabetes, cholestasis, lymphoma, leukemia, pellagra, renal failure, thyrotoxicosis, hypothyroidism, human immunodeficiency virus (HIV) disease, and deficiencies in vitamins A and D and iron. Frequently the patients with systemic diseases have generalized pruritus that indicates the diagnoses and the cause of the itching. Treatment of the systemic disease resolves the perianal symptoms.

Several *psychiatric disorders*, such as stress, anxiety, and depression, have been associated with pruritus ani. Despite these associations, scientific evidence is lacking. There is a study that attempted to link emotional disorders with pruritus ani, but it did not reach statistical significance. If any psychiatric condition is present, it should be treated concurrently

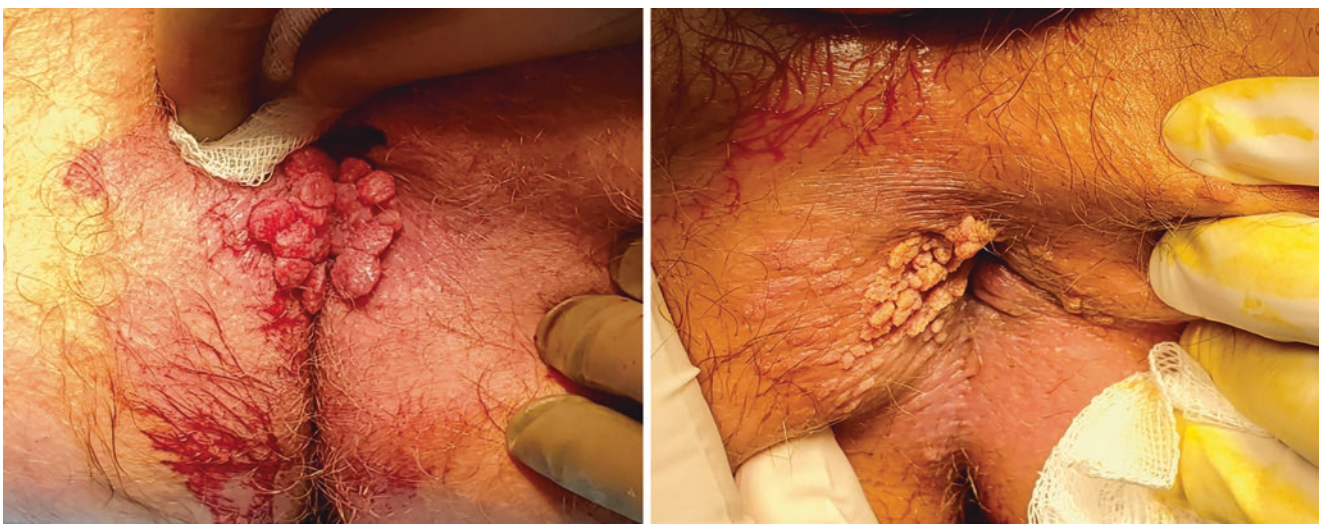

Fig. 17.5 Perianal condylomas either small or large can exacerbate skin irritation and moisture and cause anal pruritus

with the anal disease. Anxiolytic medications may benefit some patients especially at bedtime [14].

Diagnostic Approach

The clinical assessment of a patient with anal pruritus begins with a history, physical examination, and anoscopy. The decision to perform laboratory testing and endoscopic evaluation should be guided by the clinical assessment and/or response to initial therapy.

History History taking in patients with anal pruritus is critical because it can help identifying the causative factor and guide appropriate treatment. Symptoms, which usually start insidiously, are characterized by the occasional awareness of an uncomfortable perianal sensation. Some patients feel an itch, whereas others sense burning. With time, the condition may progress to an unrelenting, intolerably tormenting burning sensation in addition to the urge to scratch and otherwise irritate the area in a futile effort to obtain relief. These feelings will usually lead the patient to self-treatment with over-the-counter medications or with self-made remedies. The patient will usually overtreat the condition that will exacerbate the problem. The history of present illness should include questions related to all known risk factors for anal pruritus (Table 17.1). Thus, the physciscian should collect information on the duration of anal pruritus and the presence or not of associated symptos such as: generalized pruritus, fecal seepage, diarrhea, constipation, or a change in bowel habits, systemic symptoms including fever, night sweats, fatigue, change in appetite or weight, heat/cold intolerance, decrease in urine output, change in the color of stool or urine, and jaundice. A personal history of diabetes; dermatological, gastrointestinal, thyroid, renal, or sexually transmitted diseases; radiation; and food allergies is very important to assess. Changes in diet to include foods associated with anal pruritus or use of topical or systemic medications should be reported. Anal hygiene practices including the use of soaps, detergents, perfumes, and the frequency of cleansing or use of tight-fitting undergarments need to be described in detail. Coexisting skin and perianal conditions should be questioned. Atopy, urticaria, hay fever, allergies, and family history are key components as are the use of over-the-counter medication.

Physical Examination An examination of the whole body for any skin abnormalities or lesions should be performed before the focused exam. Dermatologic diseases are usually not limited to just one site of the body. Inguinal lymph nodes should be palpated before the patient is placed on prone jack knife position for focused examination. The presence of palpable inguinal lymph nodes is suggestive of a neoplasia or sexually transmitted diseases. The perianal exam should include a detailed inspection of the perianal area looking for skin color changes, nodules, fistula opening, skin lesions, hemorrhoids, fissures, skin rash, or ulcers. Perianal plaques with a distinct boundary are suggestive of psoriasis, erythrasma, or neoplasia. Perianal erythema may be seen in patients with chronic steroid use and candidiasis. Hyperpigmentation of the skin may result from chronic inflammation due to an infection or chronic discharge. The skin around the genitalia should also be thoroughly inspected. If sexually transmitted diseases are suspected, appropriate swabs should be obtained before the rectal examination is performed. Valsalva maneuver can exclude mucosal prolapse. A digital examination of the anorectum should be performed to identify anorectal lesions, sphincter, or pelvic floor issues. If any lesion is identified that is suspicious for malignancy, a biopsy of the lesion should be performed either in clinic under local anesthesia (punch/full-thickness biopsy) or in the operating room under general anesthetic. Every patient with pruritus ani needs to undergo an anoscopy to evaluate the anal canal and the distal rectum. Anoscopy is a quick, relatively painless, inexpensive procedure that can be performed in an unprepped patient to exclude distal anorectal disorders. Hemorrhoids, fissures, polyps, masses, and inflammatory changes can be clearly visualized with an anoscope.

Based on the physical exam, there is a clinical staging system for patients with pruritus ani. The stages represent the severity and the chronicity of the skin findings [27].

- Stage 1. No lesion is seen at inspection of anal verge, but patient finds palpation and anoscopy painful. Other anal lesions have been excluded.
- Stage 2. Red dry skin only, at times weeping skin with superficial round splits and longitudinal superficial fissures.
- Stage 3. Reddened weeping skin, with superficial ulcers and excoriations disrupted by pale, whitish areas with no more hairs.
- Stage 4. Pale, whitened, thickened, dry leathery, scaly, skin with no hairs and no superficial ulcers or excoriations (chronic condition) (Fig. 17.6).

The staging system is rarely used, but it can simplify the communication between physicians or provide structured results for research done on anal pruritus.

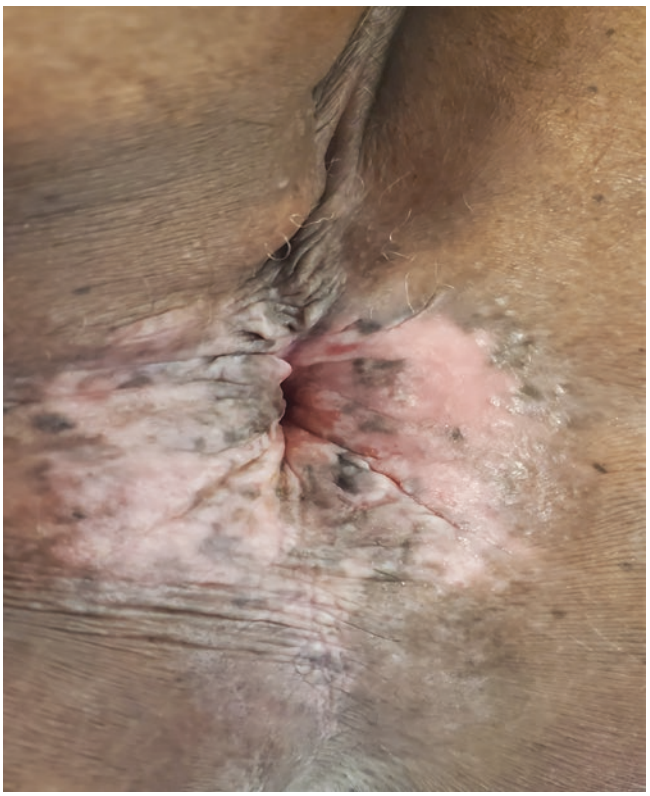

Fig. 17.6 Chronic perianal skin changes from fecal soilage and persistent anal pruritus

Laboratory Testing

Anal culture swabs for virology and microbiology are inexpensive and can be performed at the first evaluation of the patient that carries high risk for an infectious etiology. Viral cultures should be kept on ice. Fluid from vesicular lesions should be aspirated or taken with a swab from the base of an unroofed lesion and placed on a cell culture media or a microscopic slide for Tzanck smears if herpes zoster is suspected. Skin scrapings may be submitted for fungus culture or examined for hyphae with KOH prep. In patients with diarrhea, bacterial stool cultures as well as ova and parasites on three different stool samples can be useful. In patients with suspected streptococcal or staphylococcal perianal infections, nasal or throat swabs rarely detect the offending bacteria and therefore are unnecessary.

Blood testing is usually not needed during the first evaluation of the patient unless systemic symptoms are reported. Furthermore, if the patient has failed the first line of treatment, as part of the escalating diagnostic pathway, several blood tests are recommended. The physcician should obtain a complete blood count with differential to evaluate for evidence of hematologic malignancy, myeloproliferative disease, or iron deficiency anemia. Furthermore, obtaining levels of serum bilirubin, transaminases, and alkaline phosphatase to evaluate for evidence of liver disease, thyroid-stimulating hormone to evaluate for evidence of a thyroid disorder, blood urea nitrogen (BUN) and creatinine to evaluate for renal disease and human immunodeficiency virus (HIV) antibody test in patients with risk factors for HIV infection can assist in diagnosing the primary cause of the pruritus.

Endoscopic evaluation in the form of colonoscopy is indicated in patients with systemic or refractory symptoms or a change in bowel habits, diarrhea, abdominal pain, or hematochezia.

Tissue biopsies are usually not needed in the first evaluation, unless a clear lesion suspicious for malignancy is present. If the first line of treatment fails and the causative factor has not been identified, then at the second visit, tissue biopsy should be performed either in clinic under local anesthesia (punch/full-thickness biopsy) or in the operating room under general anesthetic. Tissue samples should be sent to both the microbiology and the pathology laboratories. Histopathology will demonstrate epithelial intercellular edema and vesiculation. In more chronic cases, hyperkeratosis and acanthosis will be present.

Rarely, patients with persistent or recurrent anal pruritus could benefit from anal manometry. Patients with pruritus ani have an abnormal transient internal sphincter relaxation, one that is greater and prolonged compared to controls. Thus, occult fecal leakage occurs and causes perianal itching [13].

Treatment

The care of patients with anal pruritus can be challenging. The patient should be informed about the chronic nature of the condition, not just to reduce the expectation of immediate cure but also to improve compliance with advice given. It is common for both patients and physicians to get frustrated and discouraged when initial therapy is not successful, and despite extensive testing, no definitive diagnosis can be made. The aims of treatment for any form of anal dermatitis are rapid relief of symptoms and prevention of recurrence. Successful management depends on accurate diagnosis and ruling out coexisting disorders. For patients that have an obvious factor causing the anal pruritus, the sole intervention needed is the treatment of the inciting factor, and the symptoms should resolve. Thus, all anorectal conditions should be sought and treated, as even small skin tags may hide fecal residue or trap moisture perpetuating the condition. Anal dermatophyte infections should be treated with a topical imidazole. Fungal infections should be treated with a topical imidazole if thought to be pathogenic. In rare cases per os, antifungals can be used such as fluconazole. β-Hemolytic streptococci, *S. aureus*, and *C. minutissimum* should be eliminated with topical antibiotics such as fusidic acid or mupiro-

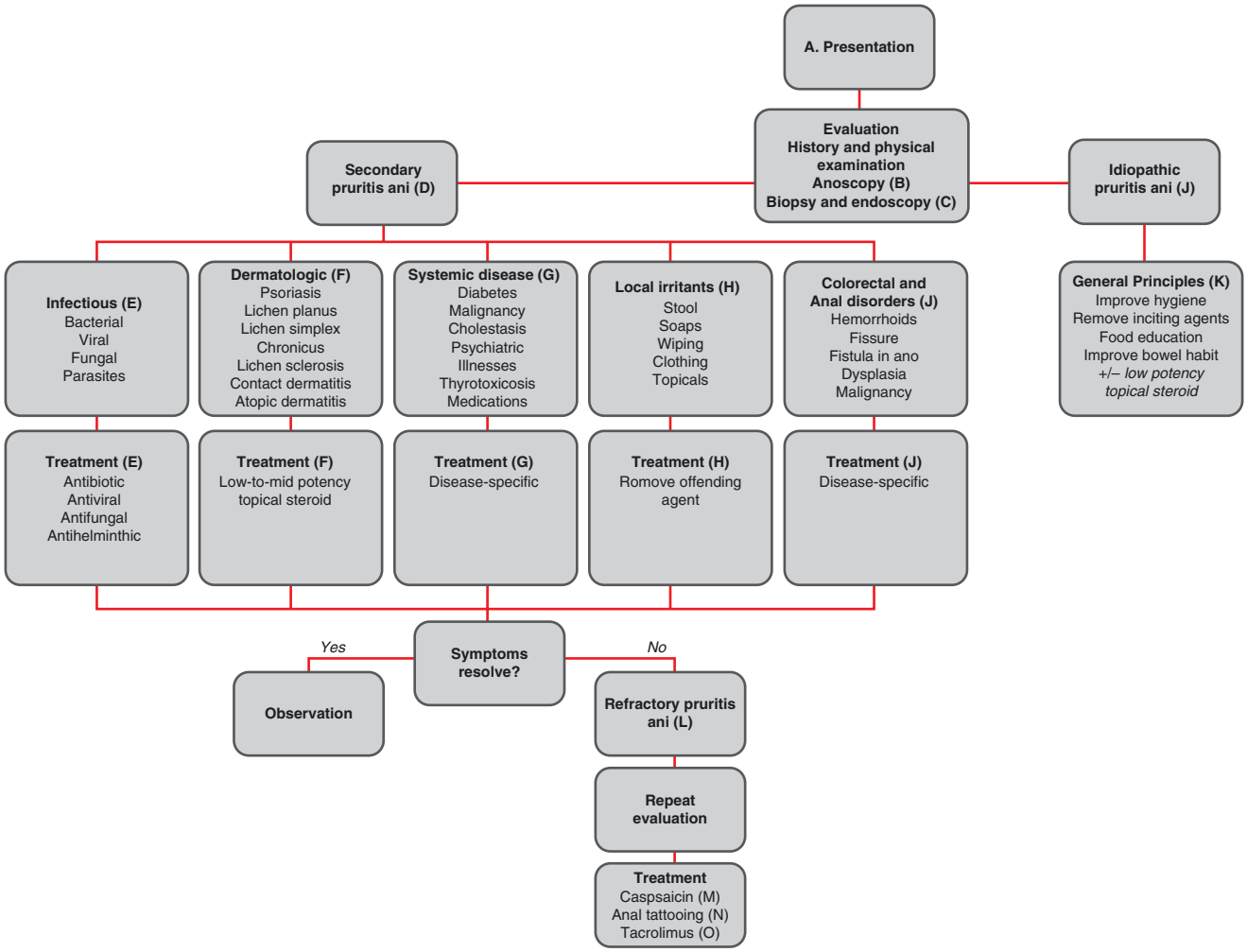

Fig. 17.7 Diagnostic and treatment algorithm for patients with anal pruritus

cin, and oral antibiotics may be necessary in more chronic and advanced cases.

For the patients that do not have an obvious risk factor causing the anal pruritus, a stepwise approach of escalating treatment and diagnostic tests is recommended. Reassurance and education are key for the success of the treatment. We have constructed an algorithm that delineates the diagnostic and therapeutic recommendations for patients with anal pruritus (Fig. 17.7).

First Encounter

The majority of patients with either secondary or primary pruritus ani will benefit from simple, general principles including improving anal hygiene, removing any potential inciting agents, food education, and improving bowel habit. These interventions can be effective in up to 90% of idiopathic cases. Key goals for treatment are the reestablishment of ideal anal hygiene and the reassurance that there is no underlying condition causing the symptoms. The ultimate goal is to restore clean, dry, and intact skin.

Inciting Agents Any inciting factors, mechanical or chemical irritants, trauma, and scratching should be avoided.

Hygiene Sitz baths without additives, taken after defecation, often help keep the perianal skin clean. Bidets are becoming more popular as an alternative. Patients should be counseled to avoid soaps, scrubbing, and aggressive wiping. Excessive moisture can cause hygiene problems. Blotting with damp toilet paper should be used instead of a moist wipe. Using a hair dryer on the lowest setting or dabbing with a towel is also beneficial. Apply corn starch powder or talc to ensure the intergluteal fold remains dry. Avoid corn-

starch powder if there is suspicion of a fungal infection as fungus is known to thrive very well in cornstarch. Soaps, perfumes, dyes in tissue or clothing, and baby wipes containing deodorants should be avoided because they can act as irritants. Handheld detachable shower heads and bidets are very effective in cleaning and washing away any remaining soap or stool residue. There are commercially available mineral oil-based preparations that can be used at home or taken along in a pocket or a purse for use in public facilities. A homemade solution for a cleaning agent is the use of diluted white vinegar. One tablespoon in an 8 ounce glass of water can be kept in the bathroom and applied with a cotton ball.

Light cotton as undergarments should be used instead of tight fitting, synthetic underwear. Clothes should be washed in non-perfumed detergent. A dry cotton ball or gauze placed at the anus can be used to limit moisture in the area. As a general rule, topical creams should be avoided initially as they may trap moisture. For cases with significant skin changes, a cream with zinc oxide or, alternatively, petroleum ointment can be applied after washing. Additional topical agents such as numbing medications, menthol, phenol, camphor, or a combination of them may be helpful. There are commercial or compound creams which are a combination of zinc oxide and menthol and can be very beneficial at relieving patients' symptoms. In specific cases, if there is any concern that there may be an infection, topical antibiotics (gentamicin, clindamycin, or bacitracin) or antifungals (clotrimazole, nystatin) may be added in conjunction with other therapies. Most creams can be applied at nighttime before bed and again in the morning after bathing.

In cases with severe skin irritation in the office, the surgeon can apply Berwick's solution (crystal violet 1%, brilliant green 1%, 95% ethanol 50%, distilled water 100%) followed by cool air drying or hair dryer. This is covered with tincture of benzoin and dried once more, and the sealant may remain on the skin for up to a week, which is enough time for skin to regenerate or re-epithelialize.

Acute itch is a marker of fecal seepage, and immediate cleansing is the most effective remedy, especially for nocturnal itch. Patients should be given advice on how to cleanse when outside their homes. If the barrier creams do not work, the patient can use ostomy powder in the perianal area three times a day. Ostomy powder is designed to protect the skin from irritation related to moisture. Although it was designed to be used around the stoma or under the ostomy barrier, it absorbs moisture in the perianal area and keeps the skin dry.

Food Education Patients should receive a list of foods (Table 17.1) that they should avoid: coffee, cola, beer, tomatoes, chocolate, tea, citrus, and lactose-containing foods. An elimination diet may be attempted. Encourage patients to keep a diary and then reintroduce the foods one at a time in an attempt to determine the offending foods.

Bowel Habits High-fiber diet and an addition of fiber supplements are highly encouraged. The fiber serves to absorb the moisture from the stool, adding bulk and allowing for complete evacuation of stool during bowel movements. High-fiber diet and bulking agents are helpful in absorbing water from stool, in turn decreasing fecal seepage. High dose of psyllium husk 2 tablespoons every am with 8–10 8 oz glasses of liquids over the day is highly recommended. If stools still remain loose, additional medications may be helpful. Antidiarrheals such as loperamide or atropine/diphenoxylate can enhance the action of the fiber and thicken or firm the stool and help decrease seepage.

Second Encounter (3–6 Weeks After First Encounter)

Clinicians should be prepared to manage refractory pruritus ani if there is no resolution of symptoms despite previous treatment. Repeating a thorough history may identify an inciting event that may have not been identified initially. Journals with foods and/or timing of symptoms should be reviewed since they can demonstrate a temporal relation to onset of symptoms. A biopsy and endoscopy should be performed if they were not done at the initial evaluation. Similar to initial evaluation, the focus should be on finding an underlying cause. These patients will need to be counseled that refractory pruritus ani may be a chronic condition requiring a long-term treatment plan and their expectations need to be set that treatments are aimed at improving symptoms rather than complete resolution. After the first line of treatment fails, a short-course trial of a low-potency topical steroid (1% hydrocortisone) can be tried twice a day for 2 weeks. This should be tapered off using a barrier cream containing zinc oxide to prevent skin atrophy [28]. In a randomized trial, patients with primary pruritus ani received 1% hydrocortisone or placebo for 2 weeks. Treatment with 1% hydrocortisone resulted in a 68% reduction of itch, and 75% of the patients had improvement in their quality of life [29]. Steroids can be used up to 8 weeks at most. Long-term use of topical steroids has been associated with atrophy of the skin. While it is unlikely that low-potency steroids (hydrocortisone 1%) have a curative effect over time, they can work as a "bridge" therapy that can alleviate symptoms long enough for the patient to stop the itch-scratch-itch cycle and allow for healing of excoriated skin. In more chronic or severe cases, the use of high-potency steroids (clobetasol propionate 0.05%) can increase the chances for symptom relief. While commonly prescribed by referring physicians, it may

be necessary to stop use of topical steroids while a causative agent is sought. Oral steroids are not indicated.

Systemic antihistamines may reduce nocturnal scratching; however, as this is probably a marker of anal seepage, the patient should be advised to wash the area immediately and apply a barrier cream. There have been no randomized trials exploring the usefulness of antihistamines in pruritus ani, but some series have reported some effect against peri-anal itch [30]. Sedative antihistamines like diphenhydramine (25–50 mg) or hydroxyzine (12.5–25 mg) are given to break the itch-scratch-itch cycle and to prevent the patient from night scratching. Sedating antihistamines may be effective by aiding sleep rather than local inhibition. Topical antihistamines are not potent enough and can sensitize or irritate the skin.

In patients who do not respond to these drugs, agents which have anti-depressive effects like doxepin (10–25 mg up to 75 mg) or amitriptyline (25 mg up to 100 mg) can be used. Doxepin, a tricyclic antidepressant, possesses both anti-H1 and anti-H2 activity. Amitriptyline is particularly useful in anogenital itch having neuropathic qualities such as stinging or burning. Gabapentin (a structural analogue of gamma-aminobutyric acid) and selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine, sertraline, fluvoxamine, mirtazapine, and citalopram may be useful for patients with intractable pruritus resistant to routine therapy [31–33].

Local anesthetics such as lidocaine gel 2–5% can provide temporary relief but have no treatment effect or long-term result. There is no place for the topical use of anesthetics as they do not alter the disease and sensitize and moisturize the skin.

Hypnosis has been used, but there is insufficient evidence available for its recommendation.

The use of capsaicin is indicated in refractory cases. Topical capsaicin produces a short burning sensation that in consequence provides an inhibitory feedback, which may eliminate the need to scratch. Furthermore, as a component of chili peppers, it has been reported that it has the ability to suppress histamine release, deplete substance P, and damage C fiber terminals, the fibers that mediate itch signaling. A randomized, crossover study showed topical 0.006% capsaicin cream applied three times a day to be superior to placebo (1% methanol) in those who had pruritus ani for greater than 3 months. Overall, 31 of 44 (70%) patients had a response to capsaicin, 8 had no response, 1 had response equally with capsaicin and methanol, and 4 withdrew because of side effects [34].

Tacrolimus is a non-corticosteroid, macrolide anti-inflammatory drug. There are some studies reporting that topical application of tacrolimus ointment for 4 weeks may decrease itch intensity and frequency in pruritus ani and improve the Dermatology Life Quality Index (DLQI), a quality of life questionnaire. The studies have small sample sizes and potential carryover effect. In general, local tacrolimus in a 0.1% concentration is well tolerated and appears to be most effective in patients with atopic dermatitis [35]. Two randomized controlled trials comparing topical tacrolimus 0.1% to placebo in a total of 53 patients with chronic idiopathic pruritus ani showed significant symptomatic improvement up to 6 weeks follow-up [35, 36]. This agent may be a good alternative to topical steroids or as a replacement when tapering off steroids to help avoid skin atrophy.

Anal tattooing with methylene blue is an intervention of last resort with good results. The exact mechanism of action is not clear, but it appears that methylene blue may be directly toxic to the nerves supplying the perianal skin, thus suppressing the desire to scratch and disrupting the vicious itch-scratch-itch cycle. The procedure is consisted of several intradermal and subcutaneous injections of 10 ml 1% methylene blue + 5 ml normal saline + 7.5 ml 0.25% bupivacaine with adrenaline (1/100,000) + 7.5 ml 0.5% lidocaine in prone jackknife under sedation or general anesthesia in the perianal region and the entrance of the anal canal. The tattoo disappears in about 3–4 weeks. The initial study [37] demonstrated a more than 80% complete or partial response, and then other reports have confirmed the initial trial [38–40]. The surgeon should be aware that there can be complications after the procedure such as decreased perianal sensation, transient fecal incontinence, and local inflammatory reactions in the injection area. A recent systematic review demonstrated that methylene blue injection can successfully treat anal pruritus; however, the evidence to support the findings was graded as weak, due to the limited number of patients participating in the studies [41].

Conclusions

Pruritus ani is a common condition that all primary care, general surgeons, and colorectal surgeons will encounter in their career. There are several etiologies for the disease, some of which are easy to diagnose and some are not. Once underlying dermatologic, food, infectious, neoplastic, and anorectal pathology has been treated, the therapy must be directed toward proper anal hygiene, avoidance of irritants, and minimizing skin trauma. If the first line of therapy is not successful, then more diagnostic and therapeutic interventions are needed to cure the disease. Managing patient expectations at the first visit is of paramount importance, as the resolution of symptoms often takes time.

References

1. Banov L Jr. Pruritus ani and anal hygiene. J S C Med Assoc. 1985;81(10):557–8.
2. Twycross R, Greaves MW, Handwerker H, et al. Itch: scratching more than the surface. QJM. 2003;96:7–26.
3. Hanno R, Murphy P. Pruritus ani. Classification and management. Dermatol Clin. 1987;5(4):811–6.
4. Daniel GL, Longo WE, Vernava AM 3rd. Pruritus ani. Causes and concerns. Dis Colon Rectum. 1994;37(7):670.
5. Wallengren J. Neuroanatomy and neurophysiology of itch. Dermatol Ther. 2005;18(4):292–303.
6. Akiyama T, Carstens E. Neural processing of itch. Neuroscience. 2013;250:697–714.
7. Potenzieri C, Undem BJ. Basic mechanisms of itch. Clin Exp Allergy. 2012;42(1):8–19.
8. Nakagawa H, Hiura A. Four possible itching pathways related to the TRPV1 channel, histamine, PAR-2 and serotonin. Malays J Med Sci. 2013;20(4):5–12.
9. Shim WS, Tak MH, Lee MH, Kim M, Kim M, Koo JY, et al. TRPV1 mediates histamine induced itching via the action of phospholipase A2 and 12-lipoxygenase. J Neurosci. 2007;27(9):2331–7.
10. Han L, Dong X. Itch mechanisms and circuits. Annu Rev Biophys. 2014;43:331–55.
11. Jeffry J, Kim S, Chen ZF. Itch signaling in the nervous system. Physiology (Bethesda). 2011;26(4):286–92.
12. Steinhoff M, Neisiuss U, Ikoma A, Fartasch M, Heyer G, Skov PS, et al. Proteinase-Activated Receptor-2 mediates itch: a novel pathway for pruritus in human skin. J Neurosci. 2003;23(15):6176–80.
13. Farouk R, Duthie GS, Pryde A, Bartolo DC. Abnormal transient internal sphincter relaxation in idiopathic pruritus ani: physiological evidence from ambulatory monitoring. Br J Surg. 1994;81(4):603.
14. Smith LE, Henrichs D, McCullah RD. Prospective studies on the etiology and treatment of pruritus ani. Dis Colon Rectum. 1982;25(4):358–63.
15. Sapan N. Food-induced pruritus ani: a variation of allergic target organ? Eur J Pediatr. 1993;152(8):701–2.
16. Kränke B, Trummer M, Brabek E, Komericki P, Turek TD, Aberer W. Etiologic and causative factors in perianal dermatitis: results of a prospective study in 126 patients. Wien Klin Wochenschr. 2006;118(3–4):90–4.
17. Ale IS, Maibach HI. Irritant contact dermatitis. Rev Environ Health. 2014;29:195.
18. Courbette O, Aupiais C, Viala J, Hugot JP, Louveau B, Chatenoud L, Bourrat E, Martinez-Vinson C. Infliximab paradoxical psoriasis in a cohort of children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2019;69(2):189–93.
19. Guglielmetti A, Conlledo R, Bedoya J, Ianiszewski F, Correa J. Inverse psoriasis involving genital skin folds: successful therapy with dapsone. Dermatol Ther (Heidelb). 2012;2(1):15.
20. Ventolini G, Patel R, Vasquez R. Lichen sclerosus: a potpourri of misdiagnosed cases based on atypical clinical presentations. Int J Womens Health. 2015;7:511–5.
21. Asgeirsson T, Nunoo R, Luchtefeld MA. Hidradenitis suppurativa and pruritus ani. Clin Colon Rectal Surg. 2011;24(1):71–80.
22. Beck DE, Fazio VW. Perianal Paget's disease. Dis Colon Rectum. 1987;30(4):263–6.
23. Handa Y, Watanabe O, Adachi A, Yamanaka N. Squamous cell carcinoma of the anal margin with pruritus ani of long duration. Dermatol Surg. 2003;29(1):108–10.
24. Jongen J, Eberstein A, Peleikis HG, Kahlke V, Herbst RA. Perianal streptococcal dermatitis: an important differential diagnosis in pediatric patients. Dis Colon Rectum. 2008;51(5):584–7.
25. Markell KW, Billingham RP. Pruritus ani: etiology and management. Surg Clin North Am. 2010;90(1):125–35.
26. Singh SP, Panda C, Rout N, Mishra AP. Anal albendazole application for pruritus ani in threadworm infestation. J Trop Pediatr. 2005;51(6):386.
27. Kuehn HG, Gebbensleben O, Hilger Y, Rohde H. Relationship between anal symptoms and anal findings. Int J Med Sci. 2009;6(2):77–84.
28. Kerscher MJ, Korting HC. Comparative atrophogenicity potential of medium and highly potent topical glucocorticoids in cream and ointment according to ultra-sound analysis. Skin Pharmacol. 1992;5:77–80.
29. Al-Ghnaniem R, Short K, Pullen A, et al. 1% Hydrocortisone ointment is an effective treatment of pruritus ani: a pilot randomized controlled crossover trial. Int J Colorectal Dis. 2007;22(12):1463–7.
30. Bernhard JD. Itch: mechanisms and management of pruritus. New York: McGraw-Hill; 1994.
31. Patel T, Yosipovitch G. Therapy of pruritus. Expert Opin Pharmacother. 2010;11(10):1673–82.
32. Stewart KM. Clinical care of vulvar pruritus, with an emphasis on one common cause, lichen simplex chronicus. Dermatol Clin. 2010;28(4):669–80.
33. Yosipovitch G, Bernhard JD. Chronic pruritus. N Engl J Med. 2013;368:1625–34.
34. Lysy J, Sistiery-Ittah M, Israelit Y, Shmueli A, Strauss-Liviatan N, Mindrul V, et al. Topical capsaicin – a novel and effective treatment for idiopathic intractable pruritus ani: a randomised, placebo controlled, crossover study. Gut. 2003;52:1323–6.
35. Suys E. Randomized study of topical tacrolimus ointment as possible treatment for resistant idiopathic pruritus ani. J Am Acad Dermatol. 2012;66(2):327–8.
36. Ucak H, Demir B, Cicek D, Dertlioglu SB, Akkurt ZM, Ucmak D, Halisdemir N. Effi cacy of topical tacrolimus for the treatment of persistent pruritus ani in patients with atopic dermatitis. J Dermatolog Treat. 2013;24(6):454–7.
37. Eusebio EB, Graham J, Mody N. Treatment of intractable pruritus ani. Dis Colon Rectum. 1990;33:770–2.
38. Botterill ID, Sagar PM. Intra-dermal methylene blue, hydrocortisone and ligno-caine for chronic, intractable pruritus ani. Colorectal Dis. 2002;4:144–6.
39. Farouk R, Lee PW. Intradermal methylene blue injection for the treatment of intractable idiopathic pruritus ani. Br J Surg. 1997;84:670.
40. Mentes BB, Akin M, Leventoglu S, Gultekin FA, Oguz M. Intradermal methylene blue injection for the treatment of intractable idiopathic pruritus ani: results of 30 cases. Tech Coloproctol. 2004;8:11–4.
41. Fransiska D, Jeo WS, Moenadjat Y, Friska D. Methylene blue effectiveness as local analgesic after anorectal surgery: a literature review. Adv Med. 2017;2017:3968278.

Sexually Transmitted Infections of the Colon and Rectum

18

Michelle Cowan and Andrew T. Schlussel

Key Concepts

- Recognize at-risk populations who are susceptible to sexually transmitted infections and to understand the growing public health concern in transmission of these organisms.
- Develop a basic understanding of anorectal immunology and how it relates to the inoculation and systematic infection by viral and bacterial organisms.
- Recognize pathology in patients with sexually transmitted infections that require operative intervention.
- Provide an overview of diagnostic and treatment recommendations for sexually transmitted infections.
- Provide prevention strategies for sexually transmitted infections.

Introduction

The term sexually transmitted disease (STD) refers to a variety of clinical syndromes and infections as a result of pathogens acquired and transmitted through sexual activity, whether it be vaginal, anal, or oral sex. The term STD has recently been replaced with sexually transmitted infection (STI), a less stigmatizing and more accurate phrase as acquiring an infection does not necessarily correlate with symptoms or disease, such as in the case of human papillomavirus (HPV). In the United States, the incidence of STIs has been on a steady climb over the last several years with an estimated 2.4 million reported cases of chlamydia, gonorrhea, and syphilis alone in 2018 [1]. Specifically, anorectal STIs are also thought to be on the rise due to the increased practice of anal receptive intercourse; however, accurate numbers are hard to quantify. In addition to anal intercourse, additional risk factors for anorectal STIs include oral-anal sex and contiguous spread from genital infections with reports demonstrating that approximately 50–60% of cases of chlamydia and gonorrhea occur at non-urethral sites [2]. Anorectal STIs are often asymptomatic; however, when present, symptoms are often similar to other common anorectal conditions. Initially, anorectal STIs may be inappropriately attributed to hemorrhoids, and thus colorectal surgeons play a critical role in the diagnosis and treatment of these pathogens, and a high level of suspicion is required to ensure an accurate diagnosis is achieved in a timely fashion. This chapter reviews sexually transmitted infections of the anus and rectum and current approaches to their presentation, diagnosis, and management.

Anorectal Immunology

The mucosal integrity of the anorectum plays a critical role in the transmission of both viral and bacterial organisms. This physical barrier protects the host from pathogens and is composed of an immune system that functions autonomously from the rest of the body. Infection ensues when a virus or bacteria diffuses through this layer and gains access to the circulatory system. Appropriate maintenance of this mucosal defense mechanism is necessary for optimal protection from disease.

Viral entry into the systemic circulation may occur through direct penetration of damaged mucosa. In the setting of human immunodeficiency virus (HIV), this organism has the distinct ability to bind secretions, facilitating its transport across the epithelial barrier to infect target cells. The abundant quantity of T cells in the gastrointestinal (GI) tract makes it a preferential target for viral replication and final introduction into the blood stream [3–6]. The ability to resist and recover from a primary infection requires an intimate balance between the innate and antigen-specific immune

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responses of the host. The pathway from inoculation to infection is a complicated process and not well understood. Cellular immunity at the level of the mucous membranes is controlled by the interaction of Langerhans (LC), or dendritic cells, and T cells which in concert become primed to identify pathogens. This process occurs rapidly in the GI tract where active T cells and dendritic cells are readily exposed to pathogens as they are located immediately beneath the epithelial surface.

Pathogens have variable effects on the immune system following infection. Human papilloma virus (HPV) has been demonstrated to increase the number of LC in the anal mucosa [7]. However, HIV is associated with a dramatic decrease in LC when coinfected with HPV, and this relationship results in a greater risk of recurrence. Furthermore, HIV is correlated with a more aggressive HPV infection due to a decrease in T lymphocytes and suppression of LC in the anorectal mucosa. This subsequently allows for HPV to persist and progress to anal dysplasia or carcinoma [8]. This viral interaction within the immune system demonstrates how HIV-positive patients are at greater risk of coinfection with secondary organisms due to the local immunosuppression of the anorectal mucosa.

Anal receptive intercourse is a mechanism for the direct delivery of pathogens into abraded and now vulnerable anal mucosa. Intercourse denudes both the protectant cell layers and the natural mucous coating of the anus and rectum. This provides a means of entry into the epithelial cell layer and subsequent release into the circulatory system [9]. Once the mucosa is damaged from a virus such as herpes simplex virus (HSV) and HPV, a separate population of lymphocytes is activated. This T-cell-mediated mechanism is considered a critical defense response against such organisms and further supports how a coinfection with HIV poses such a significant consequence in the infected host [10]. Parasitic infection such as *Entamoeba histolytica* or *Giardia lamblia* may occur through oroanal intercourse, where these trophozoites or cysts burrow into cells to gain access to the GI tract resulting in systemic illness [11]. Although the utilization of latex-based condoms is recommended to protect against the inoculation of pathogens, patients with a latex allergy may be at even greater risk of disease transmission due to the caustic immunologic response and further destruction of the immune-competent mucosal barrier.

Screening and Prevention

Sexual activity incurs the risk of receiving or transmitting a sexually transmitted disease. STDs may be asymptomatic, or symptoms are mild and unnoticed. It is critical that patients with high-risk behaviors are encouraged to undergo testing. Providers should maintain an open, non-judgmental conversation with the patient to allow them to feel comfortable in disclosing potential risk factors. The Centers for Disease Control and Prevention (CDC) has multiple recommendations regarding patient cohorts and testing [12]. All people between ages 13 and 64 should be tested at least once in their life for HIV (Table 18.1). Sexually active woman younger than 25, or those older with multiple sexual partners, should be tested yearly for chlamydia and gonorrhea. All men who have sex with men (MSM) should be tested for chlamydia and gonorrhea at least annually and should strongly consider every 3–6 months if they participate in high-risk behaviors. All contact sites including urethra, rectum, and pharynx should be tested regardless of condom use. Similar time frames are recommended for the screening of syphilis in both populations (Table 18.2). Type-specific serologic testing for HSV can be considered during initial STI screening for patients with multiple sexual partners (Table 18.3). HIV testing should be performed annually in MSM population if their status is negative or unknown or their sexual partners have had more than one partner since last being tested (Table 18.4) [12]. Anal dysplasia screening in the high-risk MSM cohorts or HIV-positive patients is also important.

Counseling and education of both the patient and their sexual partners are essential in the management of any sexually transmitted infection. Although patients should be offered

Table 18.1 Screening recommendations for common sexually transmitted infections

Chlamydia	All sexually active women <25 years old
	Pregnant women <25 years old and older women at high risk[a]
	High-risk young males
	Women ≤35 and men <30 years in correctional facilities
	MSM (annually)[b]
Gonorrhea	All sexually active women <25 years old
	Pregnant women <25 years old and older women at high risk[a]
	High-risk young males
	Women ≤35 and men <30 years in correctional facilities
	MSM (annually)[b]
Syphilis	All pregnant women[a]
	Correctional facilities based on local prevalence of disease
	MSM
HIV	All pregnant women[a]
	Offered to all adolescents
	MSM

Adapted from the Centers for Disease Control and Prevention (CDC) [14]

MSM men who have sex with men, *HIV* human immunodeficiency virus

[a]At first prenatal visit. Women at high risk or live in areas of high prevalence should be retested again at third trimester and at delivery

[b]Test urethral, rectal, and/or pharyngeal site annually based on insertive, receptive, or oral intercourse, respectively, in the last year

Table 18.2 Recommended diagnostic and treatment approach to bacterial STIs

Infection	Diagnosis	Recommended treatment
Chlamydia trachomatis	NAAT[a]	Azithromycin 1 g PO ×1 Or Doxycycline 100 mg PO twice daily × 7 days[b]
Neisseria gonorrhoeae	1. NAAT[a] 2. Culture for treatment failures and antibiotic sensitivities	Ceftriaxone 250 mg IM ×1 + Azithromycin 1 g PO ×1
Lymphogranuloma venereum	1. NAAT confirmation of *C. trachomatis* positivity 2. Culture, nucleic acid and/or immunofluorescence[c]	Doxycycline 100 mg PO twice daily for 21 days
Syphilis	1. Nontreponemal testing: VDRL +/– RPR 2. Treponemal testing	Penicillin (benzathine) G 2.4 million units IM ×1[d]
Chancroid	Gram stain and culture	Ceftriaxone 250 mg IM ×1 Or Azithromycin 1 g PO ×1
Donovanosis (granuloma inguinale)	Gram stain and culture	Azithromycin 1 g PO weekly × 3 weeks Or Azithromycin 500 mg PO daily for 3 weeks[e]

Adapted from the Centers for Disease Control and Prevention (CDC) [5]

NAAT nucleic acid amplification testing, *PO* per oral, *IM* intramuscular, *mg* milligram, *g* gram, *VDRL* venereal disease research laboratory, *RPR* rapid plasma regain

[a]Test urethral, rectal, and/or pharyngeal site based on symptoms as well as insertive, receptive, or oral intercourse. Multiple site testing is preferred

[b]Efficacy of treatments may differ between genital and extragenital sites with doxycycline possibly having greater efficacy than azithromycin in rectal STI

[c]No standardized test exists for diagnosis of LGV

[d]Tertiary or late latent syphilis may require longer duration of therapy

[e]Until all lesions have healed, doxycycline can be substituted in cases of rectal STI

Table 18.3 Recommendation for type-specific HSV serologic testing

Women	Men
All patients presenting for STD evaluation	
Multiple sexual partners	
	Men who have sex with men
	HIV-positive patient

all appropriate treatment options to include suppressive and episodic drug regimens when available, the psychosocial aspects of the disease should be addressed. This is critical in cases where patients are serologically positive for HSV-2 without experiencing any clinical signs or symptoms.

Table 18.4 Recommendations for HIV screening

Women	Men
All 13–64 years old	
Request evaluation and treatment of any other STD	
Pregnancy Screen at first prenatal visit Rescreen in third trimester	Men who have sex with men Annually: MSM if HIV status is unknown or negative Patient or partner(s) with skampskgt;1 sexual partner since last HIV screening

Table 18.5 Prevention strategies for sexually transmitted diseases

Pre-exposure vaccination
Gardasil®9: Human papillomavirus
Hepatitis A
Hepatitis B
Transmission prevention
Abstinence + reduction in sexual partners
Male condoms
Female condoms
Post-exposure prophylaxis for HIV and STI (syphilis)
Antiretroviral treatment of HIV-positive patient to prevent HIV transmission
Pre-exposure prophylaxis (PrEP) for HIV
Retesting post-treatment to detect response or repeat infections
Partner services for treatment and counseling

The most reliable means of preventing STI transmission is to abstain from oral, vaginal, and anal sex or to be part of a monogamous relationship with an uninfected partner. Especially for those patients that are being treated for an active STI, abstinence until their treatment course is completed is critical. Male condoms, when used correctly, are effective in preventing the transmission of STDs. It is important that latex condoms are not used passed their expiration date, a new condom is used after each sexual encounter, and only water-based lubricants are used on latex condoms to maintain its integrity. Patients should be provided instructions on the correct use of condoms, so they are consistently placed correctly to maximize their effectiveness in preventing the spread of HIV and STIs (Table 18.5).

Primary prevention of STI transmission requires an accurate assessment of the patient's sexual behaviors, as well as their biological risk assessment such as HIV status. HIV is not only a risk factor for STI transmission, but diagnosis of an STI puts the patient at increased risk for HIV, and testing should be implemented. In efforts to mitigate the transmission of STDs, patients should be educated on exposure avoidance and be provided pre-exposure vaccinations when available. These products exist for HPV and hepatitis A and B. HPV vaccination is recommended for both boys and girls beginning at the age of 9 with the 9-valent vaccine recommended for male patients. This vaccine known as Gardasil®9 was initially rec-

ommended in MSM up to 26; however, the Food and Drug Administration recently approved implementation in male patients up to 45 years old (Table 18.5) [12, 13].

Due the high risk of HIV transmission throughout the world, significant efforts have been made to implement both a pre-exposure and post-exposure regimen to minimize spread. In 2012, the Food and Drug Administration (FDA) approved the use of pre-exposure prophylaxis or PrEP as a one-time dose of disoproxil fumarate 300 mg and emtricitabine 200 mg, for the use in those at high risk of HIV acquisition to include MSM, heterosexual men and woman with multiple sexual partners and variable condom use, and injection drug users who share needles [14, 15]. Dosing is one tablet a day while the patient remains at risk. It is critical that the patient's HIV status is known prior to treatment as an improper treatment regimen can lead to drug resistance. McCormack and colleagues in 2016 demonstrated an 86% reduction in HIV transmission in homosexual and MSM populations [16]. A similar reduction was found by Molina et al., when on-demand dosing of PrEP was utilized. This regimen included consuming two pills prior to sexual activity and one pill for 2 days following the last sexual encounter [17]. On-demand dosing may improve compliance as the average patient in this study only took 15 pills per month. Once therapy is initiated, patients should be screened every 3 months for HIV status, renal function, and STDs. After a good sexual history is obtained, patients should be counseled on the risks and benefits of once daily dosing of PrEP, and when taken consistently, there is a 99% reduction in the risk of HIV transmission [12, 18].

Post-exposure prophylaxis (PEP) may be considered within 72 hours of exposure to bodily fluids known to be positive for HIV, or the patient is at significant risk for transmission. Rapid HIV testing should be performed when available, but testing should not delay therapy. Treatment is with a three-drug regimen to include tenofovir disoproxil fumarate 300 mg with emtricitabine 200 mg once daily and raltegravir 400 mg twice daily or dolutegravir 50 mg daily for 28 days [12].

In addition to providing treatment and confidential partner notification, certain STIs require formal reporting to support public health efforts in tracking the incidence and prevalence of diseases. Requirements are based on state law; however syphilis, gonorrhea, chlamydia, chancroid, HIV, and AIDS are reportable in every state. The reporting process can be through the provider or laboratory, and providers should be familiar with their local public health STI program policies. All reports are strictly confidential, and the public health department may contact the clinician to determine treatment rendered. There are anonymous notification services in some states; however, the patient should be encouraged to discuss their diagnosis with their partner so they can seek appropriate counseling and treatment.

Diagnosis and Initial Evaluation and Treatment

Asymptomatic

Sexually transmitted infections of the anus and rectum are often asymptomatic making the diagnosis challenging. In fact, in men who have sex with men, approximately 85% of rectal sexually transmitted infections are asymptomatic [2]. In women, solely screening the urogenital epithelium resulted in overlooking 12–30% of chlamydia and gonorrheal infections, respectively, when compared to testing multiple mucosal sites [19]. As a result, anorectal STIs may go untreated which can lead to chronic pelvic and abdominal pain, difficulty or inability to conceive, prostatitis, and epididymitis. More importantly, failure to treat extragenital STIs results in an infectious reservoir placing patients at risk of acquiring or transmitting HIV [20]. Therefore, current guidelines recommend general screening for STIs from all surfaces in asymptomatic individuals in high-risk subgroups based on sexual behavior and biologic risk profile [12]. Individuals at a greater risk of contracting or transmitting an STI include but are not limited to adolescents and young adults aged 15–24, incarcerated persons, gay and bisexual men, pregnant women, those who fail to practice safe sex or have multiple partners (i.e., swingers and sex workers), and those with a limited access to health care (Table 18.2) [12].

Symptomatic

Symptoms associated with anorectal STIs commonly encountered by a colon and rectal surgeon include anal pain, tenesmus, urgency, bleeding, and mucopurulent drainage. Physical exam may demonstrate painless or painful lesions and ulcers with or without mucosal inflammation and/or discharge. These signs and symptoms are often mistaken for other processes such as fissures, hemorrhoids, hidradenitis, fistula-in-ano, or a malignancy for which an STI is not even considered until the patient presents with persistent symptoms despite various over-the-counter and prescribed therapies. In adolescents and young adults, these symptoms along with proctitis seen on exam can closely mimic inflammatory bowel disease (IBD), specifically lymphogranuloma venereum [21]. In patients initially diagnosed with IBD but not responding to appropriate therapy as expected, infectious proctitis should be considered.

Distinguishing an anorectal STI from other potential causes of proctitis mandates a thorough workup including a sexual history and previous STIs. A complete anal exam should be performed with anoscopy +/− endoscopy to evaluate for mucosal erythema, friability, exudate, and discharge.

Table 18.6 Treatment recommendations for genital herpes simplex virus

Initial clinical episode	Suppressive therapy	Episodic therapy
Treatment duration: 7–10 days	Acyclovir 400 mg; twice/day	Acyclovir 400 mg; three times/day Duration: 5 days
Acyclovir 400 mg: Three times/day	Valacyclovir 500 mg; once/day	Acyclovir 800 mg; twice/day Duration: 5 days
Acyclovir 200 mg: Five times/day	Valacyclovir 1 g; once/day	Acyclovir 800 mg; three times/day Duration: 3 days
Valacyclovir 1 g; twice/day	Famciclovir 250 mg; twice/day	Valacyclovir 500 mg; twice/day Duration: 3 days
Famciclovir 250 mg: Three times/day		Valacyclovir 1 g; once/day Duration: 5 days
		Famciclovir 125 mg; twice/day Duration: 5 days
		Famciclovir 1 g; twice/day Duration: 1 day
		Famciclovir 500 mg once + 250 mg twice/daily for 2 days

Table 18.7 Treatment recommendations for herpes simplex virus in HIV-positive patient

Suppressive therapy	Episodic therapy
Acyclovir 400–800 mg; 2–3 times/day	Acyclovir 400 mg; three times/day Duration: 5–10 days
Valacyclovir 500 mg; twice/day	Valacyclovir 1 g; twice/day Duration: 5–10 days
Famciclovir 500 mg; twice/day	Famciclovir 500 mg; twice/day Duration: 5–10 days

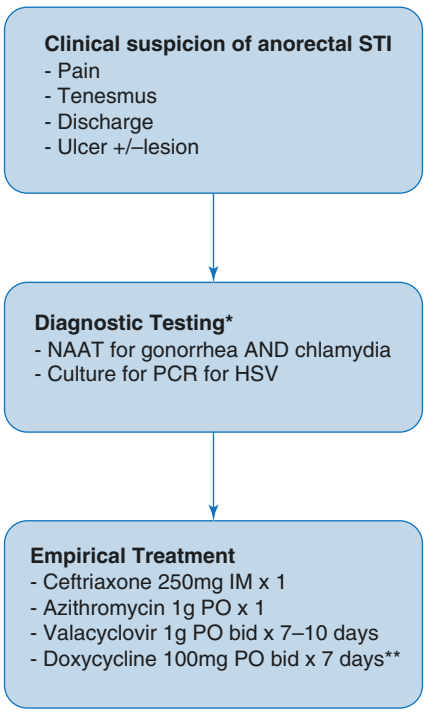

Fig. 18.1 Treatment algorithm. *NAAT* nucleic acid amplification testing; *PCR* polymerase chain reaction; *HSV* herpes simplex virus; *PO* per oral; *bid* twice daily; *IM* intramuscular; *g* gram; *mg* milligram; *MSM* men who have sex with men; *HIV* human immunodeficiency virus. *Test urethral, rectal, and/or pharyngeal site annually based on symptoms as well as anal insertive, anal receptive, or oral intercourse. **Efficiency of treatments may differ between genital and extragenital with doxycycline possibly having greater efficacy than azithromycin in rectal STI

However, it is imperative that if suspicious for an anorectal STI based on history and external exam, swabs to test for gonorrhea, chlamydia, and herpes need to be done prior to the introduction of lubricant during the anoscopy or endoscopy as many medical lubricants are bacteriostatic. Testing often requires two separate swabs, one viral (herpes) and one bacterial (gonorrhea and chlamydia); however, each institution is different, and thus each provider should familiarize themselves with their specific institutional protocols. In any patient with proctitis or proctocolitis, it is essential to rule out other infections such as enteric pathology and examine the stool for *Giardia lamblia* and *Entamoeba histolytica* which can also be inoculated by sexual contact. Lastly, endoscopic mucosal biopsies should be considered to rule out cytomegalovirus (CMV) in those with AIDS or immunocompromised state.

During their initial encounter, and in addition to swabs for gonorrhea, chlamydia, and HSV, all patients with a suspected STI should undergo serologic testing for syphilis and HIV. Once testing is complete, empiric therapy should be considered for both the patient and sexual partners. This decreases the risk of transmission and improves the rate of successful treatment outcomes. Treatment should be targeted towards gonorrhea, chlamydia, and herpes (Tables 18.2, 18.6, 18.7) (Fig. 18.1). Treatment should include dual therapy for gonococcal disease with ceftriaxone plus either doxycycline or azithromycin, both of which will also treat chlamydia. Azithromycin is currently recommended by the CDC due to a high rate of tetracycline resistance and is preferred in patients with a penicillin allergy as well as those who are noncompliant as it is a one-time dose in clinic. However, azithromycin may be inferior to doxycycline in the treatment of rectal-specific infections [22]. While awaiting final test results, patients should also be started on empiric valacyclovir to treat HSV. Patients should also be counseled and strongly encouraged to inform current and prior sexual partners in the last 3 months about their potential risk of STI so they can pursue

testing and/or start empiric therapy, both of which can reduce the risk of reinfection and diminish transmission of STIs. Providers can also refer patients to partner notification programs at several local health departments to facilitate this process and assist in counseling and testing.

Currently, the mandatory reportable STIs in all 50 states include gonorrhea, chlamydia, syphilis, HIV, and chancroid, with state-specific reporting for other infections. All reports are strictly confidential, and all states allow minors to consent for STI care without parental permissions and without requiring the provider to inform the parents; however, some states limit a minor's consent based on type of service. The accurate reporting of STIs is integral to the public health department's ability to track occurrences and also mobilize resources to underserved areas.

Bacterial Sexually Transmitted Infections

Chlamydia

Epidemiology and Presentation

Chlamydia trachomatis is the most common reportable STI in the United States with almost two million new cases in 2018; however, this number is likely an underestimation as many cases go unreported as they are often asymptomatic [1]. Infection is often seen in sexually active young adults, and it is estimated that approximately 1 in 20 women ages 14–24 has chlamydia [23]. Left untreated, chlamydial infection in women can lead to ectopic pregnancies and infertility as well as pelvic inflammatory disease (PID) in the case of chronic or repeated infections. As such, annual screening is recommended in sexually active women under the age of 25 as well as older women at high risk with data showing that screening and subsequent treatment for chlamydia lead to a lower risk of PID in women (Tables 18.1 and 18.2) [12, 24].

Chlamydia trachomatis is an obligate intracellular bacterium with at least 15 different types or serovars. Serovars D–K are typically responsible for the more common clinical spectrum of urethritis, cervicitis, and PID, as well as neonatal disease and proctitis. Serovars L1–L3 are more aggressive and most commonly responsible for lymphogranuloma venereum (LGV) and often present as a more severe form of proctitis that can include erythematous and friable rectal mucosa with ulcerations as well as potential for perianal abscesses, fistulas, and fissures and can often mimic IBD, specifically Crohn's disease [25]. The urethra is the most common site of infection in males resulting in urethritis with symptoms of pyuria, dysuria, and urinary frequency. A minority of men will present with epididymitis and symptoms of unilateral testicular pain, swelling, and tenderness. In women, the urethra and cervix are the most common site and can present with cervical discharge and bleeding. Rectal chlamydia occurs due to spread via anal receptive intercourse or contiguous spread from genital disease with some data to support that in some subpopulations, chlamydia infection is most prevalent in the rectum with over 50% of chlamydia infections in MSM being located in the rectum and also more likely to be symptomatic [2]. Symptoms of rectal involvement can include a milder form of proctitis with tenesmus, pain, and discharge. Regardless of site of infection, the incubation period for chlamydia can range from several days to up to 2–3 weeks due to its slow replication cycle [26].

Diagnosis

Testing for chlamydia is either done for patients who are otherwise asymptomatic and qualify based on screening guidelines or performed on patients based on symptoms and clinical suspicion after a thorough history and physical examination table 18.1. The recommended diagnostic test is the nucleic acid amplification test (NAAT) which has ~97% sensitivity and specificity, can be performed on easily obtainable specimens such as urine or vaginal swabs, and provides diagnosis in under 48 hours [12]. In men, the preferred specimen for diagnosis is a first-catch urine, while in women, the preferred testing site is a vaginal swab (either provider or patient collected) with a first-catch urine sample as an alternative. However, as mentioned previously, testing should be done at multiple sites, especially in high-risk populations such as MSM, and those with symptoms suggesting extragenital involvement [27]. Interestingly, while NAATs are the preferred method to detect chlamydia from urine and vaginal swabs, historically no commercial test has been approved by the FDA for use with extragenital (rectal or pharyngeal) specimens, despite the fact that more recent data demonstrates superior sensitivity and specificity of NAAT testing compared with traditional culture [28]. Therefore, culture has stayed the traditional route of testing for extragenital sites. However, in 2019, the FDA approved the first tests to detect chlamydia on extragenital samples, specifically the Aptima Combo 2 Assay and the Xpert CT/NG, which rely on transcription-mediated amplification and are both already cleared for genital and urine samples [29, 30].

Treatment

Treatment for chlamydial STI can be easily treated with antibiotics, and treatment should start empirically along with coverage for gonococcal and HSV infections at the time of the initial encounter (Fig. 18.1). Not only does this allow for early treatment of possible infections but also prevents possible adverse reproductive effects and in pregnant women can prevent transmission to neonates. Treatment should be with 1 g of azithromycin given in the office or, alternatively, doxycycline 100 mg twice daily for a total of 7 days (Table 18.2). Alternative regimens recommended by the CDC include treatment with erythromycin or with qui-

nolones such as levofloxacin or ofloxacin; however, each come with their own limitations including GI upset and resulting patient noncompliance or increased cost, respectively [12]. The benefit of azithromycin is that it can be used in those with a penicillin allergy, it is safe in pregnant patients, and it is good for patients with compliance concerns as it is a one-time dose that can be given and directly observed in clinic. Patients should be counseled to abstain from all sexual activity until resolution of symptoms as well as for 7 days from the one-time dose of azithromycin and/or until completion of a 7-day course of doxycycline. Repeat testing should occur at 3 months post-treatment since early testing <3 weeks after completion of therapy can result in false positives given continued shedding of the organisms early after therapy [12]. The exception is in pregnant women where re-testing should occur twice, first at 3–4 weeks after completion of therapy to prevent the sequelae to neonates if infection persists and again at 3 months. Treatment failure; can actually represent reinfection due to sexual activity with an infected and/or untreated partner. Accordingly, patients should be counseled to notify all partners within the last 2 months of their new diagnosis so that they can be evaluated and treated as well.

Efficacy of treatments may differ between genital and extragenital sites with doxycycline having greater efficacy [31]. While antimicrobial resistance is less common with chlamydial infections compared to gonorrheal infections, there are several reports of treatment failure for rectal chlamydial STI treated with azithromycin of up to 20%, as compared to doxycycline [32]. While most of the studies are small and the quality varies, some, including the European guidelines, recommend doxycycline as the first-line agent in rectal-specific chlamydia STI [33, 34].

Lymphogranuloma Venereum

Epidemiology and Presentation

Lymphogranuloma venereum (LGV) is caused by distinct serovars of *Chlamydia trachomatis*, serovars L1–3, with L2 thought to be most responsible for the recent increased prevalence of the disease [35]. Prior to 2003, LGV was thought to be rare in developed countries; however, there has been a recent surge with a predominance in the MSM population, especially those who are HIV positive [36]. Unlike other serovars of *C. trachomatis*, LGV is thought to be more invasive resulting in severe proctitis with ulcers that can lead to abscesses, fistulas, chronic pain, and strictures which can mimic inflammatory bowel disease. LGV also affects the lymphatic system so proctitis is followed and/or accompanied by tender femoral and inguinal lymphadenopathy that is often unilateral and responsible for the classic "bubo" on exam; however, these symptoms are uncommon with genital infection. Patients can also present with rectal pain, tenesmus, mucoid, anal discharge as well as fevers, fatigue, and weight loss.

Diagnosis

Diagnosis for LGV is based on clinical suspicion centered on symptoms and exclusion of IBD as the cause of proctitis, followed by confirmatory testing. In those patients who test positive for *C. trachomatis* from their rectal and/or genital swab NAAT, a subsequent test for LGV should be performed to confirm the diagnosis. Diagnostic testing involves cultures, direct immunofluorescence, or nuclei acid detection [12]. Endoscopic findings in patients with proctocolitis due to LGV include mucosal erythema, friability, and ulcers with biopsies demonstrating lymphocytic infiltrates, crypt abscesses, and even some cases of granulomatous changes which can mimic Crohn's disease [36]. Given the difficulty in distinguishing the diagnosis from IBD as well as varying testing capabilities, the diagnosis of LGV is often delayed or misdiagnosed. Similar to standard *C. trachomatis*, the patient should be tested for other STIs including HIV.

Treatment

The standard treatment for patients with LGV is doxycycline 100 mg twice daily for 21 days since LGV is more invasive and difficult to eradicate than standard genital chlamydia (Table 18.2). For patients with a history and symptoms suspicious for STI, empiric treatment with doxycycline is started, and once chlamydial testing returns positive and subsequent reflexive testing for LGV returns positive, the course of doxycycline therapy should be extended. For those unable to take doxycycline, an erythromycin regimen with four times a day dosing can be used; however, this can be poorly tolerated due to gastrointestinal upset and difficulty with frequent dosing compliance. Local control of any infected lymph nodes or "buboes" may be needed by aspiration and/or incision and drainage to prevent subsequent ulceration or fistulization. Many patients with LGV are coinfected with HIV and should receive the same initial therapy; however, these patients may have delayed symptom resolution and thus require a longer duration of therapy. Due to inconsistent diagnostic testing and risks of failing to treat LGV, any MSM patients who are HIV positive and present with proctitis and positive rectal chlamydial testing should be treated empirically for LGV [36].

Gonorrhea

Epidemiology and Presentation

Neisseria gonorrhoeae is an intracellular diplococci bacterium responsible for the second most common reportable STI in the United States. The incidence of this infection exceeds one million cases each year, with 500,000 new cases reported

to the CDC in 2018 [1]. Similarly, most presentations of chlamydia are asymptomatic. Specifically, in cases of positive cultures 50% of men and upwards of 95% of women remain asymptomatic [37]. Populations at high risk should undergo routine screening as the risks of leaving gonorrhea untreated are severe and include pelvic inflammatory disease (PID), fallopian tube involvement, infertility, and ectopic pregnancies (Table 18.1). Symptoms can vary, and in men, the most common presentation is urethritis with symptoms of painful urination and/or discharge, up to 2 weeks after inoculation. Epididymitis occurs less frequently. Symptomatic women infected with *N. gonorrhea* most commonly present with cervicitis, urethritis, or proctitis; however, the symptoms are usually so mild they are mistaken for a bladder or vaginal infection. Patients with proctitis due to gonorrhea will often present with tenesmus, hematochezia, or mucopurulent discharge, and if untreated, disease progression may result in pelvic pain, fevers, or an abscess. These findings should raise suspicion for PID. *N. gonorrhea* can cause more disseminated disease as well, albeit uncommon, resulting in purulent arthritis as well as polyarthritis, dermatitis, and even more serious diseases such as endocarditis and meningitis [38].

Diagnosis

Anoscopy findings include erythema and friable mucosa with thick mucopurulent discharge from the anal crypts. A vaginal exam should be performed in women to evaluate for concomitant disease, as cervicitis has been reported in 35–50% of woman diagnosed with rectal gonorrhea [39]. Definitive testing should be done with NAAT as it has a sensitivity and specificity of 100% and skampskgt;95%, respectively. Similar to chlamydia, until recently there was no FDA-approved test for extragenital gonorrhea [29, 30].

Gram stain and culture, in addition to NAAT, should be utilized in cases of treatment failure or in symptomatic patients, as it allows for antimicrobial susceptibility testing, and the selectiveness of Thayer-Martin media prevents growth of other endogenous flora. Although the sensitivity of NAAT is 90–100%, this does not allow for antibiotic susceptibility testing which is important given gonococcal resistance and additional treatment options [40]. For symptomatic men, especially MSM, a gram stain of a urethral specimen visualizing intracellular gram-negative diplococci and polymorphonuclear leukocytes is diagnostic; however, a negative test in this asymptomatic cohort does not rule out disease, and further testing is recommended [12].

Treatment

The clinical suspicion of a gonococcal STI should prompt testing followed by empiric treatment. However, gonorrhea is known for its ability to develop antibiotic resistance, initially to fluoroquinolones, followed by some cephalosporins such as cefixime, as well as tetracyclines [41]. Thus, empiric treatment starts with dual therapy against the bacteria utilizing antibiotics with two different mechanisms of action, ceftriaxone 250 mg given once intramuscularly plus 1 g of azithromycin, both of which can be given in office (Fig. 18.2). While this regimen targets chlamydia simultaneously, dual therapy is recommended for an isolated gonorrhea infection to avoid antimicrobial resistance and improve treatment efficacy for both genital and extragenital sites.

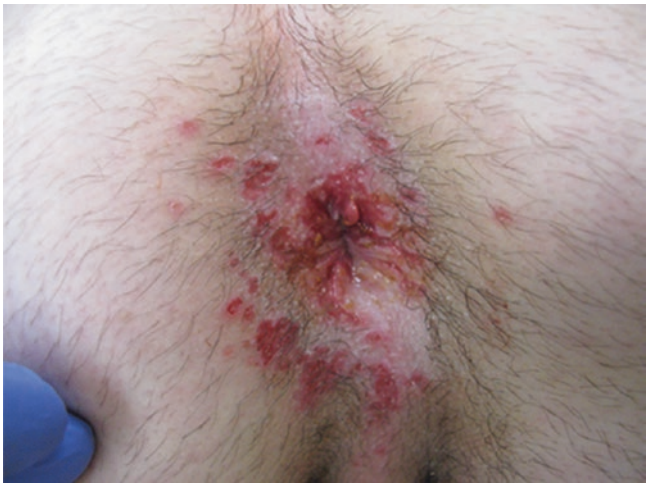

Fig. 18.2 Perianal vesicles secondary to herpes simplex virus. (Courtesy of Richard E. Burney, MD, University of Michigan)

Those who undergo successful treatment for gonococcal infection should abstain from sexual intercourse until 7 days after completion of therapy and then undergo repeat testing at 3 months post-treatment. All sexual partners in the last 2 months should be counseled in regard to testing and receiving empiric therapy. If symptoms persist after treatment, cultures should be performed to evaluate for antimicrobial resistance and sensitivities which can help guide future therapeutic options. Treatment failure can be defined as patients who test positive by culture or NAAT and/or have continued symptoms 3–5 days after completion of therapy with no sexual contact in the post-treatment time frame. While persistent symptoms are often due re-infection, in cases of treatment failure, consultation with an infectious disease specialist should be considered as these cases are reportable.

Syphilis

Epidemiology and Presentation

Syphilis is a systemic illness caused by the bacterium and spirochete *Treponema pallidum*, with estimated reports of 35,000 new cases in 2018, a substantial rise of over 70% from 2014 [1]. In the late 1990s and early 2000s, the case numbers of syphilis hit such a nadir that there was discussion regarding the elimination of the disease in the United States

[42, 43]. However, since that time the rate of syphilis has been on the rise with a resurgence of the disease in the MSM and HIV+ MSM populations such that a diagnosis of early syphilis increases the risk of being diagnosed with HIV, and the open ulcers of syphilis are thought to facilitate HIV transmission [44, 45]. However, this increasing incidence extends beyond the MSM population and includes women as well as increased number of cases of congenital syphilis.

Syphilis can present in three stages: primary, secondary, and tertiary. This is defined based on the time from infection as well as clinical presentation. In primary syphilis, an ulcer may present at the site of inoculation 1–21 days after infection; although lesions are commonly painless, extragenital ulcers are more likely to have significant pain. Ulcers often resolve within 3–6 weeks regardless of treatment, and thus only a small portion of patients are diagnosed during this stage. In HIV-positive patients, primary disease is more likely to be asymptomatic; therefore, this cohort more commonly presents in the secondary stage [44]. Secondary disease usually occurs weeks to months after the initial inoculation and can present with more systemic symptoms such as fever, malaise, arthralgias, diffuse lymphadenopathy, a rectal mass, and a rash. The rash, which signifies hematogenous spread, is often characterized by a diffuse maculopapular lesion that can involve the palms of the hands and soles of the feet. A less common presentation includes both nodular and ulcerated lesions. Failure to treat these patients results in progression to a latent asymptomatic stage for a period of 1–30 years following initial infection. Progression to tertiary syphilis occurs in a minority of patients and is characterized by cardiac involvement and gummas, non-cancerous growths with a necrotic and ulcerated center that can develop throughout the body. Neurosyphilis can occur at any stage of disease and is characterized by ocular and/or central nervous system (CNS) involvement of the brain, peripheral nerves, or spinal cord. Symptoms of neurosyphilis include meningitis, cranial nerve palsies, paralysis, dementia, and even death. There is an increase prevalence of neurosyphilis in the HIV-positive population, with findings that support HIV may accelerate the clinical course of neurosyphilis [44].

Diagnosis

Syphilis can present over a spectrum of phases with varying presentations and symptoms; therefore, the diagnosis requires a high clinical suspicion as well as appropriate dual testing to confirm positivity. Historically, the diagnosis was made by visualizing the bacterium using dark-field microscopy. Although this is still recognized as the gold standard when evaluating tissue samples of ulcers and lesions, modern testing uses serologic analysis. Diagnosis starts with nontreponemal testing followed by a treponemal-specific test for confirmation. Nontreponemal testing includes VDRL (venereal disease research laboratory) and RPR (rapid plasma reagin) testing as they are easy and inexpensive. However, they are not specific, and false-positive serologic tests can be seen in non-syphilis cases such as in other infections like HIV, autoimmune diseases, and pregnancy. Thus, patients with a positive nontreponemal test should always undergo confirmatory testing with a treponemal test including antibody testing such as FTA-ABS (fluorescent treponemal absorption tests) and other enzyme immunoassays and immunoblots [12]. Some laboratories have flipped the algorithm and are using "reverse" testing with an automated treponemal test as the initial screening test followed by a nontreponemal test, as treponemal antibodies appear prior to nontreponemal antibodies. However, interpretation is difficult given patients with reactive treponemal-specific tests will likely have reactive tests for the rest of their lives regardless of status or treatment of the disease, and some data suggests "reverse" testing is associated with increased false-positive rates [46].

Patients with clinical symptoms that suggest CNS or optical involvement should undergo organ-specific testing including cerebrospinal fluid testing or a slit lamp ophthalmologic exam. Given the high coinfection rate with syphilis and HIV, all patients should also undergo testing for HIV infection.

Treatment

The treatment of syphilis is penicillin G for all stages of the disease (Table 18.2). The duration of treatment as well as the preparation, i.e., procaine, crystalline, and benzathine, may vary as the disease can reside in sequestered sites of the body which are more difficult to treat, such as the central nervous system. For early stage disease, the recommended treatment is a single intramuscular (IM) dose of benzathine penicillin G 2.4 million units. Patients should be educated about the Jarisch-Herxheimer reaction which is an acute febrile reaction often seen in the treatment of early syphilis and is accompanied by headache, myalgia, and fever and can occur within the first 24 hours after the initiation of therapy. Treatment for this reaction is supportive; however, in pregnant women, this reaction can cause preterm labor, and thus symptoms should be recognized early. In patients with a clinical suspicion of disease but with a negative testing, empiric therapy should be given and repeat testing performed. Treatment for latent and tertiary syphilis requires a longer duration of therapy, and those with a penicillin allergy may necessitate alternative therapies; therefore, these conditions should be managed by an infectious disease specialist.

Following treatment, repeat clinical evaluation and testing should be performed at 6 and 12 months. Treatment failure and/or re-infection should be suspected in patients whose symptoms persist and/or whose antibody titers remain elevated. All persons who have had sexual intercourse with

another person who has been diagnosed with any stage of syphilis in the last 3 months should undergo evaluation and possibly empiric treatment according to CDC guidelines [12].

Chancroid

Epidemiology and Presentation

Chancroid is an anogenital ulcerative infection caused by the bacterium *Haemophilus ducreyi* and one of the reportable STIs in the United States. The overall incidence has been on the decline in the United States over the last several decades with only three cases reported in 2018 [1]. However, accounting for the incidence of this disease is challenging due to diagnostic difficulties, as this bacterium is notoriously hard to culture. Similar to other STIs, transmission is through sexual intercourse and open breaks in the skin which transmit disease. Infection with *H. ducreyi* often presents hours to days after exposure with painful lesions that may start as a papule and progresses to a pustule and open, painful ulcerations. These ulcers are often multiple in cases of chancroid and have ragged borders with overlying exudate. Similar to syphilis and other diseases causing open ulcers and lesions, chancroid can facilitate HIV transmission.

Diagnosis

The combination of a painful genital or anal ulcer along with unilateral suppurative inguinal lymphadenopathy often suggests the diagnosis of chancroid. Gram stain of the ulcer and exudate may show gram-negative rods in a chain, termed the "school of fish" appearance. However, gram stain alone has been demonstrated to have a low sensitivity ranging from 40% to 60% [47, 48]. A positive culture of this bacterium requires multiple media which are not widely available; as a result, identification of this organism is problematic. Polymerase chain reaction (PCR) is the most sensitive test to detect for *H. ducreyi*; however, no FDA-approved PCR test is available in the United States, and thus diagnosis is made based on the following criteria: presence of one or more painful genital ulcers, no evidence of syphilis infection, regional lymphadenopathy, and an ulcer exudate that is negative for HSV [12, 48]. Patients should also be offered testing for other STIs including HIV.

Treatment

Goals of treatment are to improve and resolve symptoms while also preventing transmission. The treatment for chancroid is either single-dose ceftriaxone 250 mg IM or azithromycin 1 g orally, both of which have the benefit of one-time dosing. While there are alternative treatment regimens that include ciprofloxacin and erythromycin, some data suggest intermediate resistance to these drugs [12]. Due to the difficulty of cell culture which allows for antibiotic susceptibilities and resistance, true resistance patterns are hard to define. Patients should be evaluated within 3–7 days after initiation of therapy to assess for resolution of symptoms with the expectation that ulcers will symptomatically improve in 3 days and show objective improvement in 7 days; however, full ulcer healing may take up to 2 weeks. Healing is slower in uncircumscribed men with ulcers under the foreskin, those with coinfection with HIV, and those with antimicrobial resistance and thus may require a longer duration of therapy or change in therapy. All persons diagnosed with chancroid should avoid sexual activity during treatment and while ulcers heal and should undergo repeat testing for HIV and syphilis 3 months after completion of therapy. All partners who had sexual contact with an infected person within 10 days of symptom onset should be referred for evaluation.

Donovanosis

Epidemiology and Presentation

Donovanosis, or granuloma inguinale, is caused by the intracellular bacterium *Klebsiella granulomatis*. The incidence in the United States is rare, and the disease is more prevalent in tropical and developing areas of the world such as Brazil, South Africa, and the Caribbean. Typical presentation involves a non-tender, beefy red ulcer in the genital region that may bleed due to their high vascularity. They can also occur in the anorectal area where some manifest infection with verrucous lesions and/or deep fissures with fibrotic ulcers. These ulcers can present with subcutaneous lesions and granulomas, often referred to as pseudo buboes.

Diagnosis

Like chancroid, the diagnosis of donovanosis can be difficult since the bacterium is difficult to culture. The diagnosis is typically made by identifying Donovan bodies within large mononuclear cells in Giemsa-stained smears of the presenting ulcerative lesion; however, Donovan bodies can be difficult to detect from more fibrotic or necrotic ulcers [49]. PCR has more recently become available to aid in the diagnosis. As with all STIs, patients should undergo testing for possible coinfection, specifically HIV, as this may worsen the course of the disease.

Treatment

Treatment allows for healing of the ulcers starting from the outside moving inward, and thus treatment is often prolonged to allow for full epithelization. First-line treatment recommended by the CDC is azithromycin 1 g orally every week for 3 weeks or 500 mg daily for 3 weeks [12]. If there is no clinical improvement within a few days after initiation of therapy, the addition or an aminoglycoside such as genta-

mycin should be considered. Patients should be followed until all signs and symptoms have resolved, and all partners within the last 2 months should be referred for further evaluation.

Herpes Simplex Virus

Herpes simplex virus type 2 is one of the most prevalent STDs in the United States, with greater than 20% of adults as carriers. This DNA virus is a member of the *Herpesviridae* family and is associated with the development of genital herpes and is one of the most common causes of nongonococcal proctitis in the MSM population [12, 50, 51]. Although HSV-2 is commonly associated with genital lesions, a 2006 report by Ryder and colleagues demonstrated a rising proportion of anogenital herpes secondary to HSV-1 in both heterosexual woman and MSM cohorts. This was thought to be due to a reduction in HSV-1 transmission as a child, therefore leading to a larger population of susceptible adults who engage in both oroanal and orogenital practices [52].

The human body serves as a reservoir for this virus, and transmission occurs through intimate contact. Anal receptive intercourse results in destruction of the mucosa or skin surface barriers which provides a route for inoculation. Unfortunately, most individuals are unaware of their infection status. Recurrent viral infections occur due to immunological shunting between the mucocutaneous surface and sensory nervous system. Following primary infection, the virus moves in a retrograde fashion along axons of the sensory nerve ganglia where it may lay dormant throughout the life of the host. Following reactivation, the virus spreads antegrade down neurons to infect and shed from the mucocutaneous surface. This virus has evolved to develop an intelligent ability to conceal itself from host antibody-mediated defenses, posing an inherent challenge to the immune system [10].

Anorectal herpes is characterized by recurrent blistering lesions of the mucous membranes. Symptoms typically occur 4–21 days after anal receptive intercourse, with most patients experiencing perianal pain, burning, or pruritus [53]. Physical exam of the anorectum may often be challenging due to pain. Early lesions may appear as small vesicles with surrounding erythema on the perianal skin or in the anal canal (Fig. 18.2). These vesicles may subsequently rupture and coalescence into large ulcers (Fig. 18.3). Risk of transmission occurs until an epithelial barrier is formed over the lesion in approximately 3 weeks [11]. Vesicles and pustules are less common in HSV proctitis. Endoscopic findings typically demonstrate friable mucosa and diffuse ulcerations limited to the distal 10 cm of the rectum. Symptoms may include mucoid bowel movements, hematochezia, tenesmus, or systemic symptoms of fevers, chills, and malaise during the primary episode. Lumbosacral radiculopathy may also occur resulting in urinary dysfunction, sacral paresthesia, impotence, and pain [54]. The risk of recurrence in the first year following seroconversion is reported as high as 90% in HSV-2 patients [55]. Recurrent infections typically lack systemic symptoms, are less painful, and occur for a shorter duration as compared to the primary infection. In patients with impaired humoral defenses such as leukemia and HIV or those on T-cell-compromising medications, the genital and mucosal effects of the virus are exacerbated and may result in life-threatening ulcer disease [10].

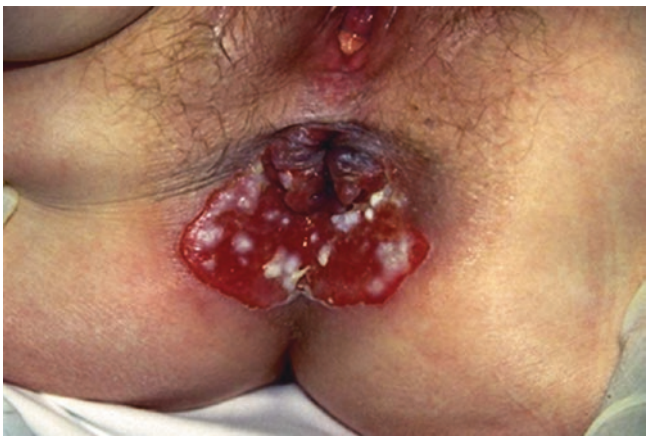

Fig. 18.3 Perianal ulcers and vesicles secondary to herpes simplex virus. (Courtesy of William B. Sweeney, MD, Uniformed Services University of the Health Sciences)

The diagnoses of HSV include both type-specific virologic and type-specific serologic testing. These results dictate the patient's prognosis and guide counseling and education for the patient and their partner [12]. Cell culture growth may detect viral presence in 90% of active vesicular lesions and has been a primary method of detection for decades. The logistics required of this diagnostic method is challenging; however, it allows for viral typing and antiviral sensitivity testing [56]. The classic use of the Tzanck preparation and direct immunofluorescences is insensitive and lacks accuracy; therefore, they are not recommended [57].

Serologic testing with polymerase chain reaction (PCR) assays allows for nucleic acid amplification of the HSV DNA and is currently the gold standard test for systemic HSV infections of the central nervous system. This rapid and sensitive method of viral detection has become recognized as a feasible option in the diagnosis of all herpes associated lesions. HSV-specific glycoproteins should be requested to detect HSV-1 or HSV-2, as knowledge of the offending organism may guide treatment and counseling for patients. HSV-1 lesions tend to have better outcomes with a shorter duration of viral shedding. Type-specific serologic testing may be utilized in patients without active lesions, and positive results suggest previous infections. Due to its low specificity, high

false-positive rate, and lack of confirmatory testing, the approved and available serologic test for HSV-2 is not a suitable option for screening the general population [6, 56].

Oral systemic antiviral medications are the mainstay in management of genital herpes; however, there is no cure. These agents function to partially decrease the signs and symptoms of episodes when recognized early. Antiviral agents are indicated for the onset of symptoms or as a daily suppressive medication. Once discontinued, this does not affect the risk or timing of recurrence. Three antiviral medications have been validated through randomized controlled trials and include valacyclovir, acyclovir, and famciclovir [58–61]. All patients should be considered for antiviral treatment during their initial clinical episode as this may result in a severe systemic response or neurological injury (Table 18.6) [12]. Once seroconversion occurs, patients may elect to begin continuous suppressive therapy or on-demand treatment when outbreaks occur [59]. Diaz-Mitoma and colleagues demonstrated that daily suppressive famciclovir resulted in a recurrence-free interval three times the rate of the control group, with 70–80% of patient's disease free at 1 year [62]. In addition, patients had an increased satisfaction in their treatment with suppressive therapy; however, this did not meet statistical significance (64% vs. 50%; $p = 0.13$) [63]. Once-daily valacyclovir has been demonstrated to be safe and efficacious in decreasing the risk of transmission of HSV-2 in both heterosexual couples and those with multiple sexual partners [12, 60, 64].

Recommendations supporting the treatment of proctitis secondary to HSV are limited; however, antivirals are recommended to shorten the duration of symptoms [65]. Patients with severe HSV infection, systemic sequelae of the disease, or neurologic complications that necessitate hospitalization should be considered for intravenous acyclovir [12]. As the use of antimicrobial agents increase, therapeutic resistance becomes a significant issue. Acyclovir resistance has been reported at a rate of 5% in HIV-positive patients, with a risk <1% in the immunocompetent population [66]. Albeit low, untreated HSV infection in the immunosuppressed patient may lead to significant consequences to include severe persistent ulcers, aseptic meningitis, and extragenital lesions. The recommended treatment in the setting of drug-resistant HSV infections includes foscarnet or cidofovir, with limited data in the use of topical imiquimod or cidofovir gel [67, 68]. HIV-positive patients should be monitored for persistent disease despite therapy (Table 18.7), and appropriate serological testing should be performed (Table 18.3).

Genital Warts

Human papilloma virus is one of the most prevalent sexually transmitted infections in the world, with over 20 million patients affected in the United States and five million cases diagnosed annually. This virus and its development into genital warts present various indications for treatment by a colorectal surgeon [69, 70]. Anogenital condylomas are common among all genders and sexual orientations; however, this infection is more prevalent among the MSM population, with rates as high as 57% in those HIV-negative and over 90% in HIV-positive patients [71]. Furthermore, HIV-positive MSM are at a twofold increased risk of HPV infection and subsequent condyloma formation as compared to non-MSM patients [72]. There are over 120 known HPV serotypes, with subtype 6 and 11 identified as the most common cause of benign condylomas, typically seen as unsightly warts of the genitalia, anus, and rectum. Subtypes 16 and 18 are more commonly associated with cellular changes in the mucosa resulting in anal dysplasia and invasive carcinoma [73]. These lesions lack a severe inflammatory response; however, in an immunocompromised state, HPV can be challenging to manage.

Transmission typically occurs through sexual contact with a 3-month incubation period. The utilization of condoms may help protect spread of the virus to some degree; however, inoculation may occur from the uncovered skin beyond the latex material. Although intra-anal lesions are more common in those who engage in anal receptive intercourse, autoinoculation has been demonstrated from genitourinary warts to the perianal region without direct contact [74, 75].

Symptoms depend on the degree and location of the lesions. Genital warts are typically diagnosed based on clinical exam and appear as raised gray or pink fleshy, cauliflower-like growths that may result in bleeding, pruritus, pain, or hygiene difficulty (Fig. 18.4). Anoscopy is recommended to evaluate for extension into the anal canal. If small papules are visualized, they rarely develop proximal to the dentate line [76]. Consideration should be given to fully examine the genitalia, perineum, and groins and perform a speculum exam of the vagina with Pap smear in women. Subtyping of the virus is not recommended for ano-

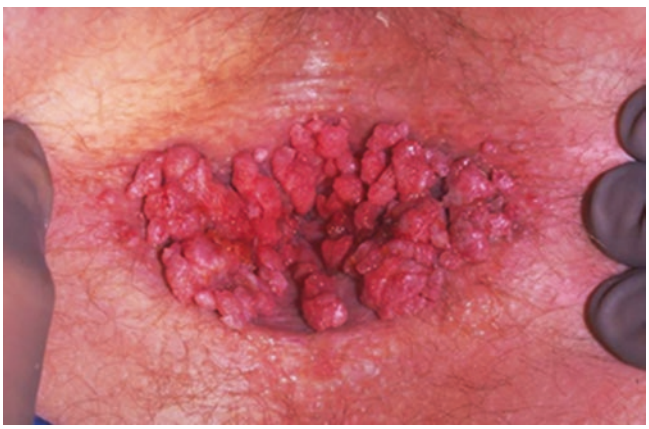

Fig. 18.4 Perianal condylomas secondary to human papilloma virus

Table 18.8 Treatment recommendations for anorectal warts

Patient-applied therapy	Provider-administered therapy	Intra-anal lesion therapy
Imiquimod 3.75% or 5% cream	Cryotherapy	Cryotherapy
Podofilox 0.5% solution or gel	Surgical removal	Surgical removal
Sinecatechins 15% ointment	Trichloroacetic or bichloroacetic acid 80–90% solution	Trichloroacetic or bichloroacetic acid 80–90% solution

genital warts as results are difficult to confirm and do not guide management [12]. Histologic confirmation is only recommended when the patient is immunocompromised, the diagnosis is uncertain, there is failure to respond to therapy, or the lesion worsens during treatment. The clinician should have a greater index of suspicion for malignancy in patients who are immunocompromised, those that have large atypical or pigmented lesions, and disease refractory to standard treatment [77].

High-resolution anoscopy, a technique similar to colposcopy, is a tool utilized to evaluate the anal epithelium and should be considered in high-risk populations such as MSM- and HIV-positive patients. This may be performed in the office setting or operating room with the application of 3% acetic acid or Lugol's solution. Lesions that turn a distinct acetowhite or do not take up the Lugol's solution are at greater risk of dysplasia [78]. Features of dysplasia include punctation, mosaicism, neovascularization, and an abnormal vascular pattern [79, 80].

The management of condylomas is focused on the destruction or clearance of all visible disease while minimizing harm to surrounding tissue (Table 18.3). Similar to HSV, local destruction of HPV does not eradicate the virus. The immunocompetent patient may even spontaneously clear all lesions if left untreated. Treatment options include tangential excision, cryotherapy, fulguration, and topical therapies (Table 18.8). Smaller lesions may be treated under local anesthesia in the outpatient setting, but larger or multiple lesions require treatment in the operating room. Recurrence rates are reported between 4% and 29% and may vary based on the patient's immune function [81, 82]. A single treatment may result in clearance of the virus in up to 75% of patients; however, those with intra-anal lesions, a more extensive initial presentation, and requirement for combination therapy with topical medication and those who have not received the HPV vaccination are at a greater risk of recurrence and need for additional therapy within 2 years [83].

Electrosurgical ablation may be utilized for lesions in any location, and this allows for full-thickness destruction of the condyloma. Adequate fulguration occurs when the superficial layer of the wart is cauterized and the lesion changes to a gray-white appearance. The lesion should then be mechanically debrided with a curette or gauze. Care should be taken to avoid burning into the deep dermis or subcutaneous fat as this can result in significant scaring and poor cosmesis. Carbon dioxide laser therapy is an alternative ablative technique for the appropriately trained clinician. This may be beneficial for large, multiple, or recurrent warts and is particularly useful for intraurethral lesions. In addition, warts can be transected at their base using scissors or a scalpel. Electrodesiccation of anogenital warts should be performed in an appropriately ventilated room utilizing standard precautions and smoke evacuator techniques. Based on the size and extent of the lesion, adjuvant patient-applied topical therapy may be recommended to aid in minimizing the risk of recurrence. Presently, there are no FDA-approved topical therapies for intra-anal lesions.

Trichloroacetic acid and bichloroacetic acid are provider-applied agents that can be placed topically in the clinic and for small lesions in the anal canal or perianal skin. These chemicals are caustic agents that destroy warts through protein coagulation. Care should be taken to avoid contact with healthy tissue as this may result in unnecessary damage. Once the acid is applied, a white frost material forms on the tissue. The chemical should then be allowed to dry before the patient moves. Applying sodium bicarbonate, liquid soap, or powdered talc can neutralize the acid if pain from the application is not well tolerated. Cryotherapy is another provider-applied therapy that causes thermal-induced cytolysis to destroy warts. Patients may experience pain from this application and subsequent tissue necrosis or blistering at the treatment area. Alternative provider-applied therapies include podophyllum resin, intralesional interferon, photodynamic therapy, and topical cidofovir. These agents are less utilized and not recommended for first-line treatment of genital warts due to a paucity of outcomes data and greater side effect profile.

Patient-applied topical therapies for non-intra-anal condylomas include imiquimod 5% cream, podofilox 0.5%, or sinecatechins 15% which is a green tea extract containing catechins as its active component. Imiquimod is a class of medications known as an immune response modifier that has antiviral properties by stimulating interferon activity and cytokines involved in a T-cell-mediated response [84]. Treatment success following a 16-week period is reported as high as 87% with this medication alone, and a combination of imiquimod with laser ablation therapy has additional benefits in sustained wart clearance [85]. The cream may be applied at bedtime three times a week and should be left in place for 6–8 hours and removed with washing. Side effects include pain, burning, itching, irritation, induration, ulcerations, ero-

sions, and even vesicle formation. Treatment may be implemented as initial therapy alone or following other ablative techniques. Patients should be counseled to fully wash off all applied medications prior to engaging in sexual activity as these products may weaken the protective effects of latex condoms, increasing the risk of contracting sexually transmitted organisms. The utilization of imiquimod-containing suppositories following ablation has been investigated for intra-anal lesions with complete clearance of disease and minimal side effects [86].

Application of podofilox 0.5%, an antimitotic drug derived from the plant resin podophyllum, results in wart necrosis. This can be applied twice a day for 3 days followed by a 1-day break. This therapy can be repeated for up to four cycles. Due to the risk of skin irritation and systemic toxicity, the total volume of podofilox should be limited to 0.5 mL per day and should be applied on a cotton swab or finger. Initial treatment application can be performed in the clinic to provide instructions to the patient. The successful rate of wart clearance is reported at 37%, with a 4–38% risk of recurrence [87].

The management of recalcitrant anal warts can be frustrating for both the surgeon and patient alike. Although there is no consensus regarding therapeutic modalities, the utilization of a topical immunotherapy in combination with ablative techniques should be considered. O'Mahony and colleagues recommend the application of topical immunotherapy for 2 months prior to ablative techniques in the initial treatment of patients with greater than five warts. This algorithm could also be considered for recurrent disease [88]. Although ongoing investigations are required, the potential application of the HPV vaccine has been considered in the treatment of existing HPV-related conditions. When administered in the prophylactic setting, this vaccine elicits a virus-neutralizing antibody response to prevent entry of the virus into the host cell. Clinical trials of novel vaccines have reported encouraging results; however, only one case report has demonstrated efficacy of the quadrivalent vaccine in the treatment of anogenital warts [89]. Although data is limited, the current literature and ongoing investigations support the use of the HPV vaccine as an off-label therapeutic agent for HPV-associated cutaneous and mucosal lesions [90, 91]. Intralesional immunotherapy has also been considered as an adjunct in the management of anogenital warts. The local injection of antigens to *Candida albicans*; measles, mumps, and rubella (MMR); *Trichophyton*; and tuberculin antigens have been evaluated. This technique induces a T-cell-mediated response releasing cytokines and interferon. This results in the upregulation of a local immune response targeting the virus. Although further studies are required to fully elucidate the treatment effect of these vaccines, they may be considered in the management of complicated cases or recurrent disease [92].

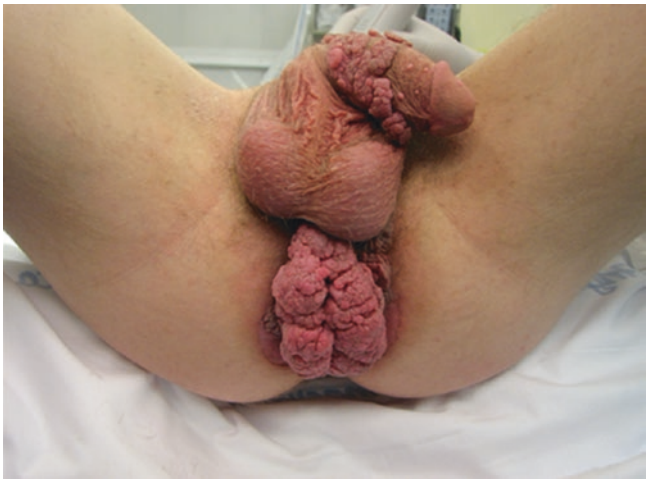

Fig. 18.5 Giant condyloma acuminata and genital warts secondary to human papilloma virus

Giant Condyloma

Giant condyloma acuminata (GCA) was first described by Bushke and Loewenstein in 1925; however, it was not until 1967 when Knoblich reported the first case of perianal GCA. These lesions are associated with HPV types 6, 11, 16, and 18 but differ from condylomas in that they have marked papillomatosis, acanthosis, and thickened rete ridges with greater mitotic activity. These lesions are more prevalent in immunosuppressed patients and are characterized by large destructive verrucous lesions on the anogenital region (Fig. 18.5) [93]. This entity may represent the continuum of benign condyloma to invasive squamous cell carcinoma [94]. Histologically GCA has been demonstrated to infiltrate tissue and has a risk of malignant transformation in up to 56% of patients [95, 96].

The treatment of choice is wide local excision with one centimeter margins. Aggressive resection is necessary as the risk of recurrence is 65%, with a greater rate in HIV-positive patients [95–97]. Radical excision allows for adequate surgical margins, as well as complete histologic examination to guide additional therapeutic interventions. While most wounds heal by secondary intent, rotational S flaps, advancement flaps, V-Y flaps, or skin grafts may be required to cover large surgical defects [98]. Abdominoperineal resection is required if the anal sphincter is involved. Successful outcomes have been reported with the use of chemoradiation alone in poor surgical candidates or those whom complete surgical margins cannot be safely achieved [99, 100]. Guttadauro describes a sleeve resection of the lesion by creating a cylindrical mucocutaneous excision with a radiofrequency dissector. This allows for removal of the entire lesion creating an anastomosis of proximal viable mucosa to the excised distal margin. This technique places the dentate line

in the correct anatomic position while avoiding a mucosal ectropion. Utilization of this procedures resulted in a short hospital stay, with no incidence of anal stenosis or recurrence at 1 year [98]. GCA may be challenging to manage especially in the immunocompromised patient; therefore, resection and reconstruction should be individualized to minimize the risk of recurrence while avoiding significant morbidity.

Molluscum Contagiosum

Molluscum contagiosum, a member of the poxvirus family, results in small contagious skin lesions. This virus has an incubation period between 1 week and 6 months and could last multiple months if no intervention is rendered. Transmission occurs through direct contact of the skin and mucous membranes of active lesions. In addition, this pathogen is transmitted via fomites, such as towels or other clothing objects. Molluscum has been associated with pools or bathing facilities, and patients can auto inoculate themselves in various locations throughout the body.

The lesions are typically flesh-colored or gray-white, and symptoms include itching and pain. The virus is typically self-limiting in the immunocompetent host; however, in those with an impaired immune system such as HIV, these lesions may become quite large, verrucous, and hyperkeratotic. Treatment with phenol or trichloroacetic acid, tangential excision, electrocautery, or cryotherapy is all effective. In addition, patient-applied topical therapies include podophyllotoxin and imiquimod. These interventions control the risk of transmission and improve potential cosmetic outcomes [101–103].

Human Immunodeficiency Virus

Although the spread of HIV was reported prior to 1980, it was not until 1981 when the Centers for Disease Control and Prevention recognized this viral transmission as an epidemic. HIV is a single-stranded ribonucleic acid (RNA) retrovirus which allows for incorporation into the human genome via reverse transcriptase. The virus initially attacks CD4 receptors to enter the cell, resulting in abnormal immune system activation and eventually the destruction of T lymphocytes. The virus has the ability to become latent for a number of years making treatment strategies and eradication challenging (104). Since its initial report, approximately 1.7 million people have been infected with HIV in the United States, with over 500,000 deaths. Presently, 1.2 million patients are living with the disease, and 14% are unaware of their infectious status. Fortunately, between 2010 and 2016, the annual incidence of HIV has decline by 9% in the United States; however, the prevalence remains greatest in MSM, especially the African American population [12, 104].

The life span of HIV has been divided into three stages. The first, or acute stage, also referred to as HIV-1 infection syndrome, occurs within in a few weeks of transmission. The patient may suffer from flu-like symptoms and a rash [104]. This phase occurs as multiple cells of the immune system and lymphatic tissue are targeted by the virus. Following the acute infection, the virus enters a dormancy phase where reproduction occurs but at a low level. When left untreated, CD4 counts will begin to fall, and once levels are <500 mm^3 the immune system, reserves will be compromised, and resultant viral infections such as HSV or HPV may ensue. Once the CD4 count is <200 mm^3, patients become vulnerable to opportunistic infections and cancer leading to acquired immunodeficiency syndrome (AIDS) or end-stage HIV disease. Disease progression has been shown to be influenced by both physiologic and psychosocial factors. Drug use, high-risk sexual behaviors, and mental health all play a factor in outcomes, as well as the utilization of appropriate treatment and prevention strategies [105]. With the advent of highly active antiretroviral therapy (HAART) and virus-specific intervention, there has been a significant reduction in HIV-related morbidity and mortality. The goal of treatment is to suppress the circulating viral load and preserve immune function. Studies have shown that the implementation of HAART has the ability to recover and restore both adaptive and innate immune parameters [106].

Although HIV does not manifest as a specific anorectal disorder, benign anorectal pathology in the HIV-infected patients is the most common operative indication [107]. Anal pathology can present in three ways: (1) HIV-specific condition (anal ulcer); (2) routine condition (hemorrhoid, fissures, fistulas, perirectal abscess); and (3) routine condition that manifests differently due to HIV status (anal condylomas and herpetic anal ulcers) [108, 109]. In addition, AIDS is associated with malignancies to include anal squamous cell carcinoma, lymphoma, and Kaposi's sarcoma [109]. The surgeon should have an understanding for the patient's disease stage and medication regimen to ensure appropriate treatment is rendered. Previously, surgeons have been hesitant to operate due to the concerns of delayed or poor wound healing secondary to the aggressive nature of the virus, decreased leukocyte and CD4 count, and association with AIDS. Safavi and colleagues demonstrated that T4 cell count had no predictive value associated with wound healing [109]. Furthermore, many studies which have reported poor surgical outcomes in AIDS patients are greater than 20 years old and predate the era of HAART [110–112]. Based on the knowledge regarding immune reconstitution following HAART treatment, HIV-positive patients on appropriate virus-targeted agents are most likely at no increased risk for complications following anorectal surgery, and their pathology should be treated in a standard fashion regardless of their immune status [104].

An anorectal abscess should be drained with a small incision close to the anal verge. Cultures should be obtained, and patients in an immunocompromised state should be placed on antibiotics. Anal fistulas are typically cryptoglandular in origin and should be treated with setons or sphincter-preserving operations. Fistulotomies should be performed in low uncomplicated fistulas. However, prior to any sphincter-sacrificing procedure, a thorough evaluation should be performed to detail the patient's bowel habits, history of diarrhea, and sphincters control. Although these common anorectal manifestations should be treated in a similar fashion, it should be remembered that HIV is not a static disease and the treatment of the current condition may have a significant effect on the patient's quality of life in the future.

Anal fissures among MSM may result from anal receptive intercourse and must be distinguished from HIV-/AIDS-related ulcers and other ulcerating infections such as HSV or syphilis which are more prevalent in the HIV population [109]. HIV-related ulcers are typically tender, necrotic, and exudative with deep irregular overhanging borders. They typically form off the midline; however, when midline, they are more proximal in the anal canal and closer to the dentate line as compared to simple fissures. These lesions tend to be the most disabling of any anal disease and are associated with a hypotonic sphincter. Occasionally there is a superficial layer of purulent material mimicking an abscess [107]. Anal ulcers remain a common disorder in this population, as they are not affected by antiviral medications [113].

Treatment for anal fissures in the HIV-positive population should be similar to the general population; however, internal sphincterotomy is not advised unless the diagnosis is clearly distinguished from ulcerating disease. Those with diarrhea secondary to proctocolitis should be treated appropriately to minimize trauma to the anal canal, and abstinence from anal receptive intercourse is recommended. Safavi and colleagues report the use of intralesional steroids in the treatment of anal ulcers in six patients with significant improvement, suggesting inflammatory mediators contribute to ulcer formation [109]. Ulcer excision followed by mucosal advancement flap should be reserved for those who fail medical treatment; however, a more aggressive surgical approach has been associated with symptomatic relief and successful wound healing [107].

Ectoparasitic Sexually Transmitted Diseases

Pediculosis pubis or pubic lice is an infestation of the parasite *Pthirus pubis*. Transmission is secondary to contamination of pubic hair and the perianal region during close sexual contact. Following egg deposit onto the contaminated surface, the incubation period is less than 1 week, with the entire life cycle of the adult parasite less than 1 month. The primary symptoms are typically pruritus. The affected skin becomes crusted, and rust-colored flecks of fecal material can then be seen. A diagnosis is based on clinical findings; however, a dermascope can visualize the parasites within hair follicles [114].

Table 18.9 Treatment recommendations for ectoparasitic sexually transmitted diseases

Primary treatment	Alternative treatment
Pediculosis pubis	
Permethrin 1% cream; apply and wash off after 10 minutes	Malathion 0.5% lotion; apply and wash off after 8–12 hours
Pyrethrins with piperonyl butoxide; apply and wash off after 10 minutes	Ivermectin 250 μg/kg orally; repeat in 2 weeks
Scabies	
Permethrin 5% cream; apply to affected areas wash off after 8–14 hours	Lindane 1%: 1 oz of lotion or 30 g of cream; apply thin layer, wash off after 8 hours
Ivermectin 200 μg/kg orally; repeat in 2 weeks	

Patients diagnosed with pubic lice should be screened for other sexually transmitted diseases, including HIV, as there is a 30% risk of coinfection [115]. First-line therapy typically involves permethrin 1% cream or pyrethrins with piperonyl butoxide. Alternative therapy options include malathion 0.5% lotion or ivermectin 250 μg/kg orally for 2 weeks. Lindane is an additional treatment option when other therapies fail; however, side effects include aplastic anemia and seizures (Table 18.9) [116]. The skin should be cool and dry prior to applying topical agents. In addition to topical medications, the patient should comb the affected area to remove all nits; however, shaving is generally not necessary. All clothing and bedding should be washed [114]. The patient is considered clear of infestation if no parasites are present 1 week after treatment.

Scabies, or *Sarcoptes scabiei*, is a parasitic infection frequently transmitted in adults through sexual activity [117]. This eight-legged creature can survive up to 36 hours at room temperature and can be transmitted through fomites. Following infection, scabies results in nocturnal pruritus with a symmetrical distribution of papules, pustules, and excoriations. Clinical findings are more common in the interdigital webs, nipples, or genitals. The diagnosis is classically made by identifying the mite in its burrow. Although challenging to capture the organism in this form, the diagnosis is typically made through findings of fecal material. Recommended treatment options include permethrin 5% cream or ivermectin orally for 2 weeks. Lindane is also an alternative treatment options but should be used in limited cases with refractory disease due to toxicity. Caution must be had with all treatment options as they can be caustic to the

skin and result in a contact dermatitis (Table 18.9). As with pediculosis, close contact should be restricted, and all clothing should be carefully washed [118]. To minimize excoriation from scratching, patients should be advised to keep their fingernails short.

The HIV or immunocompromised patient is at increased risk for crusted or Norwegian scabies. This species has a greater ease of transmission in this at-risk population with a significantly aggressive rate of infestation. Combination therapy is recommended with 25% benzyl benzoate or 5% permethrin cream and oral ivermectin. Destructive effects on the skin are severe, and Lindane should be avoided due to increased risk of systemic toxicity [119]. This subgroup of scabies is challenging to eradicate, and close follow-up should be considered at 2 weeks with additional therapy if needed. All sexual contacts should be evaluated and treated accordingly [12].

Conclusion

Despite the advancements in diagnostic and therapeutic modalities, anorectal STIs remain a public health concern. The most effective method of treatment is prevention, and that starts with the education of patients and providers alike. High-risk population, such as MSM and those in a low socioeconomic status, should be screened and offered appropriate vaccines and prevention methods to mitigate the transmission of these infectious organisms. All patients presenting with a concern for an STI require specific testing and screening for all related organisms and HIV. Although effective antibiotic and antiviral therapies exist and operative intervention may not be required for the majority of STIs, the colorectal surgeon should provide an environment of support to ensure patients receive the required treatment and sexual health counseling.

References

1. 2018 STD Surveillance Report. https://www.cdc.gov/nchhstp/newsroom/2019/2018-STD-surveillance-report.html. Accessed on 18 Feb 2020.
2. Kent CK, et al. Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. Clin Infect Dis. 2005;41(1):67–74.
3. Kozlowski PA, Neutra MR. The role of mucosal immunity in prevention of HIV transmission. Curr Mol Med. 2003;3(3):217–28.
4. Fujimura Y. Evidence of M cells as portals of entry for antigens in the nasopharyngeal lymphoid tissue of humans. Virchows Arch. 2000;436(6):560–6.
5. Neutra MR, Pringault E, Kraehenbuhl JP. Antigen sampling across epithelial barriers and induction of mucosal immune responses. Annu Rev Immunol. 1996;14:275–300.
6. Bibbins-Domingo K, et al. Serologic screening for genital herpes infection: US Preventive Services Task Force recommendation statement. JAMA. 2016;316(23):2525–30.
7. McClung NM, et al. Estimated number of cases of high-grade cervical lesions diagnosed among women – United States, 2008 and 2016. MMWR Morb Mortal Wkly Rep. 2019;68(15):337–43.
8. Sobhani I, et al. Effect of anal epidermoid cancer-related viruses on the dendritic (Langerhans') cells of the human anal mucosa. Clin Cancer Res. 2002;8(9):2862–9.
9. Wiley DJ, et al. Evidence that anoreceptive intercourse with ejaculate exposure is associated with rapid CD4 cell loss. AIDS. 2000;14(6):707–15.
10. Simmons A. Anogenital mucosal immunology and virology. Springer; London, 2006.
11. Wexner SD. Sexually transmitted diseases of the colon, rectum, and anus. The challenge of the nineties. Dis Colon Rectum. 1990;33(12):1048–62.
12. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64(Rr-03):1–137.
13. FDA approves expanded use of Gardasil 9 to include individuals 27 through 45 years old. https://www.fda.gov/news-events/press-announcements/fda-approves-expanded-use-gardasil-9-include-individuals-27-through-45-years-old. 2018. Accessed Dec 2019.
14. Grant RM, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363(27):2587–99.
15. Baeten JM, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367(5):399–410.
16. McCormack S, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet. 2016;387(10013):53–60.
17. Molina JM, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. N Engl J Med. 2015;373(23):2237–46.
18. Riddell J 4th, Amico KR, Mayer KH. HIV preexposure prophylaxis: a review. JAMA. 2018;319(12):1261–8.
19. Koedijk FD, et al. The value of testing multiple anatomic sites for gonorrhoea and chlamydia in sexually transmitted infection centres in the Netherlands, 2006–2010. Int J STD AIDS. 2012;23(9):626–31.
20. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect. 1999;75(1):3–17.
21. Hoentjen F, Rubin DT. Infectious proctitis: when to suspect it is not inflammatory bowel disease. Dig Dis Sci. 2012;57(2):269–73.
22. Khosropour CM, et al. Comparing azithromycin and doxycycline for the treatment of rectal chlamydial infection: a retrospective cohort study. Sex Transm Dis. 2014;41(2):79–85.
23. Torrone E, Papp J, Weinstock H. Prevalence of Chlamydia trachomatis genital infection among persons aged 14–39 years--United States, 2007–2012. MMWR Morb Mortal Wkly Rep. 2014;63(38):834–8.
24. Low N, et al. Screening for genital chlamydia infection. Cochrane Database Syst Rev. 2016;9(9):CD010866.
25. Levy I, et al. Delayed diagnosis of colorectal sexually transmitted diseases due to their resemblance to inflammatory bowel diseases. Int J Infect Dis. 2018;75:34–8.
26. Sigle GW, Kim R. Sexually transmitted proctitis. Clin Colon Rectal Surg. 2015;28(2):70–8.
27. Johnson Jones ML, et al. Extragenital chlamydia and gonorrhea among community venue-Attending men who have sex with men – five cities, United States, 2017. MMWR Morb Mortal Wkly Rep. 2019;68(14):321–5.

28. Bachmann LH, et al. Nucleic acid amplification tests for diagnosis of Neisseria gonorrhoeae oropharyngeal infections. J Clin Microbiol. 2009;47(4):902–7.
29. FDA clears first diagnostic tests for extragenital testing for chlamydia and gonorrhea. https://www.fda.gov/news-events/press-announcements/fda-clears-first-diagnostic-tests-extragenital-testing-chlamydia-and-gonorrhea. 2019. Accessed Feb 2020.
30. Bristow CC, et al. Meta-analysis of the Cepheid Xpert(R) CT/NG assay for extragenital detection of Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (NG) infections. Sex Health. 2019;16(4):314–9.
31. Chan PA, et al. Extragenital infections caused by Chlamydia trachomatis and Neisseria gonorrhoeae: a review of the literature. Infect Dis Obstet Gynecol. 2016;2016:5758387.
32. Kong FY, et al. The efficacy of azithromycin and doxycycline for the treatment of rectal chlamydia infection: a systematic review and meta-analysis. J Antimicrob Chemother. 2015;70(5):1290–7.
33. Kong FY, et al. Azithromycin versus doxycycline for the treatment of genital chlamydia infection: a meta-analysis of randomized controlled trials. Clin Infect Dis. 2014;59(2):193–205.
34. Lanjouw E, et al. 2015 European guideline on the management of Chlamydia trachomatis infections. Int J STD AIDS. 2016;27(5):333–48.
35. Nieuwenhuis RF, et al. Resurgence of lymphogranuloma venereum in Western Europe: an outbreak of Chlamydia trachomatis serovar l2 proctitis in The Netherlands among men who have sex with men. Clin Infect Dis. 2004;39(7).
36. Stoner BP, Cohen SE. Lymphogranuloma venereum 2015: clinical presentation, diagnosis, and treatment. Clin Infect Dis. 2015;61(Suppl 8):S865–73.
37. Whitlow CB. Bacterial sexually transmitted diseases. Clin Colon Rectal Surg. 2004;17(4):209–14.
38. Pfennig CL. Sexually transmitted diseases in the emergency department. Emerg Med Clin North Am. 2019;37(2):165–92.
39. Assi R, et al. Sexually transmitted infections of the anus and rectum. World J Gastroenterol. 2014;20(41):15262–8.
40. Schachter J, et al. Nucleic acid amplification tests in the diagnosis of chlamydial and gonococcal infections of the oropharynx and rectum in men who have sex with men. Sex Transm Dis. 2008;35(7):637–42.
41. Bolan GA, Sparling PF, Wasserheit JN. The emerging threat of untreatable gonococcal infection. N Engl J Med. 2012;366(6):485–7.
42. Prevention, D.o.S., S. National Center for HIV, TB Prevention, C.f.D.C.a. Prevention. The national plan to eliminate syphilis from the United States. 1999.
43. Golden MR, Dombrowski JC. Syphilis control in the post-elimination era: implications of a new syphilis control initiative for STD/HIV programs. Sex Transm Dis. 2018;45(9S Suppl 1):S86–92.
44. Lynn WA, Lightman S. Syphilis and HIV: a dangerous combination. Lancet Infect Dis. 2004;4(7):456–66.
45. Katz DA, et al. HIV incidence among men who have sex with men after diagnosis with sexually transmitted infections. Sex Transm Dis. 2016;43(4):249–54.
46. Centers for Disease Control and Prevention (CDC). Discordant results from reverse sequence syphilis screening--five laboratories, United States, 2006–2010. MMWR Morb Mortal Wkly Rep. 2011;60(5):133–7.
47. Cone MM, Whitlow CB. Sexually transmitted and anorectal infectious diseases. Gastroenterol Clin N Am. 2013;42(4):877–92.
48. Copeland NK, Decker CF. Other sexually transmitted diseases chancroid and donovanosis. Dis Mon. 2016;62(8):306–13.
49. Muller EE, Kularatne R. The changing epidemiology of genital ulcer disease in South Africa: has donovanosis been eliminated? Sex Transm Infect. 2020;96(8):596–600.
50. Goodell SE, et al. Herpes simplex virus proctitis in homosexual men. Clinical, sigmoidoscopic, and histopathological features. N Engl J Med. 1983;308(15):868–71.
51. Fleming DT, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. N Engl J Med. 1997;337(16):1105–11.
52. Ryder N, et al. Increasing role of herpes simplex virus type 1 in first-episode anogenital herpes in heterosexual women and younger men who have sex with men, 1992–2006. Sex Transm Infect. 2009;85(6):416–9.
53. Wexner SD, et al. The surgical management of anorectal diseases in AIDS and pre-AIDS patients. Dis Colon Rectum. 1986;29(11):719–23.
54. Catterall RD. Sexually transmitted diseases of the anus and rectum. Clin Gastroenterol. 1975;4(3):659–69.
55. Benedetti J, Corey L, Ashley R. Recurrence rates in genital herpes after symptomatic first-episode infection. Ann Intern Med. 1994;121(11):847–54.
56. Scoular A. Using the evidence base on genital herpes: optimising the use of diagnostic tests and information provision. Sex Transm Infect. 2002;78(3):160–5.
57. Caviness AC, et al. Direct immunofluorescence assay compared to cell culture for the diagnosis of mucocutaneous herpes simplex virus infections in children. J Clin Virol. 2010;49(1):58–60.
58. Leone PA, Trottier S, Miller JM. Valacyclovir for episodic treatment of genital herpes: a shorter 3-day treatment course compared with 5-day treatment. Clin Infect Dis. 2002;34(7):958–62.
59. Aoki FY, et al. Single-day, patient-initiated famciclovir therapy for recurrent genital herpes: a randomized, double-blind, placebo-controlled trial. Clin Infect Dis. 2006;42(1):8–13.
60. Chosidow O, et al. Famciclovir vs. aciclovir in immunocompetent patients with recurrent genital herpes infections: a parallel-groups, randomized, double-blind clinical trial. Br J Dermatol. 2001;144(4):818–24.
61. Wald A, et al. Two-day regimen of acyclovir for treatment of recurrent genital herpes simplex virus type 2 infection. Clin Infect Dis. 2002;34(7):944–8.
62. Diaz-Mitoma F, et al. Oral famciclovir for the suppression of recurrent genital herpes: a randomized controlled trial. Collaborative Famciclovir Genital Herpes Research Group. JAMA. 1998;280(10):887–92.
63. Bartlett BL, et al. Famciclovir treatment options for patients with frequent outbreaks of recurrent genital herpes: the RELIEF trial. J Clin Virol. 2008;43(2):190–5.
64. Corey L, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med. 2004;350(1):11–20.
65. Rompalo AM, et al. Oral acyclovir for treatment of first-episode herpes simplex virus proctitis. JAMA. 1988;259(19):2879–81.
66. Reyes M, et al. Acyclovir-resistant genital herpes among persons attending sexually transmitted disease and human immunodeficiency virus clinics. Arch Intern Med. 2003;163(1):76–80.
67. Perkins N, Nisbet M, Thomas M. Topical imiquimod treatment of aciclovir-resistant herpes simplex disease: case series and literature review. Sex Transm Infect. 2011;87(4):292–5.
68. McElhiney LFPR. Topical cidofovir for treatment of resistant viral infections. Int J Pharm Compd. 2006;10(5):324–8.
69. Cates W Jr. Estimates of the incidence and prevalence of sexually transmitted diseases in the United States. American Social Health Association Panel. Sex Transm Dis. 1999;26(4 Suppl):S2–7.
70. Koshiol JE, Laurent SA, Pimenta JM. Rate and predictors of new genital warts claims and genital warts-related healthcare utilization among privately insured patients in the United States. Sex Transm Dis. 2004;31(12):748–52.
71. Chin-Hong PV, et al. Age-specific prevalence of anal human papillomavirus infection in HIV-negative sexually active men who have sex with men: the EXPLORE study. J Infect Dis. 2004;190(12):2070–6.

72. Darwich L, et al. Condylomata, cytological abnormalities and human papillomavirus infection in the anal canal in HIV-infected men. HIV Med. 2012;13(9):549–57.
73. Lorincz AT, et al. Oncogenic association of specific human papillomavirus types with cervical neoplasia. J Natl Cancer Inst. 1987;79(4):671–7.
74. Baldwin SB, et al. Condom use and other factors affecting penile human papillomavirus detection in men attending a sexually transmitted disease clinic. Sex Transm Dis. 2004;31(10):601–7.
75. El-Attar SM, Evans DV. Anal warts, sexually transmitted diseases, and anorectal conditions associated with human immunodeficiency virus. Prim Care. 1999;26(1):81–100.
76. Assi R, et al. Anorectal human papillomavirus: current concepts. Yale J Biol Med. 2014;87(4):537–47.
77. Gunter J. Genital and perianal warts: new treatment opportunities for human papillomavirus infection. Am J Obstet Gynecol. 2003;189(3 Suppl):S3–11.
78. O'Connor JJ. The study of anorectal disease by colposcopy. Dis Colon Rectum. 1977;20(7):570–2.
79. Richel O, et al. High-resolution anoscopy: clinical features of anal intraepithelial neoplasia in HIV-positive men. Dis Colon Rectum. 2013;56(11):1237–42.
80. Kreuter A, et al. High-grade dysplasia in anogenital warts of HIV-positive men. JAMA Dermatol. 2016;152(11):1225–30.
81. Beck DE, Jaso RG, Zajac RA. Surgical management of anal condylomata in the HIV-positive patient. Dis Colon Rectum. 1990;33(3):180–3.
82. D'Ambrogio A, et al. Human papilloma virus type and recurrence rate after surgical clearance of anal condylomata acuminata. Sex Transm Dis. 2009;36(9):536–40.
83. Silvera RJ, et al. Anal condyloma treatment and recurrence in HIV-negative men who have sex with men. Dis Colon Rectum. 2014;57(6):752–61.
84. Miller RL, et al. Imiquimod applied topically: a novel immune response modifier and new class of drug. Int J Immunopharmacol. 1999;21(1):1–14.
85. Hoyme UB, et al. Effect of adjuvant imiquimod 5% cream on sustained clearance of anogenital warts following laser treatment. Infect Dis Obstet Gynecol. 2002;10(2):79–88.
86. Kaspari M, et al. Application of imiquimod by suppositories (anal tampons) efficiently prevents recurrences after ablation of anal canal condyloma. Br J Dermatol. 2002;147(4):757–9.
87. Wiley DJ, et al. External genital warts: diagnosis, treatment, and prevention. Clin Infect Dis. 2002;35(Suppl 2):S210–24.
88. O'Mahony C, et al. Position statement for the diagnosis and management of anogenital warts. J Eur Acad Dermatol Venereol. 2019;33(6):1006–19.
89. Lee HJ, et al. Condyloma accuminatum treated with recombinant quadrivalent human papillomavirus vaccine (types 6, 11, 16, 18). J Am Acad Dermatol. 2011;64(6):e130–2. United States.
90. Murray ML, et al. Human papillomavirus infection: protocol for a randomised controlled trial of imiquimod cream (5%) versus podophyllotoxin cream (0.15%), in combination with quadrivalent human papillomavirus or control vaccination in the treatment and prevention of recurrence of anogenital warts (HIPvac trial). BMC Med Res Methodol. 2018;18(1):125.
91. Pham CT, et al. The human papillomavirus vaccine as a treatment for human papillomavirus-related dysplastic and neoplastic conditions: a literature review. J Am Acad Dermatol. 2020;82(1):202–12.
92. Aldahan AS, et al. Efficacy of intralesional immunotherapy for the treatment of warts: a review of the literature. Dermatol Ther. 2016;29(3):197–207.
93. Haycox CL, Kuypers J, Krieger JN. Role of human papillomavirus typing in diagnosis and clinical decision making for a giant verrucous genital lesion. Urology. 1999;53(3):627–30.
94. Knoblich R, Failing JF Jr. Giant condyloma acuminatum (Buschke-Lowenstein tumor) of the rectum. Am J Clin Pathol. 1967;48(4):389–95.
95. Creasman C, et al. Malignant transformation of anorectal giant condyloma acuminatum (Buschke-Loewenstein tumor). Dis Colon Rectum. 1989;32(6):481–7.
96. Chu QD, et al. Giant condyloma acuminatum (Buschke-Lowenstein tumor) of the anorectal and perianal regions. Analysis of 42 cases. Dis Colon Rectum. 1994;37(9):950–7.
97. de la Fuente SG, Ludwig KA, Mantyh CR. Preoperative immune status determines anal condyloma recurrence after surgical excision. Dis Colon Rectum. 2003;46(3):367–73.
98. Guttadauro A, et al. Circumferential anal giant condyloma acuminatum: a new surgical approach. Dis Colon Rectum. 2015;58(4):e49–52.
99. Butler TW, et al. Squamous-cell carcinoma of the anus in condyloma acuminatum. Successful treatment with preoperative chemotherapy and radiation. Dis Colon Rectum. 1987;30(4):293–5.
100. Trombetta LJ, Place RJ. Giant condyloma acuminatum of the anorectum: trends in epidemiology and management: report of a case and review of the literature. Dis Colon Rectum. 2001;44(12):1878–86.
101. Skinner RB Jr. Treatment of molluscum contagiosum with imiquimod 5% cream. J Am Acad Dermatol. 2002;47(4 Suppl):S221–4.
102. Syed TA, Lundin S, Ahmad SA. Topical 0.3% and 0.5% podophyllotoxin cream for self-treatment of condylomata acuminata in women. A placebo-controlled, double-blind study. Dermatology. 1994;189(2):142–5.
103. Hengge UR, Cusini M. Topical immunomodulators for the treatment of external genital warts, cutaneous warts and molluscum contagiosum. Br J Dermatol. 2003;149(Suppl 66):15–9.
104. Klimas N, Koneru AO, Fletcher MA. Overview of HIV. Psychosom Med. 2008;70(5):523–30.
105. Kalichman SC. Co-occurrence of treatment nonadherence and continued HIV transmission risk behaviors: implications for positive prevention interventions. Psychosom Med. 2008;70(5):593–7.
106. Stebbing J, et al. Highly active anti-retroviral therapy (HAART)-induced maintenance of adaptive but not innate immune parameters is associated with protection from HIV-induced mortality. Clin Exp Immunol. 2006;145(2):271–6.
107. Nadal SR, et al. Management of idiopathic ulcer of the anal canal by excision in HIV-positive patients. Dis Colon Rectum. 1999;42(12):1598–601.
108. Weiss EG, Wexner SD. Surgery for anal lesions in HIV-infected patients. Ann Med. 1995;27(4):467–75.
109. Safavi A, Gottesman L, Dailey TH. Anorectal surgery in the HIV+ patient: update. Dis Colon Rectum. 1991;34(4):299–304.
110. Barrett WL, Callahan TD, Orkin BA. Perianal manifestations of human immunodeficiency virus infection: experience with 260 patients. Dis Colon Rectum. 1998;41(5):606–11.
111. Morandi E, et al. Prospective study of healing time after hemorrhoidectomy: influence of HIV infection, acquired immunodeficiency syndrome, and anal wound infection. Dis Colon Rectum. 1999;42(9):1140–4.
112. Nadal SR, et al. Healing after anal fistulotomy: comparative study between HIV+ and HIV- patients. Dis Colon Rectum. 1998;41(2):177–9.
113. Gonzalez-Ruiz C, et al. Anorectal pathology in HIV/AIDS-infected patients has not been impacted by highly active antiretroviral therapy. Dis Colon Rectum. 2004;47(9):1483–6.
114. Salavastru CM, et al. European guideline for the management of pediculosis pubis. J Eur Acad Dermatol Venereol. 2017;31(9):1425–8.
115. Ko CJ, Elston DM. Pediculosis. J Am Acad Dermatol. 2004;50(1):1–12.

116. Nolan K, Kamrath J, Levitt J. Lindane toxicity: a comprehensive review of the medical literature. Pediatr Dermatol. 2012;29(2):141–6.
117. Bouvresse S, Chosidow O. Scabies in healthcare settings. Curr Opin Infect Dis. 2010;23(2):111–8.
118. Orion E, Matz H, Wolf R. Ectoparasitic sexually transmitted diseases: scabies and pediculosis. Clin Dermatol. 2004;22(6):513–9.
119. Roberts LJ, et al. Crusted scabies: clinical and immunological findings in seventy-eight patients and a review of the literature. J Infect. 2005;50(5):375–81.

Anal Intraepithelial Neoplasia

19

Wolfgang B. Gaertner and Mukta K. Krane

Key Concepts

- Anal intraepithelial neoplasia is a dysplastic condition and is considered to be a premalignant stage of anal cancer.
- Its histologic and cellular findings mirror cervical dysplasia.
- Anal cytology is a useful tool to identify anal neoplasia in high-risk groups.
- When anal cytology is concerning, high-resolution anoscopy with targeted ablation of dysplasia is indicated.
- Treatment should be individualized according to the degree of dysplasia, risk factors, immune status, symptoms, and the likelihood of progression.

Introduction

AIN is defined as the dysplastic growth of squamous epithelial cells at the transition zone of the anal canal. Cells of the anal and cervical canals share embryologic, cytologic, and histopathologic characteristics. Embryologically, fusion of endodermal and ectodermal tissue forms a squamocolumnar epithelial junction (anal transition zone) at the dentate line. AIN has a clear association with HPV and is more prevalent in at-risk populations, including those with human immunodeficiency virus (HIV), men who have sex with men (MSM), as well as liquid- and solid-organ transplant patients. In these populations, the rates of anal cancer are dramatically elevated, despite it being a relatively uncommon disease [1].

The Lower Anogenital Squamous Terminology Standardization (LAST) project for HPV-associated lesions provided guidelines for a unified nomenclature that includes a two-tiered system, designated as low- or high-grade squamous intraepithelial lesion (LSIL or HSIL, respectively). In the anal canal, LSIL correlates with anal intraepithelial neoplasia (AIN)-1 or anal condyloma, while HSIL correlates with AIN-2 and AIN-3 (Fig. 19.1) [3]. Cytologically, abnormal squamous cells of the anus are classified as (a) atypical squamous cells of undetermined significance (ASCUS); (b) atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion; (c) low-grade squamous intraepithelial lesion (LSIL); and (d) high-grade squamous intraepithelial lesion (HSIL) [4].

Incidence

The incidence of AIN in the general population is difficult to estimate, and LSIL may regress or progress to HSIL, whereas HSIL typically does not regress, although this may be influenced by the underlying immune status [5]. Although rates of anal cancer are low (approximately 1.8 cases per 100,000) [6], epidemiologic studies have shown increasing rates of high-grade AIN and anal cancer in both men and women, probably reflecting higher rates of screening [7]. Using statistical models for analysis, rates for new anal cancer cases have been rising on average 2% each year over the last 10 years [8].

Most reports on AIN are retrospective and are heavily biased by heterogeneous populations with significant differences in immune status. Within these, AIN (I–III) has been reported in 6–22% of women with genital (cervical, vaginal, and/or vulvar) intraepithelial dysplasia [9, 10]. The rate of conversion of AIN to anal cancer remains controversial. Prospective studies have suggested that the rate is similar to that of cervical cancer, with a reported 9–13% conversion for AIN-3 within a 5-year period for untreated patients [11, 12], but there is also significant variability among different risk populations. A large meta-analysis from 2012 found that the

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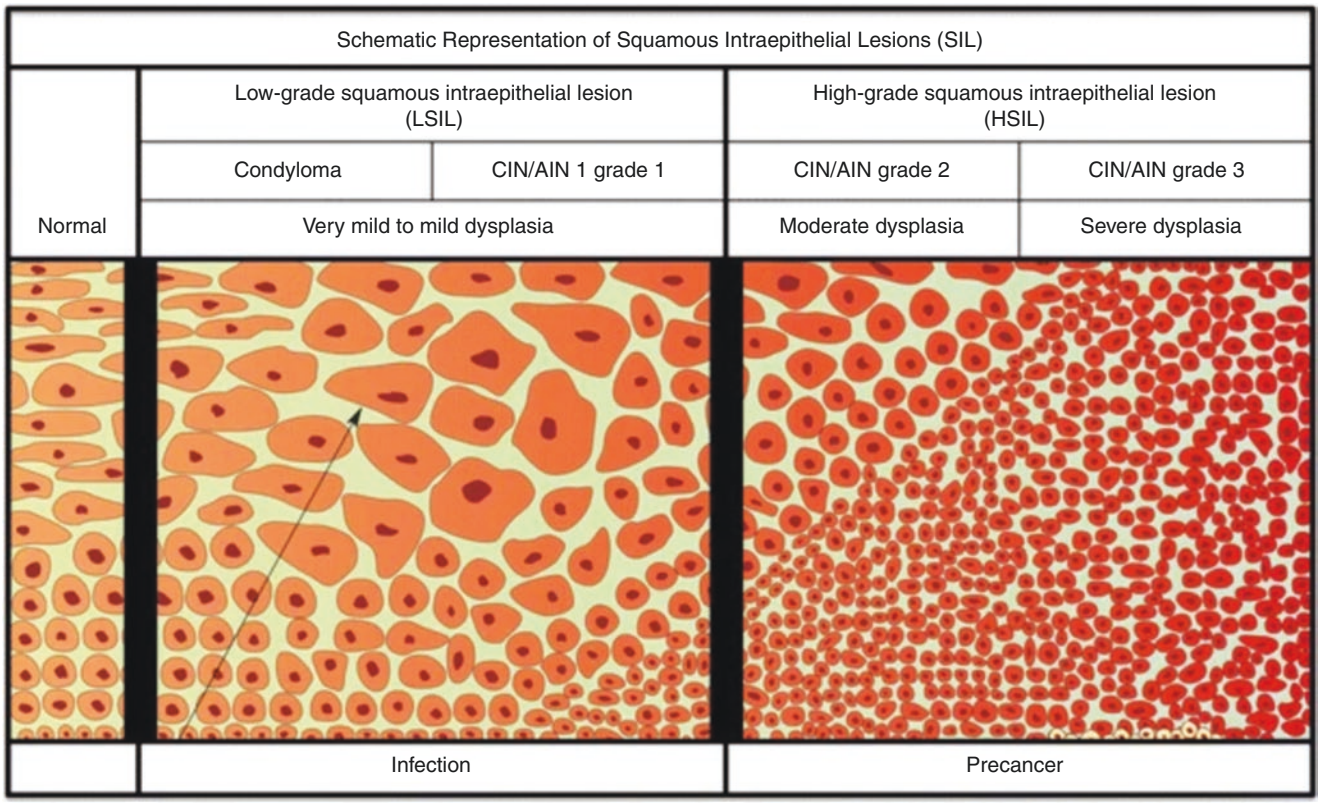

Fig. 19.1 Schematic representation of squamous intraepithelial lesions (SIL). With increasing severity of SIL of the anus, the proportion of the epithelium replaced by immature cells with large nuclear-cytoplasmic ratios increases. Invasive cancer likely arises from one or more foci of high-grade SIL (HSIL). (With permission from Brickman and Palefsky [2]. Copyright © 2015 Springer Nature)

rate of conversion was much lower, with progression rates of 1 in 600 per year for HIV+ MSM and 1 in 4000 per year for HIV– MSM [13]. This discrepancy may be attributed to the mix of AIN-2 and AIN-3 patients within the meta-analysis.

Epidemiology

Anal intraepithelial neoplasia develops from HPV contact generally through direct exposure. The Centers for Disease Control and Prevention indicate that "nearly all sexually active men and women will acquire at least one type of HPV at some point in their lives." In fact, 79 million persons are currently infected with HPV with equal prevalence in both the developed and developing world [14, 15]. Approximately 90% of all immunocompetent patients remain asymptomatic, and those that are infected will resolve without treatment within 2 years [16]. Disease progression and presence of condyloma or neoplasia are likely related to immune status.

HPV infection is mainly subclinical but can present as grossly apparent (i.e., condyloma), microscopically apparent, and latent (i.e., an infection that becomes clinically apparent months or years after exposure) and has the potential to migrate from the genitalia to the anus. Risk factors for HPV infection include uncircumcised men, number of sex partners (directly proportional), sex with a partner who has had many sex partners, sex with uncircumcised men, and first sexual contact at an early age. There are >150 HPV serotypes. Those that are considered high risk include 16, 18, 31, 33, 35, and 45 and produce E6 and E7 proteins, which in turn inhibit two important tumor suppressor proteins, p53 and Rb [15, 17, 18]. HPV subtypes 6 and 11 cause 90% of genital warts [19], while 79% of patients diagnosed with anal squamous cell carcinoma are attributable to type 16 or 18 [15].

With the introduction of the HPV vaccine in 2006, the prevalence of HPV types 6, 11, 16, and 18 identified by cytology specimens decreased by over 50% among teens and young women [20]. Additionally, genital wart cases appear to have decreased since 2011 [21], presumably because of increased vaccination (Fig. 19.2). In 2017, Oliver and colleagues [22] demonstrated a decrease in prevalence of 71% among 14- to 19-year-olds and 61% among 20- to 24-year-olds.

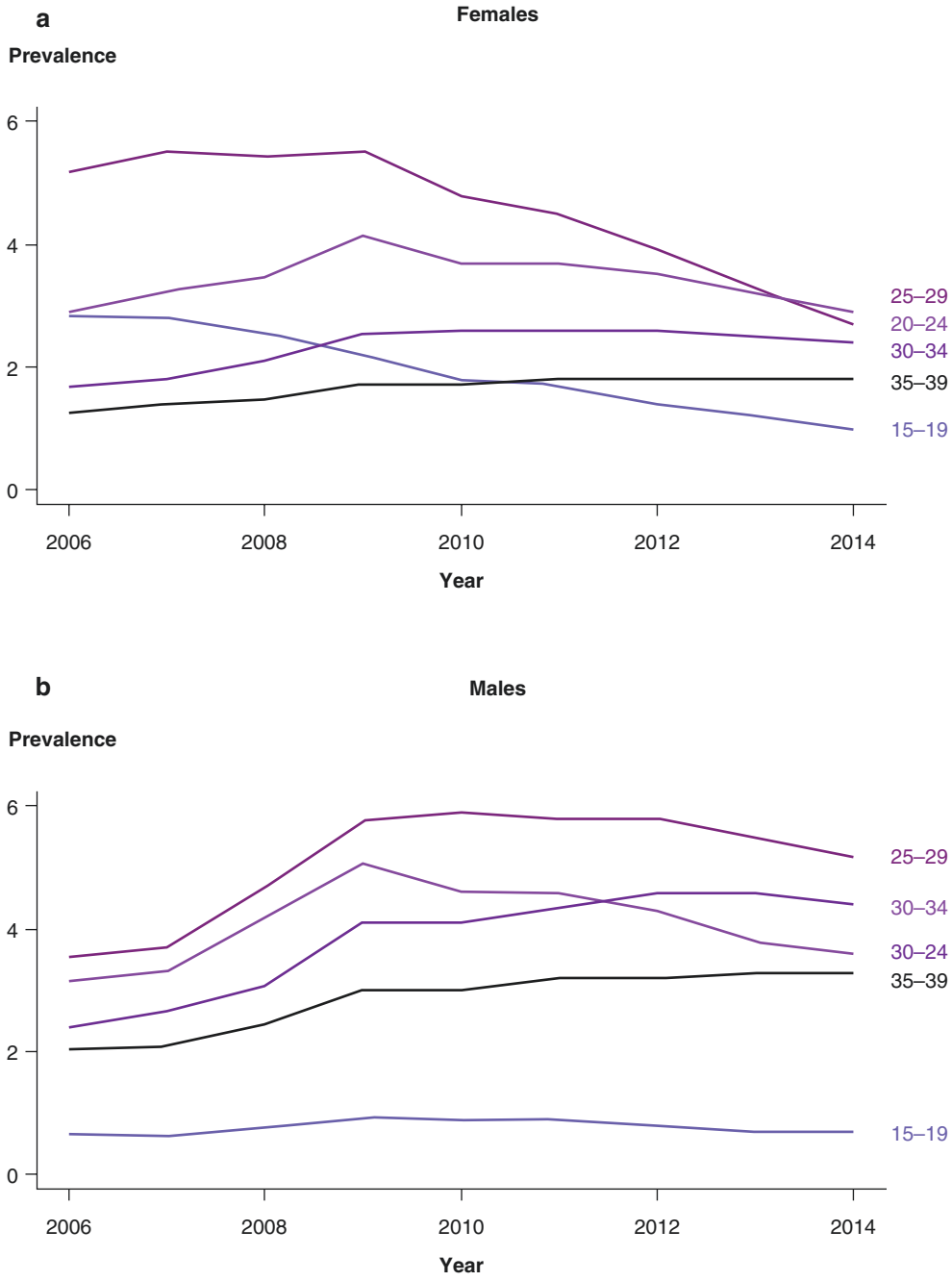

Fig. 19.2 Anogenital warts – Prevalence per 1000 person-years among enrollees in private health plans, age 15–39 by gender ((**a**) females, (**b**) males), age group, and year (2006–2014). (2018 STD Surveillance [21])

Screening and Surveillance

The majority of patients at risk for anal neoplasia undergo screening with digital rectal examination, anal cytology, and anoscopy. Anal cytology is an easily performed procedure in which an unlubricated, moistened Dacron swab is inserted into the anus about 3–4 cm, then removed slowly in a circular motion, and finally preserved most often in liquid medium used for cervical cytology. Although slide preparation with a fixative is also acceptable, liquid-based is the preferred method as it avoids obscuring factors including fecal material, bacteria, and air-drying artifact; plus, residual tissue may be used for ancillary studies. Bowel preparation before the examination and swabbing is unnecessary, and cytology must be performed before any instrumentation of the anus and before lubrication is used. Following completion, a digital rectal examination and anoscopy can be performed.

Anal cytology is graded with the same classification used in gynecologic samples. This may return as insufficient, normal, atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, or anal cancer.

Based on these results, physical examination, and medical history, recommendations may include continued surveillance or more detailed evaluation with high-resolution anoscopy (HRA). Cytology results of ASCUS or higher are typically referred for HRA. Although anal cytology results continue to be difficult to interpret given its sensitivity (69–93%) and specificity (32–59%), this may lead to a considerably large population requiring further evaluation with HRA [23–25]. Also, false-negative rates may differ according to specific risk factors such as MSM (23% in HIV– versus 45% in HIV+) [26]. Recent data from Morency and colleagues [27] including a total of 1185 patients undergoing anal cytology, of which 376 (26.5%) had follow-up biopsy, showed that unsatisfactory cases with squamous intraepithelial lesion (SIL) on biopsy showed LSIL in 19%, ASCUS had an 84% rate of biopsy-proven disease, and sensitivity was higher (92%) for high-grade anal intraepithelial neoplasia or worse (AIN2+). Another retrospective study including a total of 327 anal cytology results demonstrated dysplasia (75% low grade and 25% high grade) in 182 patients. Seventy-five percent of dysplastic anal cytology were followed by clinical examination within 1 year, and 50% were biopsied [28]. The probability of dysplasia on histology after dysplasia on cytology was 72%, and 28% of low-grade cytology results were upgraded to advanced disease (high-grade or invasive cancer) on histology. Although results are not yet available, the Anal Cancer HSIL Outcomes Research (ANCHOR) trial aims to determine whether treating precancerous anal high-grade squamous intraepithelial lesions (HSIL), versus active surveillance, is effective in reducing anal cancer incidence in HIV-infected individuals. At this time, any abnormal cytology indicates the possibility of a high-grade lesion. Likewise, cytology may not correlate with histology. Patients with high-grade cytology, but negative anoscopy and/or pathology, should be followed closely (Fig. 19.3).

The risk of anal neoplasia is highest in immunosuppressed individuals as they appear to have difficulty clearing HPV from their body. Rates of anal dysplasia in all HIV+ patients are substantial regardless of sexual practices, indicating a value for anal cancer screening, although the highest risk has been reported in HIV+ MSM [29–31]. This group should

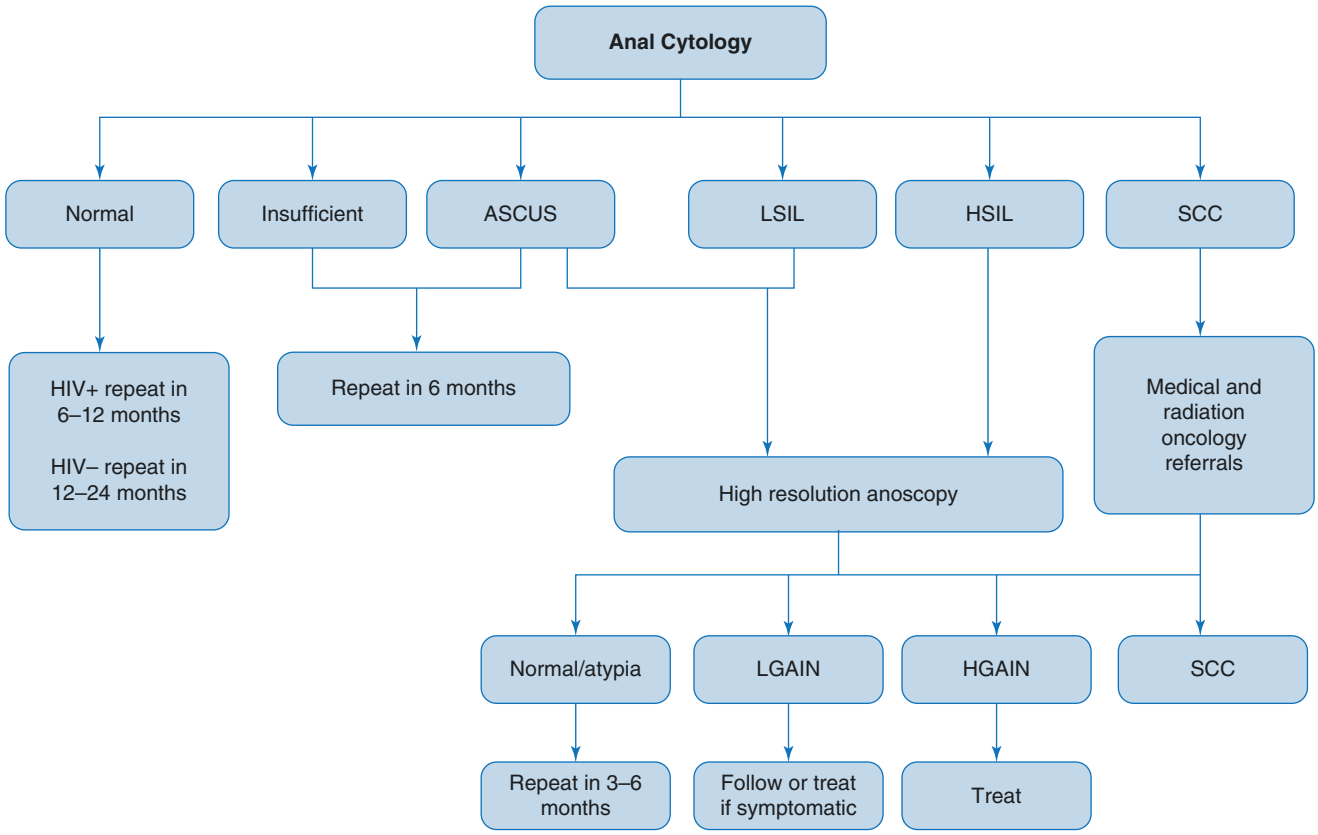

Fig. 19.3 Anal cytology algorithm. Management should be individualized based on many factors, which may increase or decrease the interval of evaluation. *ASCUS* atypical squamous cells of undetermined significance (cannot rule out high-grade squamous intraepithelial lesion); *HGAIN* high-grade anal intraepithelial neoplasia; *HIV* human immunodeficiency virus; *HRA* high-resolution anoscopy; *HSIL* high-grade squamous intraepithelial lesion; *LGAIN* low-grade anal intraepithelial neoplasia; *LSIL* low-grade squamous intraepithelial lesion; *SCC* squamous cell cancer/carcinoma

also include organ transplant patients; women with a past history of cervical, vulvar, or perineal dysplasia; and patients with medically induced immunosuppressive conditions [32–35]. Individuals with a past history of sexually transmitted infections may also represent an important screening population. Although a past history of condyloma is generally a sign of prior contact with HPV, it is unclear whether those individuals have a tendency to develop benign warts rather than cancer. In addition, it is difficult to prove any synergy between HPV and other sexually transmitted infections such as syphilis, gonococci, and herpes simplex that may speed up transformation to AIN [36].

The value of anal cancer screening is difficult to quantify. Screening HIV+ homosexual and bisexual men for anal dysplasia with anal cytology offers quality-adjusted life expectancy benefits at a cost comparable with other accepted clinical preventive interventions [37]. For patients with a history of high-grade dysplasia and immunosuppression, there seems to be a benefit for surveillance given the high rate of recurrence in this population [38]. HRA may be more cost-effective than other strategies; the cost per HSIL found has been estimated to be $809.39. A prospective screening study of 284 high-risk MSM evaluated all 3 modalities of HPV testing, cytology, and HRA [39]. Only 15% of the cohort tested negative for HPV, representing a methodologic weakness in this study. Cytology missed nearly one third of high-risk lesions, suggesting that HRA would have the most clinical use for screening. The effectiveness of HRA to prevent the progression of dysplasia or development of cancer has only been evaluated in retrospective cohort studies. In a retrospective review of 246 patients treated with HRA-targeted destruction of HSIL/LSIL over a 10-year period [40], recurrent HSIL was seen in 57% of patients at an average of 19 months. Despite treatment, only 1.2% progressed to invasive cancer.

Progression

Much of what is known regarding the transformation of AIN to squamous cell cancer has been extracted from the cervical cancer literature. A number of genetic changes are proposed to occur after viral integration leading to phenotypic changes of the squamous epithelium. Abnormalities to chromosomes 1, 3, 7, 8, 11, 15, and 20 have all been reported with varying frequency [41, 42]. One of the most frequently reported changes in chromosomal structure is a gain in the long arm of chromosome 3q [38], which is also reported to occur in the transition from low-grade to severe cervical dysplasia and cervical cancer [41]. Following incorporation of the viral genome into host DNA, cellular changes and atypia of squamous epithelium occur [43–45]. Ultimately these changes correspond to AIN I which then can progress to AIN II and III and ultimately dedifferentiate into squamous cell cancer. It is unclear whether the development of anal neoplasia must traverse all these steps or if a squamous cell cancer can skip one or more phases. Ultimately, the oncogenetic pathway is similar to the pathway described in cervical cancer.

Once the presence of AIN has been established, dysplasia of the anus rarely regresses [46]; however, data proving persistence of AIN are incomplete as many patients do not follow up for surveillance. It is also unclear why anal dysplasia is thought to be more persistent than equivalent degrees of cervical dysplasia given the common pathogenic pathway of these two conditions. In fact, it is estimated that approximately 60% of low-grade cervical lesions will spontaneously regress [47, 48]. Small reports with limited follow-up on the natural history of AIN have shown higher rates of progression to anal cancer, especially in immunosuppressed patients [11, 12]. The rate of progression from AIN to invasive cancer is still unclear at this time due to few studies and limited follow-up periods. Many retrospective studies have associated high-grade squamous intraepithelial lesions as a common precursor in men who have developed anal cancer [44, 49]. Scholefield et al. [11] followed 35 patients (74% women) with AIN III for a median duration of 63 months. All subjects were HIV negative; however, six were on long-term systemic immunosuppressants. Three patients (8.5%) progressed to invasive anal SCC (all of whom were on long-term systemic immunosuppressants). Watson et al. [12] followed 72 patients (72% women) with AIN I–III for a median of 60 months. The majority of patients (94%) had prior genital malignancy, 7% were HIV+, and 23% were on chronic immunosuppression. Fifteen percent of subjects had histologic progression of their disease (AIN II to AIN III, or AIN III to anal SCC), and 11% developed anal SCC.

Diagnosis

AIN is typically asymptomatic but may cause symptoms such as pruritus, bleeding, discharge, irritation, tenesmus, and pain. Direct examination of the anus and a detailed digital rectal exam are important components in the diagnosis of AIN. It is imperative that patients with AIN also have a thorough history and physical examination, with emphasis on other HPV-related diseases such as oral cancer, gynecologic dysplasia [50], and other genital lesions. Physical examination should include a head-to-toe evaluation for squamous cell lesions, considering all lymph node basins. Appropriate referrals to gynecology and urology should be considered on an individual basis.

The diagnosis of AIN is made from cytology or biopsy. The sensitivity of digital rectal exam and anoscopy is fairly low, although anoscopy may identify macroscopic areas of AIN, which often appear to be benign condylomata but may

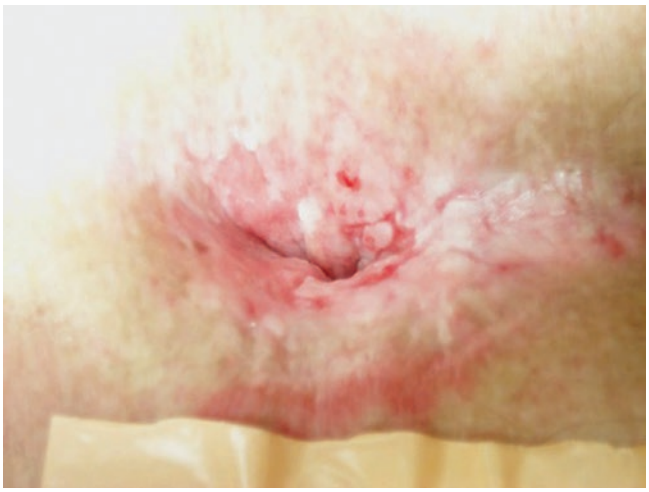

Fig. 19.4 AIN 3. (Courtesy of Richard Billingham, MD)

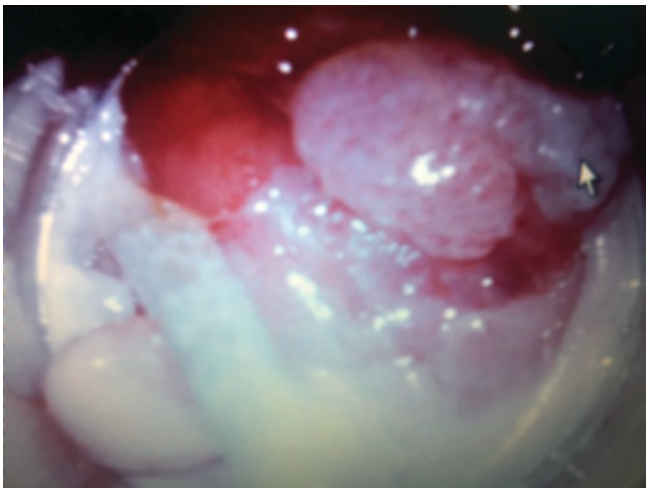

Fig. 19.5 AIN on high-resolution anoscopy. The arrow indicates an area of high-grade dysplasia. (Courtesy of Rocco Ricciardi, MD)

return with AIN on biopsy (Fig. 19.4). If screening is positive for HSIL or LSIL, then patients should be referred to a surgeon who has experience with these lesions, for a formal biopsy. The sensitivity and specificity of anal cytology for the detection of any-grade AIN vary significantly and have been reported to range from 47 to 90% [35, 40] and 32 to 60% [36, 37], respectively. Formal biopsy can be performed via conventional anoscopy or HRA and will typically provide sufficient tissue for microscopic evaluation to determine the presence of LSIL or HSIL. Tissue biopsy allows for a more definitive diagnosis compared to cytology alone.

HRA is an office-based tool, similar to colposcopy of gynecologic neoplasia, which can be utilized to diagnose and treat AIN [51]. HRA is typically performed in the left or right lateral positions, no bowel preparation is necessary, and is most commonly performed without analgesia. After the application of 3–5% acetic acid for 2–5 minutes, a magnifying anoscope is used to examine the anus and lower rectum. Acetic acid causes dysplastic cells to be more visible compared with surrounding tissue. Iodine-based Lugol's solution may also be added to further detect dysplastic tissue. The mechanism for Lugol's utility is that only healthy epithelium absorbs this compound which causes normal tissue to appear wood-like, and dysplastic tissue does not absorb the solution giving these tissues a yellowish hue. Our protocol is to avoid Lugol's solution as it interferes with proper dysplasia differentiation (i.e., AIN I versus AIN II or III), and we believe that acetowhitening from acetic acid is sufficient to identify dysplastic tissues. The entire anal canal and anal verge should be examined, emphasizing detailed visualization of the transition zone. Dysplastic epithelium will absorb acetic acid and appear as scaly white with greater disarray of vascular patterns and tissue friability as the grade of dysplasia increases (Fig. 19.5). The microscopic appearance of variable grades of anal squamous intraepithelial lesions has also been described as similar to those described for the cervix [52].

The impact of HRA was recently evaluated in a cohort of 727 MSM who underwent ablation of all HRA-identified lesions and followed for a median of 2.2 years. With regular follow-up, the rate of recurrence at 1 year was 53% in HIV+ patients and 49% in HIV– patients. Over the follow-up period, five patients developed cancer, with the probability of cancer 1.9% at 3 years [53]. There are few comparisons of HRA with other treatment strategies. A retrospective review of 424 patients compared HRA with expectant management in 2 cohorts, 1 treated by 3 clinicians who followed patients with expectant management and the other treated by 2 clinicians who followed patients with HRA [54]. Anal cancer occurred in one of the HRA patients and two of the expectant management patients. The 5-year progression rate was similar in the two cohorts.

Treatment

Progression of AIN to squamous cell cancer is relatively rare; however, diagnosis and differentiation of AIN and determination of which patients benefit from treatment and with what modality require expertise. It is therefore recommended that patients found to have positive anal cytology or biopsy-proven AIN should be referred to expert centers. Even among those specializing in the identification and treatment of AIN, there is a significant variability in guidelines for management and surveillance paradigms which can lead to confusion and controversy. Currently, the spectrum of management includes observation, topical therapies, local ablations, and surgical excision (Table 19.1). However, recommendations are mostly based on literature from single institution case controls series rather than large randomized trials. The goal of treating dysplastic lesions is to reduce the rate of progression to anal cancer while decreasing morbidity and preserving function.

Table 19.1 Common treatment options for AIN

Treatment	Advantages	Disadvantages	Cure	Recurrence
Observation	Low cost No side effects	Low cure rate Time-consuming	Poor	High
Imiquimod	Minimal pain Easy to use	Burning Moderate cost	Poor	High after stopping
5-FU	Easy to use	Burning Moderate cost	Poor	High after stopping
Infrared coagulation	Clinic-based	Special equipment	Good	Moderate in immunosuppressed
Ablation	Single use	Painful Costly	Good	Moderate in immunosuppressed
Wide local excision	Removes all tissue	Painful Operating room Cosmetic and functional issues	Good	Low

Expectant Management

Observation or an expectant management approach is a conservative strategy that is advocated by some for select patients with AIN [55]. In general, patients with low-grade dysplasia undergo observation alone with close clinical follow-up every 4–6 months. A more intense program including cytology, HRA, and targeted biopsies has demonstrated a clearance rate of 78% with a 1.2% rate of progression to invasive squamous cell cancer over a 10-year period [40]. A recent large retrospective review comparing HRA versus expectant management for AIN demonstrated no difference in progression to squamous cell cancer as long as patients were compliant with frequent follow-up [54]. The expectant management strategy is based on the relatively low rate of disease progression and malignant potential of AIN and the increased rates of adverse effects and morbidity of topical and ablative or surgical treatments [56].

Topical Therapies

Trichloroacetic Acid (TCA)

TCA is generally well tolerated by patients with no reported systemic side effects and can be efficacious after only a few applications with further treatment possible if necessary. It is typically applied by a provider and thus has the advantage over other topical agents of not requiring patient adherence. Two small retrospective studies with biopsy-confirmed AIN have examined the use of TCA. Cranston et al. [57] reviewed the course of 72 patients with HSIL 3–6 months after TCA treatment and noted resolution or downgrading to LSIL in 79% of lesions. Single TCA treatment improved or resolved 49% of lesions with 28% requiring two treatments. However, the recurrence rate was 21%. Singh and colleagues reported that 72% of lesions were either resolved or downgraded to LSIL in 54 men with HSIL [58]. Men who had fewer than three lesions had greater clearance. TCA offers a clinic-based treatment for HSIL with relatively few side effects but may not be appropriate for bulky or more extensive disease.

5-Flurorouracil (5FU)

Two retrospective studies evaluating the use of topical fluorouracil reported response rates of 55–57% [59, 60]. One study of 46 HIV-positive patients with LSIL or HSIL reported a complete response in 12 of the 34 (39%). However, recurrence rates of 50% were observed in the complete responders at 6 months [59]. Seventy-three to 85% of patients report experiencing adverse effects including anal pain, irritation, and hypopigmentation, but only one to two patients in each study discontinued treatment [59, 60].

Cidofovir

One prospective pilot study and one retrospective cohort study have assessed the effectiveness of 1% cidofovir applied three times per week for 4 weeks [61]. Sixteen HIV-positive patients with HSIL were included in the pilot study which demonstrated a complete response rate in 63% at 12 weeks. However, at 24 weeks, 20% of these patients had recurred. A single-arm clinical trial enrolled 33 HIV-positive patients with perianal HSIL to self-apply 1% cidofovir gel to lesions daily for a 2-week cycle consisting of 5 consecutive days on and 9 days without treatment [62]. This was repeated for six cycles with a 79% completion rate. Of the 24 patients that completed treatment, 51% had a response (15% complete and 36% partial). Two patients had progression of their disease over the course of the study. Cidofovir can only be prepared by compounding pharmacies and may not be covered by standard insurance limiting its potential use.

Imiquimod

Imiquimod is the most tested topical agent used in treating SIL and has been examined in two randomized trials and one prospective cohort study. A double-blinded randomized placebo-controlled trial of 64 HIV-positive MSM compared self-application of 5% imiquimod cream versus placebo in the anal canal three times per week for 4 months. Response

rates assessed by cytology, HRA, and biopsy in the 53 patients that completed the study demonstrated superior response with imiquimod (43% vs. 4%), and 61% of imiquimod responders exhibited sustained response at 36 months [63]. A prospective study by van der Snoek et al. [64] aimed to establish the effectiveness of imiquimod found that of 44 patients with histologically proven perianal or intra-anal HSIL treated with 5 consecutive days per week of self-administered 5% imiquimod, complete or partial response was noted in 45% of patients after 16 weeks of treatment. Patients who did not demonstrate a response underwent an additional 16 weeks of treatment resulting in a total response rate of 66%.

Topical therapies are relatively efficacious for patients with LSIL and HSIL and have few severe side effects. The most common is a localized skin reaction at the application site, with erythema, itching, and burning being reported most often. Generally, imiquimod is well accepted, with few patients choosing to discontinue therapy or withdrawal from clinical trials due to intolerable side effects. Patients who find the side effects bothersome typically respond well to topical analgesics, warm baths, and/or dose modification. A substantial number of patients who respond have recurrence once treatment is discontinued, and consideration should be given to using them in patients that cannot undergo ablative therapy or in conjunction with ablative therapy.

Local Ablative Therapies

Local ablative therapy consists of targeted destruction of dysplastic lesions using fulguration with electrocautery, excision, or infrared coagulation (IRC) in conjunction with HRA or anoscopy and is effective in achieving high rates of complete response particularly in immunocompetent patients. Procedures are often performed in the operating room but are increasingly becoming clinic-based using local anesthesia. Ablation is typically targeted to areas with evidence of dysplasia with no need for margins, and as the disease is limited to the epidermis, destruction of deeper dermal tissues is unnecessary.

Rates of response with electrocautery may initially be as high as 75–80%, but recurrence is common. An observational study by Burgos and colleagues of 83 HIV-positive MSM with HSIL demonstrated a 33% complete response and 34% partial response after treatment with electrocautery with increased success seen in patients who underwent multiple sessions. However, consistent with other studies, recurrence was observed in 25% of patients after a median follow-up of 30 months [65].

Short-term efficacy of infrared coagulation was demonstrated in a retrospective clinical study of 74 HIV-positive MSM with HSIL in which 64% of patients were found to have a complete or partial response. Long-term results were assessed in a recent retrospective analysis of 96 MSM with HSIL treated with IRC which demonstrated resolution in 82% of HIV-positive and 90% of HIV-negative [66]. However, after 1 year from first treatment, recurrence (mainly metachronous) was observed in 38% and 61% of HIV-negative and HIV-positive MSM, respectively. An advantage of IRC is that is it associated with less pain and can often be performed in a clinic setting.

In general, local ablative therapies are associated with minimal morbidity and are reasonably well tolerated. Often, multiple sessions are required and recurrence remains common. Care should be taken to avoid large field defects, scarring, or stricture formation, with the goal of preserving healthy tissues as patients will often need further surveillance and intervention.

Wide Local Excision

Historically, mapping biopsies with wide local excision was the mainstay of treatment for AIN. This often resulted in the removal of large amounts of healthy and uninvolved tissue along with the dysplastic lesions. In addition, 9–63% of patients would develop recurrences, with repeated procedures resulting in long-term complications including anal stenosis and fecal incontinence particularly in patient with circumferential lesions or those with significant disease burden [67, 68]. With alternative techniques now available, mapping with wide local excision is not recommended even for cases of diffuse disease.

Treatment Summary

Few studies have compared different treatment modalities. In one study, 148 HIV-positive MSM with SIL (57% with HSIL) were randomized to 4 months of treatment with 2% 5FU, 5% imiquimod, or monthly electrocautery [69]. Complete response as assessed by post-treatment biopsies was 17%, 24%, and 39%, and partial/complete response in the HSIL group was 43%, 46%, and 68%, respectively. Side effects were reported in 27%, 43%, and 18%, and at 72 weeks post-treatment, recurrence rates were 58%, 71%, and 68%, respectively.

Due to the lack of high-quality randomized control trials comparing various treatment strategies, it is difficult to develop guidelines for the care of AIN. We recommend basing treatment decisions on patient goals, history of immunosuppression and dysplasia, comorbidities, and underlying bowel function (Fig. 19.6). For patients with LSIL who will be compliant with surveillance, expectant management with or without the addition of HRA may be the best management

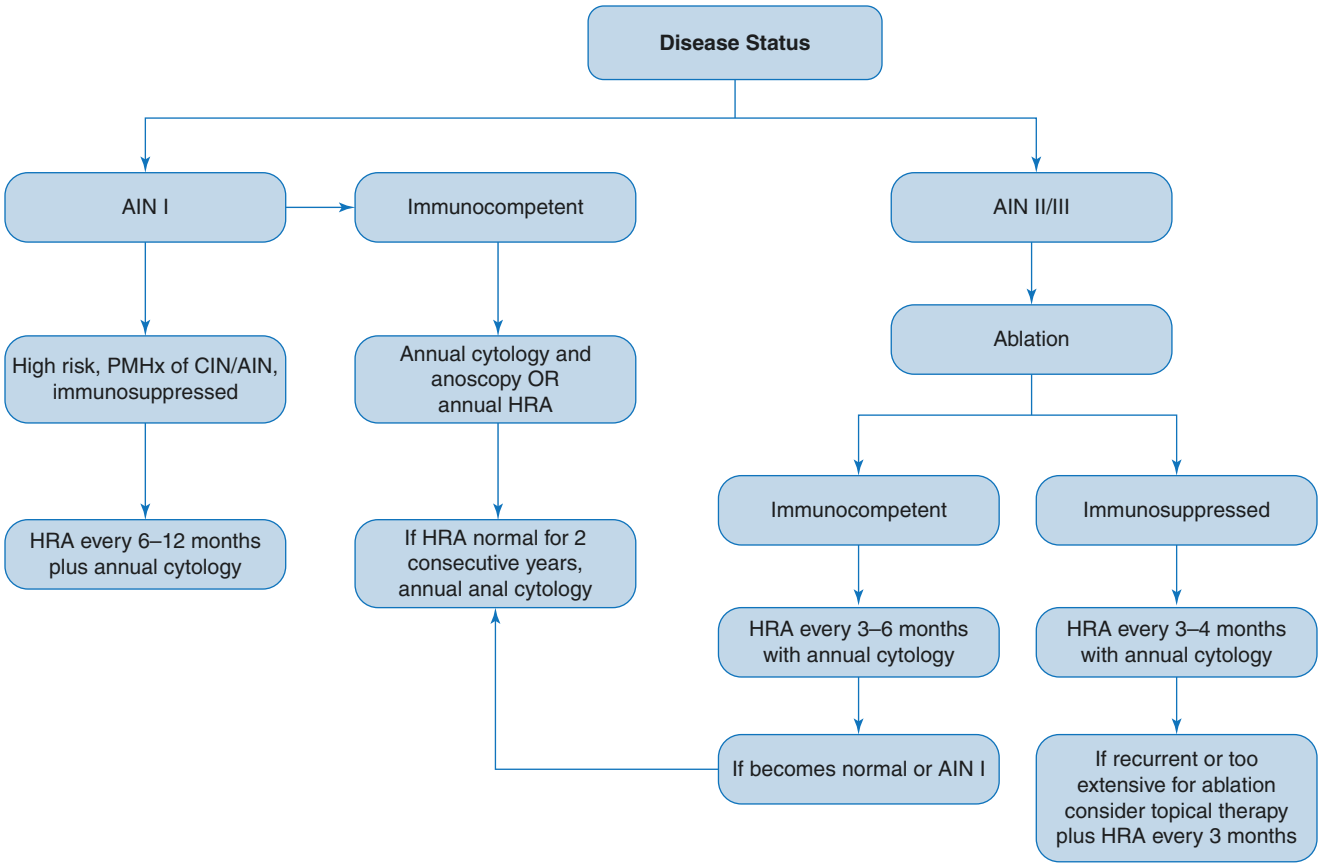

Fig. 19.6 Algorithm for the treatment of AIN based on immune status and biopsy results

strategy. For immunocompetent patients with HSIL, targeted surgical ablation guided by HRA is the most effective at eradicating dysplasia and generally well tolerated. Defining which treatment modality to employ in immunocompromised patients with SIL is more difficult. This population presumably has a higher likelihood of progressing from LSIL to HSIL and squamous cell cancer which would favor more aggressive interventions. However, they also have increased rates of recurrence which would necessitate repeated treatments, potentially resulting in increased scarring and stenosis. In this patient population, the best approach is likely a combination of close observation and topical therapy versus ablative treatments depending on the extent and severity of disease.

Surveillance/Prevention

The recurrence rate of AIN is high after all treatment modalities, and thus surveillance is necessary. However, there are no definitive data or guidelines on what is the appropriate surveillance strategy. In a large retrospective review, patients with biopsy-proven AIN were enrolled in a surveillance program after ablative or topical therapy. All patients were followed with annual digital rectal exams and anal cytology. Of the 424 enrolled patients, 220 underwent regular HRA examinations, while the remaining 204 underwent HRA if DRE or cytology was positive. No significant differences were seen between the groups in the 5-year anal cancer rate. In both groups, those that progressed to squamous cell anal cancer were less compliant with surveillance. Therefore, the authors concluded that the key to reducing progression and recurrence of disease was patient compliance rather than a particular surveillance program [54]. Further studies need to be conducted to help determine best practices for the treatment and follow-up of patients with AIN.

In recent years, there has been increased data suggesting that HPV vaccines may be associated with a decrease in the incidence of AIN. In a large randomized, placebo-controlled, double-blinded clinical trial of over 4000 boys and men, Giuliano et al. demonstrated the efficacy of the HPV quadrivalent vaccine in preventing external genital lesions in patients who had no prior evidence of HPV infection [70]. In a subset analysis of 602 MSM, the efficacy of preventing AIN, including grades 2 and 3, associated with HPV 6, 11, 16, or 18 was 50.3% in the intention-to-treat population and 77.5% in the per-protocol efficacy population [71]. The efficacy in preventing AIN associated with HPV of any type was

25.7% and 54.9% in the intention-to-treat and per-protocol efficacy populations, respectively. A trial aimed at determining the efficacy of the quadrivalent HPV vaccine in prevention of AIN in HIV+ MSM, Vaccine Therapy in Preventing Human Papillomavirus Infection in Young HIV-Positive Male Patients Who Have Sex with Males, is completed, but the results are pending [72]. It is postulated that administration of the HPV vaccine to girls and boys prior to the onset of sexual activity may reduce the incidence of AIN, prevent the recurrence of AIN 2 and 3, and halt progression to squamous cell carcinoma of the anus, but more robust data is needed.

Conclusion

Anal intraepithelial neoplasia is a precursor to squamous cell cancer of the anus. The actual rate of progression from AIN to SCC of the anus is unknown, but detection and treatment of dysplastic lesions likely decrease the risk of progression. Risk factors in the development and progression of AIN include infection with HPV (particularly high-risk strains), HIV positivity, men who have sex with men, and transplant patients. Treatment modalities include expectant management, application of topical agents, local ablation, and surgical excision and need to be individualized based on a number of patient and disease factors. Regardless of treatment approach, recurrence is common, and therefore ongoing surveillance is recommended for all patients with a history of AIN, and patient compliance is critical. In the future we hope to improve prevention and detection of early lesions and develop consensus guidelines regarding nomenclature, treatment, and surveillance.

References

1. Stanley MA, Winder DM, Sterling JC, Goon PK. HPV infection, anal intra-epithelial neoplasia (AIN) and anal cancer: current issues. BMC Cancer. 2012;12:398.
2. Brickman C, Palefsky JM. Human papillomavirus in the HIV-infected host: epidemiology and pathogenesis in the antiretroviral era. Curr HIV/AIDS Rep. 2015;12(1):6–15.
3. Darragh TM, Colgan TJ, Thomas Cox J, Members of the LAST Project Work Groups, et al. The lower anogenital squamous terminology standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Int J Gynecol Pathol. 2013;32:76–115.
4. Roberts JR, Siekas LL, Kaz AM. Anal intraepithelial neoplasia: a review of diagnosis and management. World J Gastrointest Oncol. 2017;9:50–61.
5. Tong WW, Jin F, McHugh LC, et al. Progression to and spontaneous regression of high-grade anal squamous intraepithelial lesions in HIV-infected and uninfected men. AIDS. 2013;27:2233–43.
6. Johnson LG, Madeleine MM, Newcomer LM, Schwartz SM, Daling JR. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973–2000. Cancer. 2004;101:281–8.
7. Nielsen A, Munk C, Kjaer SK. Trends in incidence of anal cancer and high-grade anal intraepithelial neoplasia in Denmark, 1978–2008. Int J Cancer. 2012;130:1168–73.
8. SEER Stat Fact Sheet-Anal Cancer. http://seer.cancer.gov/statfacts/html/anus.html. Accessed on 5 Mar 2020.
9. Santoso JT, Long M, Crigger M, et al. Anal intraepithelial neoplasia in women with genital intraepithelial neoplasia. Obstet Gynecol. 2010;116:578–82.
10. Tatti S, Suzuki V, Fielder L, et al. Anal intraepithelial lesions in women with human papillomavirus-related diseases. J Low Genit Tract Dis. 2012;16:454–9.
11. Scholefield JH, Castle MT, Watson NF. Malignant transformation of high-grade anal intraepithelial neoplasia. Br J Surg. 2005;92:1133–6.
12. Watson AJ, Smith BB, Whitehead MR, Sykes PH, Frizelle FA. Malignant progression of anal intra-epithelial neoplasia. ANZ J Surg. 2006;76:715–7.
13. Machalek DA, Poynten M, Jin F, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. Lancet Oncol. 2012;13:487–500.
14. Centers for Disease Control and Prevention. Genital HPV infection-fact sheet. 2014. Available at: http://www.cdc.gov/std/hpv/stdfact-hpv.htm. Accessed 4 Mar 2020.
15. Dunne EF, Markowitz LE, Saraiya M, et al. CDC grand rounds: reducing the burden of HPV-associated cancer and disease. MMWR Morb Mortal Wkly Rep. 2014;63:69–72.
16. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. N Engl J Med. 1998;338(7):423–8.
17. American Cancer Society. Anal cancer. 2014. Available at: http://www.cancer.org/acs/groups/cid/documents/webcontent/003083-pdf.pdf. Accessed 5 Mar 2020.
18. Poggio JL. Premalignant lesions of the anal canal and squamous cell carcinoma of the anal canal. Clin Colon Rectal Surg. 2011;24:177–92.
19. Garland SM, Steben M, Sings HL, James M, Lu S, Railkar R, Barr E, Haupt RM, Joura EA. Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine. J Infect Dis. 2009;199(6):805–14.
20. Markowitz LE, Hariri S, Lin C, Dunne EF, Steinau M, McQuillan G, Unger ER. Reduction in human papillomavirus (HPV) prevalence among young women following HPV vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003–2010. J Infect Dis. 2013;208(3):385–93.
21. 2018 STD Surveillance – Figure 52. IMS Health, Integrated Promotional Services™. IMS Health Report, 1966–2018. https://www.cdc.gov/std/stats18/figures/52.htm. Accessed 10 Mar 2020.
22. Oliver SE, Unger ER, Lewis R, McDaniel D, Gargano JW, Steinau M, Markowitz LE. Prevalence of human papillomavirus among females after vaccine introduction-National health and nutrition examination survey, United States, 2003–2014. J Infect Dis. 2017;216(5):594–603.
23. Arain S, Walts AE, Thomas P, Bose S. The anal pap smear: cytomorphology of squamous intraepithelial lesions. Cytojournal. 2005;2(1):4.
24. Palefsky JM, Holly EA, Hogeboom CJ, Berry JM, Jay N, Darragh TM. Anal cytology as a screening tool for anal squamous intraepithelial lesions. J Acquir Immune Defic Syndr Hum Retrovirol. 1997;14(5):415–22.
25. Fox PA, Seet JE, Stebbing J, Francis N, Barton SE, Strauss S, Allen-Mersh TG, Gazzard BG, Bower M. The value of anal cytology and human papillomavirus typing in the detection of anal intraepithelial

neoplasia: a review of cases from an anoscopy clinic. Sex Transm Infect. 2005;81(2):142–6.
26. Chin-Hong PV, Vittinghoff E, Cranston RD, Browne L, Buchbinder S, Colfax G, Da Costa M, Darragh T, Benet DJ, Judson F, Koblin B, Mayer KH, Palefsky JM. Age-related prevalence of anal cancer precursors in homosexual men: the EXPLORE study. J Natl Cancer Inst. 2005;97(12):896–905.
27. Morency EG, Harbert T, Fatima N, Samolcyzk J, Maniar KP, Nayar R. Anal cytology: institutional statistics, correlation with histology, and development of multidisciplinary screening program with review of the current literature. Arch Pathol Lab Med. 2019;143(1):23–9.
28. Geltzeiler CB, Son J, Carchman EH, Lawson EH, Harms BA, Striker R, Selvaggi S, Voils CI. Anal intraepithelial neoplasia screening with anal pap tests: follow-up and corresponding histology. J Surg Res. 2019;244:117–21.
29. Gaisa M, Sigel K, Hand J, Goldstone S. High rates of anal dysplasia in HIV-infected men who have sex with men, women, and heterosexual men. AIDS. 2014;28(2):215–22.
30. Gandra S, Azar A, Wessolossky M. Anal high-risk human papillomavirus infection and high-grade anal intraepithelial neoplasia detected in women and heterosexual men infected with human immunodeficiency virus. HIV AIDS (Auckl). 2015;7:29–34.
31. del Amo J, González C, Geskus RB, Torres M, Del Romero J, Viciana P, Masiá M, Blanco JR, Hernández-Novoa B, Ortiz M, CoRIS-HPV Study Group. What drives the number of high-risk human papillomavirus types in the anal canal in HIV-positive men who have sex with men? J Infect Dis. 2013;207(8):1235–41.
32. Palefsky JM, Rubin M. The epidemiology of anal human papillomavirus and related neoplasia. Obstet Gynecol Clin N Am. 2009;36(1):187–200.
33. Sillman FH, Sentovich S, Shaffer D. Ano-genital neoplasia in renal transplant patients. Ann Transplant. 1997;2(4):59–66.
34. Edgren G, Sparén P. Risk of anogenital cancer after diagnosis of cervical intraepithelial neoplasia: a prospective population-based study. Lancet Oncol. 2007;8(4):311–6.
35. Hemminki K, Dong C, Vaittinen P. Second primary cancer after in situ and invasive cervical cancer. Epidemiology. 2000;11(4):457–61.
36. Sobhani I, Walker F, Roudot-Thoraval F, Abramowitz L, Johanet H, Hénin D, Delchier JC, Soulé JC. Anal carcinoma: incidence and effect of cumulative infections. AIDS. 2004;18(11):1561–9.
37. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Welton ML, Palefsky JM. The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. JAMA. 1999;281(19):1822–9.
38. Ricciardi R, Burks E, Schoetz DJ, Verma Y, Kershnar E, Kilpatrick MW, Tsipouras P, Walat RJ. Is there a gain in chromosome 3q in the pathway to anal cancer? Dis Colon Rectum. 2014;57(10):1183–7.
39. Schofield AM, Sadler L, Nelson L, et al. A prospective study of anal cancer screening in HIV-positive and negative MSM. AIDS. 2016;30:1375–83.
40. Pineda CE, Berry JM, Jay N, Palefsky JM, Welton ML. High resolution anoscopy targeted surgical destruction of anal high grade squamous intraepithelial lesions: a ten-year experience. Dis Colon Rectum. 2008;51:829–35.
41. World Health Organization, International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. https://monographs.iarc.fr/monographs-available/. Accessed on 10 Mar 2020.
42. Gagne SE, Jensen R, Polvi A, Da Costa M, Ginzinger D, Efird JT, Holly EA, Darragh T, Palefsky JM. High-resolution analysis of genomic alterations and human papillomavirus integration in anal intraepithelial neoplasia. J Acquir Immune Defic Syndr. 2005;40(2):182–9.
43. Stewart DB, Gaertner WB, Glasgow SC, Herzig DO, Feingold D, Steele SR, Prepared on Behalf of the Clinical Practice Guidelines Committee of the American Society of Colon and Rectal Surgeons. The American Society of colon and rectal surgeons clinical practice guidelines for anal squamous cell cancers (Revised 2018). Dis Colon Rectum. 2018;61(7):755–74.
44. Berry JM, Jay N, Cranston RD, Darragh TM, Holly EA, Welton ML, Palefsky JM. Progression of anal high-grade squamous intraepithelial lesions to invasive anal cancer among HIV-infected men who have sex with men. Int J Cancer. 2014;134(5):1147–55.
45. Samdani T, Nash GM. Anal cancer. In: Steele SR, Hull TL, Read TE, et al., editors. The ASCRS textbook of colon and rectal surgery. New York: Springer; 2016. p. 357–71.
46. Palefsky JM, Holly EA, Ralston ML, Arthur SP, Jay N, Berry JM, DaCosta MM, Botts R, Darragh TM. Anal squamous intraepithelial lesions in HIV-positive and HIV-negative homosexual and bisexual men: prevalence and risk factors. J Acquir Immune Defic Syndr Hum Retrovirol. 1998;17(4):320–6.
47. Ostör AG. Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol. 1993;12(2):186–92.
48. Giudice A, Rizzo M, Rossi RT, Bonaffini O, Buda CA, Pettineo G. Diagnosis and survey of abnormal/atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesions: a retrospective study. Anticancer Res. 2000;20(2B):1195–9.
49. Tinmouth J, Peeva V, Amare H, Blitz S, Raboud J, Sano M, Steele L, Salit IE. Progression from perianal high-grade anal intraepithelial neoplasia to anal cancer in HIV-positive men who have sex with men. Dis Colon Rectum. 2016;59(9):836–42.
50. Saleem AM, Paulus JK, Shapter AP, Baxter NN, Roberts PL, Ricciardi R. Risk of anal cancer in a cohort with human papillomavirus-related gynecologic neoplasm. Obstet Gynecol. 2011;117(3):643–9.
51. Palefsky JM. Practising high-resolution anoscopy. Sex Health. 2012;9:580–6.
52. Jay N, Berry JM, Hogeboom CJ, Holly EA, Darragh TM, Palefsky JM. Colposcopic appearance of anal squamous intraepithelial lesions: relationship to histopathology. Dis Colon Rectum. 1997;40(8):919–28.
53. Goldstone SE, Johnstone AA, Moshier EL. Long-term outcome of ablation of anal high-grade squamous intraepithelial lesions: recurrence and incidence of cancer. Dis Colon Rectum. 2014;57:316–23.
54. Crawshaw BP, Russ AJ, Stein SL, et al. High-resolution anoscopy or expectant management for anal intraepithelial neoplasia for the prevention of anal cancer: is there really a difference? Dis Colon Rectum. 2015;58:53–9.
55. Devaraj B, Cosman BC. Expectant management of anal squamous dysplasia in patients with HIV. Dis Colon Rectum. 2006;49(1):36–40.
56. Cajas-Monson LC, Ramamoorthy SL, Cosman BC. Expectant management of high-grade anal dysplasia in people with HIV: long-term data. Dis Colon Rectum. 2018;61(12):1357–63.
57. Cranston RD, Baker JR, Liu Y, Wang L, Elishaev E, Ho KS. Topical application of trichloroacetic acid is efficacious for the treatment of internal anal high-grade squamous intraepithelial lesions in HIV-positive men. Sex Transm Dis. 2014;41(7):420–6.
58. Singh JC, Kuohung V, Palefsky JM. Efficacy of trichloroacetic acid in the treatment of anal intraepithelial neoplasia in HIV-positive and HIV-negative men who have sex with men. J Acquir Immune Defic Syndr. 2009;52(4):474–9.
59. Richel O, Wieland U, de Vries HJ, Brockmeyer NH, van Noesel C, Potthoff A, Prins JM, Kreuter A. Topical 5-fluorouracil treatment of anal intraepithelial neoplasia in human immunodeficiency virus-positive men. Br J Dermatol. 2010;163(6):1301–7.
60. Snyder SM, Siekas L, Aboulafia DM. Initial experience with topical fluorouracil for treatment of HIV-associated anal intraepithelial neoplasia. J Int Assoc Physicians AIDS Care (Chic). 2011;10(2):83–8.
61. Sendagorta E, Bernardino JI, Álvarez-Gallego M, Feíto M, Feltes R, Beato MJ, Pérez-Molina JA, Yllescas M, Díaz-Almirón M,

Arribas JR, González-García J, Herranz P, CIDAN127412 GESIDA Study Group. Topical cidofovir to treat high-grade anal intraepithelial neoplasia in HIV-infected patients: a pilot clinical trial. AIDS. 2016;30(1):75–82.
62. Stier EA, Goldstone SE, Einstein MH, Jay N, Berry JM, Wilkin T, Lee JY, Darragh TM, Da Costa M, Panther L, Aboulafia D, Palefsky JM. Safety and efficacy of topical cidofovir to treat high-grade perianal and vulvar intraepithelial neoplasia in HIV-positive men and women. AIDS. 2013;27(4):545–51.
63. Fox PA, Nathan M, Francis N, Singh N, Weir J, Dixon G, Barton SE, Bower M. A double-blind, randomized controlled trial of the use of imiquimod cream for the treatment of anal canal high-grade anal intraepithelial neoplasia in HIV-positive MSM on HAART, with long-term follow-up data including the use of open-label imiquimod. AIDS. 2010;24(15):2331–5.
64. van der Snoek EM, den Hollander JC, van der Ende ME. Imiquimod 5% cream for five consecutive days a week in an HIV-infected observational cohort up to 32 weeks in the treatment of high-grade squamous intraepithelial lesions. Sex Transm Infect. 2015;91(4):245–7.
65. Burgos J, Curran A, Landolfi S, Navarro J, Tallada N, Guelar A, Crespo M, Ocaña I, Ribera E, Falcó V. The effectiveness of electrocautery ablation for the treatment of high-grade anal intraepithelial neoplasia in HIV-infected men who have sex with men. HIV Med. 2016;17(7):524–31.
66. Goldstone RN, Goldstone AB, Russ J, Goldstone SE. Long-term follow-up of infrared coagulator ablation of anal high-grade dysplasia in men who have sex with men. Dis Colon Rectum. 2011;54(10):1284–92.
67. Long KC, Menon R, Bastawrous A, Billingham R. Screening, surveillance, and treatment of anal intraepithelial neoplasia. Clin Colon Rectal Surg. 2016;29(1):57–64.
68. Marchesa P, Fazio VW, Oliart S, Goldblum JR, Lavery IC. Perianal Bowen's disease: a clinicopathologic study of 47 patients. Dis Colon Rectum. 1997;40(11):1286–93.
69. Richel O, Hallensleben ND, Kreuter A, van Noesel CJ, Prins JM, de Vries HJ. High-resolution anoscopy: clinical features of anal intraepithelial neoplasia in HIV-positive men. Dis Colon Rectum. 2013;56(11):1237–42.
70. Giuliano A, Palefsky J, Goldstone S, Moreira E, Penny M, Aranda C, Vardas E, Moi H, Jessen H, Hilman R, Chang Y, Ferris D, Rouleau D, Bryan J, Marshall J, Vuocolo S, Barr E, Radley D, Haupt R, Guris D. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. NEJM. 2011;364(5):401–11.
71. Palefsky J, Giuliano A, Goldstone S, Moreira E, Penny M, Aranda C, Jessen H, Hilman R, Ferris D, Coutlee F, Stoler J, Marshall J, Radley D, Vuocolo S, Haupt R, Guris D, Garner E. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. NEJM. 2011;365(17):1576–85.
72. Vaccine therapy in preventing human papillomavirus in young HIV-positive male patients who have sex with males. In: ClinicalTrials.gov NCT01209325 [Internet].

Part III

Malignant Disease

Anal Cancer

20

Dana R. Sands and Najjia N. Mahmoud

Key Concepts

- Tumors of the anal region are divided into anal and perianal cancers with different paths of lymphatic drainage.
- Squamous cell carcinoma (SCC) is the most common type of anal cancer.
- Chemoradiotherapy is the mainstay for anal (SCCa). The standard chemotherapy consists of 5-FU and mitomycin. The minimum dose of radiation is 45 Gy to the primary tumor.
- Inguinal node metastasis can be diagnosed with PET-CT and managed with radiation.
- Surgery for anal canal cancer is limited to very small lesions and salvage situations following failed chemoradiotherapy.
- Anal adenocarcinoma can arise from an anal gland or chronic fistula tract. They can be difficult to distinguish from distal rectal cancers. These tumors are staged and treated similar to rectal cancers with a lower overall survival.
- Verrucous carcinomas are characterized by large size and lack of invasion. Treatment is mainly wide surgical excision.
- Anal melanoma is a rare and aggressive tumor. Survival is very poor. Abdominoperineal resection may help to control local disease but does not prolong life expectancy; therefore, local excision is often a first choice when possible.
- Perianal Paget's disease – or intraepithelial adenocarcinoma – is frequently associated with other malignancies. Treatment is focused on surgical excision and may require mapping biopsies to plan resection.
- Basal cell carcinoma of the perianal region is treated with wide local excision.
- Gastrointestinal stromal tumors can be managed with wide local excision or radical excision depending on margin status. Preoperative treatment with tyrosine kinase inhibitors may enhance resectability.

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Introduction and Epidemiology

Although anal cancers encompass a variety of histologic types, the overwhelming majority of these tumors are of squamous cell origin. Adenocarcinoma, gastrointestinal stromal tumors (GISTs), melanomas, and neuroendocrine tumors can be found in the anal canal as well, and this chapter will touch on those rare tumors, but emphasis will be on the diagnosis, staging, and treatment of anal canal and perianal squamous cell carcinoma.

In contrast to many cancers that have seen a decrease in incidence related to better detection, treatment, and in some cases prevention, the incidence of SCCa continues to rise worldwide [1]. The increased prevalence of human papillomavirus (HPV) infection is thought to be the major driver of this trend. From 2001 to 2015, the incidence of SCCa rose 2.7% per year [2]. The number of those found to have distant disease at the time of diagnosis has tripled in this time period [2]. The rise has not affected all races equally – the rate in young black men has risen fivefold while doubling in whites of both genders [2]. Overall, anal cancer mortality rates have increased 3.1% per year particularly in those greater than 50 years of age [2]. It is estimated that there will be 8590 new cases of anal cancer in 2020 in the United States with a preponderance of women diagnosed (5900 female/2690 male). Deaths from anal cancer will total 1350 (810 female) [3].

Effective treatment of cancer of the anus requires a thorough understanding of the anatomy of the anus and anal canal and of the various histologic types of tumors that can

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Table 20.1 World Health Organization (WHO) histological classification of malignant tumors of the anal canal

Carcinoma
Squamous cell carcinoma
Adenocarcinoma
Rectal type
Of anal glands
Within anorectal fistula
Mucinous adenocarcinoma
Small cell carcinoma
Undifferentiated carcinoma
Others
Carcinoid tumor
Malignant melanoma
Nonepithelial tumors
Secondary tumors

Adapted from World Health Organization (WHO)

Table 20.2 Risk factors commonly associated with anal malignancy

HIV infection
Immunosuppression after transplantation
Immunosuppression with chronic glucocorticoid therapy
HPV infection
Cigarette smoking
Multiple sexual partners
Anoreceptive intercourse
History of previous or current intraepithelial neoplasia of the cervix and vulva or anus

HPV human papillomavirus, *HIV* human immunodeficiency viruses

afflict this area. The most common type of cancer arising from the anus is squamous cell carcinoma, accounting for approximately 85% of cases [4, 5]. Evolution of the treatment of squamous cancer of the anal canal has shifted away from radical surgery toward a nonsurgical multidisciplinary team approach. The cooperation of the members of the team – surgeon, radiologist, medical oncologist, radiation oncologist, and pathologist – has resulted in improved quality of life and survival for patients with squamous cell carcinoma.

While squamous cell cancer is certainly the most common, there are a number of less common tumors that are often associated with abysmal survival rates, as mentioned previously. Table 20.1 summarizes the current World Health Organization histologic classification for tumors of the anus [6]. The widely recognized risk factors for anal carcinoma are summarized in Table 20.2.

Evaluation and Staging

The initial evaluation and staging of patients with anal cancer begins with a history and physical examination. Patients with anal cancer are often diagnosed at an advanced stage because of confusion of symptoms with those of common benign conditions. Pain, bleeding, small masses, and irritation are often misattributed by both patients and physicians alike to hemorrhoids or fissures. Duration of symptoms may be different from benign disease, with those suffering from neoplasia noting a relatively recent onset in pain and bleeding that worsens with time, often with an associated palpable mass and duration of symptom onset of months rather than years.

Table 20.3 Relevant historical information in the evaluation of patients with anal cancer

Bleeding
Pain
Presence of mass
Skin irritation
Obstructive symptoms
Weight loss
Continence
Duration of symptoms
History of STD/HPV
Anoreceptive intercourse
History of dermatologic conditions
History of other malignancies
Prior colonoscopy

STD sexually transmitted disease, *HPV* human papillomavirus

Social history, including sexual practices and HIV status, is relevant for patients with suspected squamous cell carcinoma. Of particular importance is a history of gynecologic malignancies, abnormal pap smears, or head and neck squamous cell carcinoma, given the common etiology (HPV). Diagnosis of anal dysplasia, the precursor lesion to anal squamous cell carcinoma, or anal squamous cell carcinoma should prompt evaluation for cervical dysplasia in women who lack current testing (within 1 year). Please see Table 20.3 for a list of pertinent historical information [7]. There is no association between squamous cell cancer of the anus and colonic malignancies; thus colonoscopy is not indicated, unless otherwise warranted for colorectal cancer/polyp screening or investigation of other symptoms. However, patients with Paget's disease of the anus should undergo colonoscopy to rule out associated adenocarcinoma.

Physical Examination

A complete physical examination is mandatory, with attention paid to the inguinal region as well as the anus and perineum. The anal examination should carefully characterize the mass. The size and location in the anal canal or perineum, with attention to both laterality and distance from the anal verge, sphincter muscles, and adjacent structures (vagina, prostate), are critical. The mobility of the mass and presence of ulceration should be noted. Abdominal palpation and the assessment for inguinal adenopathy are important. Evaluation of the rest of the anogenital region for any synchronous HPV-related lesions completes the physical

evaluation. HIV testing for newly diagnosed SCCa may help with management of the chemotherapy or radiation regimens and helps evaluate for other health-related issues that may be present. Histologic confirmation of the diagnosis is necessary prior to initiation of treatment, but large excisional biopsies should usually be avoided so as not to delay treatment due to the resultant large wounds. Tissue sampling in the office or operating room should suffice in most cases.

Radiologic Evaluation

Systemic staging is completed with computed tomography (CT) scan of the chest, abdomen, and pelvis. Positron emission tomography (PET) scan can be an important component of the staging and management of patients with anal cancer and should be utilized for evaluation of any suspicious lesions on conventional CT scans. Initial staging PET scan has been shown to alter the field of radiation when compared to standard CT scan [8]. Although it is not recommended routinely, it can result in both up- and downstaging in a small percentage of patients (between 5% and 38%) [9, 10]. Some studies suggest that although it can change locoregional nodal staging in up to 40% of patients, it does not typically change treatment planning and it does not replace the need for a contrast-enhanced CT of the chest, abdomen, and pelvis. Negative post-treatment PET/CT is associated with a very good 2-year disease-free survival (DFS) [11]. Pelvic magnetic resonance imaging (MRI) may be helpful for staging and treatment planning of locally advanced disease.

Table 20.4 Anal cancer TNM staging (AJCC manual 8th edition)

Primary tumor (*T*)			
T category	*T criteria*		
TX	Primary tumor not assessed		
T0	No evidence of primary tumor		
Tis	High-grade squamous intraepithelial lesion (previously deemed carcinoma in situ, Bowen disease, and intraepithelial neoplasia II–III, high-grade anal intraepithelial neoplasia)		
T1	Tumor ≤2 cm		
T2	Tumor >2 cm but ≤5 cm		
T3	Tumor >5 cm		
T4	Tumor of any size invading adjacent organ(s), such as the vagina, urethra, or bladder		
Regional lymph nodes (*N*)			
N category	*N criteria*		
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes		
N1a	Metastasis in inguinal, mesorectal, or internal iliac lymph nodes		
N1b	Metastasis in external iliac lymph nodes		
N1c	Metastasis in external iliac with any N1a nodes		
Distant metastasis (M)			
M category	*M criteria*		
M0	No distant metastasis		
M1	Distant metastasis		
Prognostic stage groups			
When T is	*When N is*	*When M is*	*Then the stage group is*
Tis	N0	M0	0
T1	N0	M0	1
T1	N1	M0	IIIA
T2	N0	M0	IIA
T2	N1	M0	IIIA
T3	N0	M0	IIB
T3	N1	M0	IIIC
T4	N0	M0	IIIB
T4	N1	M0	IIIC
Any T	Any N	M1	IV

TNM tumor, node, metastasis, *AJCC* American Joint Committee on Cancer, *UICC* Union for International Cancer Control

Unlike colorectal or anal adenocarcinoma, for which staging is staged based on the depth of invasion, SCCa is staged based on the size of the primary lesion and locoregional lymphadenopathy. The staging of anal squamous and adenocarcinoma is summarized in Table 20.4 according to the eighth edition *AJCC Cancer Staging Manual* [12].

Anal Anatomy

A thorough understanding of the anatomy of the anal canal is necessary to properly categorize anal cancers (Fig. 20.1a, b). The length of the anal canal is somewhat variable but in many adults is between 3 and 4 cm in length. Clinically, the proximal extent of the anal canal is at the apex of the puborectalis sling, which is palpable as the anorectal ring. The distal extent is the mucocutaneous junction with the perianal skin. This includes 1–2 cm of glandular mucosa and the transitional mucosa near the dentate line. The dentate line appears as mucosal undulations formed by the anal glands and the vertical columns of Morgagni. The transition to non-keratinized squamous mucosa occurs at this level. The varied cellularity of this region, also called the "anal transition zone," accounts for the histologically diverse nature of anal cancers. The pathology of anal cancer is of squamous cell origin and has been called "basaloid" in the past to describe the microscopic appearance of the cells. Transformed, carcinogenic squamous cells are thought to originate in the anal transition zone (ATZ) in the anal canal. The more distal the anal canal tumor is, the more likely it is to lack glandular elements and have keratinizing features and appear more like perianal tumors [13].

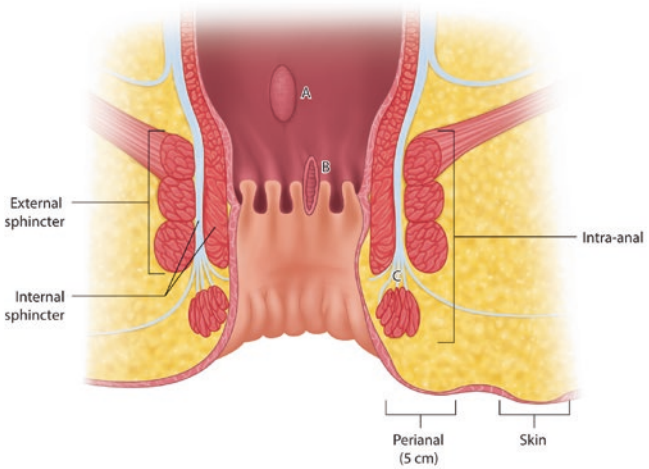

Fig. 20.1 Anatomy of the anal canal with possible locations of anal squamous cell cancers

The dentate line provides a reference point to predict lymphatic drainage. Tumors situated proximal to the dentate line typically drain via the superior rectal channels to the inferior mesenteric nodes and laterally along the middle and inferior rectal vessels to the internal iliac nodes. Lesions distal to the dentate line will have a drainage pattern via the inguinal and femoral lymphatics. Tumors situated at the dentate line can follow any or both of the above patterns. The perianal skin, previously referred to as the anal margin, is characterized by the keratinized stratified squamous epithelium-lined hair-bearing skin beginning at the anal verge and extending 5 cm radially outward. Anal tumors can therefore be categorized as either anal canal or perianal in origin.

Anal canal cancers are tumors that develop from mucosa (either keratinized or non-keratinized) that cannot be visualized entirely while gentle traction is placed on the buttocks. Perianal cancers are tumors that arise within the skin at or distal to the squamous mucocutaneous junction and can typically be seen entirely with gentle traction on the buttocks and are within 5 cm of the anus.

Perianal Squamous Cell Carcinoma

The perianal region is defined as the keratinized squamous epithelium extending from the anal verge radially for a distance of 5 cm. This area was formerly classified as the anal margin. Tumors of the perianal region are five times less common than anal canal tumors and occur with a frequency of 1–1.5 per 100,000 persons [14]. They represent 15% of all tumors of the anal region [15]. It has been suggested that perianal tumors have a different histogenetic origin than their counterparts in the anal canal. As opposed to anal canal carcinomas, perianal carcinomas show expression of CK 5/6 and CK 13, whereas CK7, CK18, and CK19 were rarely expressed [16]. This may account for the different biologic behavior of the two lesions. Few series look exclusively at perianal tumors; thus, characterizing behavior is somewhat challenging. Overall, the prognosis of perianal SCCa is considered better than SCCa of the anal canal [17]. Tumors are typically slow growing and well differentiated, with a female predominance and a peak incidence in the seventh and eighth decade [18]. Metastasis is uncommon. Recurrences are typically locoregional. Small lesions, less than 2 cm, rarely have lymph node metastasis. Nearly one quarter of lesions 2–5 cm in size will have lymph node metastasis, and large tumors have been shown to have nodal spread in 67% of cases [19]. Symptoms of perianal tumors are often attributed to hemorrhoids, often leading to a delay in diagnosis. Jensen et al. noted that SCCa of the perianal

skin is misdiagnosed in nearly 1/3 of cases resulting in a delay in diagnosis of a median of 6 months [20]. Perianal SCCa resembles SCCa of the skin in other areas of the body with a distinct border, raised edge, and central ulceration (Fig. 20.2).

Primary treatment of stage I perianal squamous cell cancer consists of wide local excision with a 1 cm margin when technically feasible. Re-excision is recommended for margin positivity [21]. More advanced lesions are often not amenable to local excision without harm to the anal sphincter and require radiation- and/or chemotherapy-based treatment regimens. Radiotherapy or chemoradiotherapy can be considered as a primary treatment when a perianal tumor is large and/or threatens the anal sphincter muscle or as an adjunct to surgical treatment when there is a close or positive margin and re-excision would require partial anal sphincter resection [22]. Newlin et al. reported use of radiation with or without chemotherapy for a cohort of 19 patients with perianal carcinoma [23]. Local control was achieved in all patients. One patient developed distant disease. No patient required a colostomy. The authors recommended that patients with well or moderately well-differentiated small tumors undergo excision with clear margins and those with poorly differentiated lesions or larger tumors undergo radiotherapy with inguinal node treatment. Chemotherapy was added for T3 and T4 tumors or those patients with involved inguinal nodes. Treatment regimens for both radiotherapy and chemoradiotherapy for perianal tumors, when utilized, are similar to that given for anal canal SCCa.

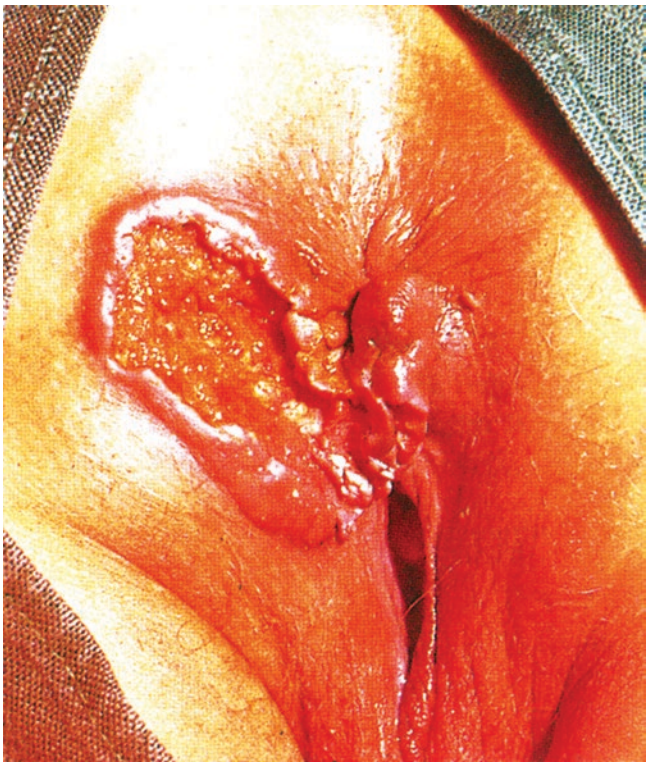

Fig. 20.2 Perianal squamous cell carcinoma. (With permission from Beck [125] © Copyright 2019)

Anal Canal Squamous Cell Carcinoma

While perianal tumors are typically treated like skin cancer and locally excised as described above, the treatment of anal canal SCCa is fundamentally different. These tumors are not completely visualized with traction of the buttocks and extend into the anal canal. Figure 20.3a, b illustrates the gross and histopathologic appearance of SCCa. Historically treated with wide local excision or abdominoperineal resection (APR), current treatment of SCCa takes advantage of the exquisite sensitivity of anal canal SCCa to the combination of radiation and chemotherapy. Local excision or radical resection of anal canal cancers is reserved for special circumstances, with chemoradiotherapy as the initial treatment in nearly all cases.

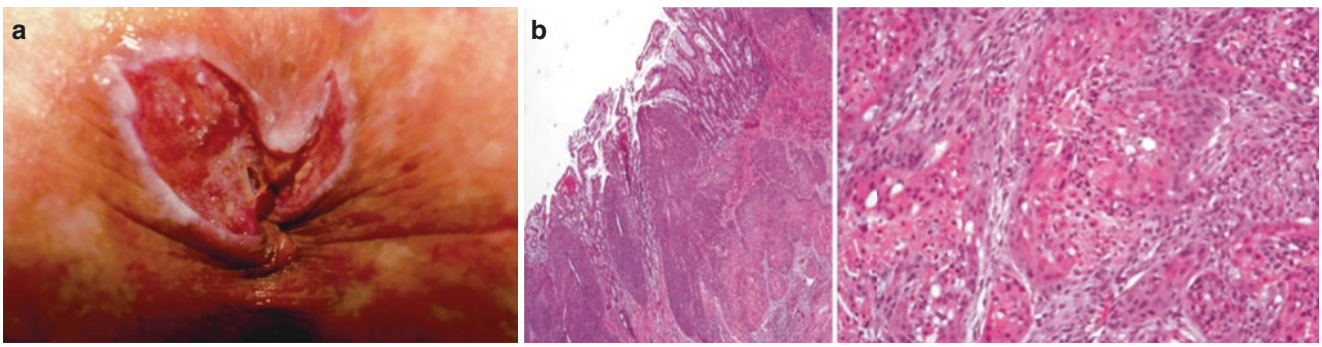

Fig. 20.3 (**a**) Anal canal squamous cell carcinoma. (**b**) Histology of anal squamous cell carcinoma 10× and 40×

Prior to 1974, most anal canal cancers were treated with either wide local excision or APR. Overall survival rates were poor, even after radical resection, ranging from 30% to 70% in most small series with local recurrence rates of 25–70% depending upon stage [24]. In the early 1970s, Norman Nigro, a colorectal surgeon at Wayne State University in Detroit and president of the American Board of Colon and Rectal Surgery, began using neoadjuvant chemoradiotherapy prior to APR and observed a complete histologic response (pCR) in a sizeable fraction of patients after neoadjuvant treatment with a modest dose (3000 Gy) of radiation and 5-fluorouracil (5-FU) and mitomycin C [25]. Based on these encouraging results, Nigro and colleagues then suggested that chemoradiotherapy may be considered as definitive treatment for SCCa. This observation was transformative and provided the foundation for the direction of treatment of SCCa for the next 35 years [26].

Chemotherapy

It has become clear that the addition of chemotherapy to radiotherapy treatment is necessary to maximize clinical and pathologic response. Studies from Europe (EORTC Phase III and the UKCCCR ACT I) comparing the use of 5-FU and mitomycin with radiation alone definitively showed that both locoregional control and overall survival were positively affected by the addition of a chemosensitizing regimen to the use of radiation [27, 28]. An 18% higher rate of local control at 5 years coupled with data showing an increase in median survival from 5.4 in the radiation alone to 7.6 years in those treated with chemoradiation is convincing [27, 28].

Studies aimed at refining the exact chemotherapeutic regimen that is most effective support the use of 5-FU or capecitabine combined with mitomycin C. Efforts to omit mitomycin resulted in a lower 4-year disease-free survival rate of 51% vs 73% for those with combination therapy [29]. Also, the need for salvage surgery increased from 9% to 22% [29]. Capecitabine has been used effectively in rectal adenocarcinoma treatment as an alternative to infusional 5-FU, and retrospective studies evaluating it as a substitute for infusional 5-FU in SCCa treatment support its use in combination with mitomycin C [30]. In multiple small retrospective reviews, efficacy is identical, and in one study, high-grade toxicity was significantly reduced [31–33]. Overall survival, colostomy-free survival, locoregional recurrence rates, and clinical complete response rates are the same, with 6-month locoregional control for stage I–IIII cancers at 86% [34]. In sum, capecitabine is an acceptable alternative to infusional 5-FU in treatment algorithms for stage I–III SCCa.

The role of cisplatin in the treatment of SCCa has been the subject of numerous investigations in an effort to refine and identify the most effective and least toxic regimen. The Phase III ACT I UK trial directly compared the use of cisplatin with mitomycin C [35]. Both trial arms used infusional 5-FU, and both used 50.4 Gy radiation. Additionally, this trial tested the hypothesis that giving more chemotherapy after chemoradiotherapy (5-FU with cisplatin for two cycles) would be beneficial. The trial concluded that there was no difference in any of the primary or secondary trial endpoints (disease-free survival, overall survival, locoregional recurrence, or colostomy-free survival) between the two groups. Furthermore, the addition of more chemotherapy as an adjunct treatment failed to improve long-term disease-specific metrics [35]. Similarly, the RTOG 98-11 trial compared mitomycin with cisplatin but added the two cycles of 5-FU and cisplatin prior to chemoradiation. In contrast to the ACT I study, the RTOG 98-11 trial found that the mitomycin arm had a superior 5-year DFS and OS with a 5-year colostomy-free survival that trended toward an advantage [36].

Retrospective studies and a recent meta-analysis have examined the use of chemotherapy without radiation in the neoadjuvant setting in the treatment of anal cancer, and there seems to be no clear advantage [37, 38]. However, patients with T4 lesions, in special circumstances, may benefit from induction chemotherapy [37]. Patients who have been treated with prior pelvic radiation and those who are minimally symptomatic or have widespread systemic disease may be candidates for this approach.

Other approaches to chemotherapy for SCCa have included the use of concurrent cisplatin and mitomycin as well as a regimen that includes the use of the epidermal growth factor receptor (EGFR) inhibitor cetuximab. Both strategies resulted in unacceptable toxicity that abbreviated the clinical trials that featured them [39–42].

Radiation Therapy

The most efficacious dose of radiation associated with least toxicity is desired when treating anal cancer. In general, increasing dosages of radiation correlate with increased local control and disease-free survival; however, increased dosage can be accompanied by symptoms that necessitate treatment breaks such as local tissue destruction, fatigue, nausea, and pain [43, 44]. Treatment breaks during radiation are associated with reduced locoregional control, so striking a balance between dosage, symptoms, and efficacy is of paramount importance [45]. The RTOG 98-11 trial set forth protocols that are considered optimal for both tumor control and symptom mitigation, and recommendations regarding doses follow the multifield technique used in this trial. All patients should receive a minimum radiation dose of 45 Gy to the primary tumor. The recommended initial dose is 30.6 Gy to the pelvis, anus, perineum, and inguinal nodes with patients

clinically staged as node-positive or T2–T4 receiving an additional boost of 9–14 Gy. Carefully planned intensity-modulated radiation therapy (IMRT) is preferred over 3D conformal radiation therapy in the treatment of anal carcinoma as outlined by NCCN guidelines [46].

Complications of radiation therapy are particularly difficult in those with anal canal cancer. The radiation fields affect the perineum, sphincter complex, and pelvic bones. Both acute and chronic problems may result from radiation and can be dose related. Acute radiation injury to the perineal skin, vagina, and urinary bladder can produce pain, bleeding, and urinary frequency. Chronic injury can result in vaginal stenosis, fecal incontinence, impotence, and pelvic or hip fractures. It is important to counsel patients in advance that these symptoms may develop. Efforts to mitigate damage in the acute and chronic phase include barrier ointments, creams, and mechanical aids such as vaginal dilators to alleviate stenosis. Patients who experience acute effects of radiation can be expected to improve gradually over time; however, the interval it takes to see improvement may take months, and some symptoms, like fecal incontinence and impotence, may improve but never fully resolve.

Inguinal Lymph Node Metastases

Recent data suggests that inguinal lymph node metastases detected via palpation or through imaging are present in about 13% of patients who have SCCa [47]. Evidence from case series indicates that the presence of inguinal lymph node metastases increases with tumor size or stage and with age. Older patients with larger tumors harbor these metastases in 20–25% of cases [47]. These data support administration of routine inguinal radiation as part of initial therapy. As expected, inguinal node tumor recurrence is stage dependent – for patients with N0 or N1 disease at presentation, the rate of development of post-radiation malignant inguinal adenopathy is less than 2%. For those who present with N3 or N4 disease, that rate increases to 11–15% [48]. Radiation is effective at treating both occult, latent inguinal disease and more obvious cases detected at initial diagnosis by physical exam or imaging.

Some advocate fine needle aspiration (FNA) of palpable inguinal enlarged lymph nodes prior to treatment of SCCa. If positive for tumor, FNA establishes a baseline should the groin basin be resistant to treatment or develop a recurrence post-therapy. It can also help establish accurate staging in cases where the primary is inaccessible (completely excised for example), an additional or different malignancy is suspected, or if concomitant infection clouds the diagnostic picture. FNA is not helpful in routine cases given the possibility of sampling error, the relative accuracy of CT-PET, and the fact that treatment rarely changes based on the results of FNA. It is not necessary to surgically excise suspicious LNs or do a superficial inguinal groin dissection pre-chemoradiation – the morbidity and high rate of wound complications for this operation could compromise timely administration of therapy that is very effective for treatment of both the primary and the inguinal nodal metastasis. Those with inguinal nodal metastases that are not palpable, but are suspicious on CT scan, do not require FNA. NCCN guidelines suggest that radiation planning or simulation be accomplished via PET-CT; therefore, a metabolic signal would be seen prior to treatment if it were indeed neoplastic, as anal squamous tumors are typically FDG avid and signal strongly with PET imaging. Comparison of pre- and post-PET images can, in most of these cases, establish the diagnosis and be used for surveillance [49].

Surgery

Local excision is utilized rarely in the treatment of anal canal SCCa, although it is the predominant therapy used for perianal squamous tumors. However, there are several situations where local excision followed by close local surveillance may be appropriate. APR for anal cancer is typically reserved as a salvage therapy in those patients with a persistent primary tumor despite chemoradiotherapy, although there are rare situations where surgery as a primary approach may be indicated.

Superficially invasive anal cancer, defined as anal cancer that is excised with negative margins, with less than 3 mm basement membrane invasion and a maximal spread of less than 7 mm (T1NX) may be treated with excision alone [50]. These lesions are seen with growing frequency because anal cancer screening in high-risk populations has become more common. Small cancers are often completely excised at the time of biopsy, and local surgical resection with negative margins may be adequate treatment. Studies done in patients with close surgical margins (less than 2 mm) or with microscopically positive margins subsequently treated with radiation therapy showed no difference in 5-year outcomes when compared with those who had superficial locally excised anal canal cancers with negative margins and no chemoradiation [51].

A retrospective cohort study that included 2243 adults from the National Cancer Database diagnosed with T1N0 anal canal cancer between 2004 and 2012 found that the use of local excision in this population increased over time (17.3% in 2004 to 30.8% in 2012; $P < .001$). No significant difference in 5-year OS was seen based on management strategy (85.3% for local excision; 86.8% for chemoradiotherapy; $P = .93$) [52]. The limitations of this study should be noted – it was a large database review, and local and regional recurrence rates were not available. An older but more spe-

cific study, with good follow-up, suggests that small (specifically ≤1 cm), well-differentiated anal canal SCCas that are completely excised with negative margins are safe to excise locally with no adjuvant or neoadjuvant treatment [53]. Overall, it is likely that only those with small, well-differentiated superficially invasive anal cancers that can be excised with negative margins qualify for consideration of a local excision strategy. Although this is sometimes intentionally done, local excision is often done unintentionally while excising anal lesions for therapeutic or diagnostic reasons.

The goal of surveillance in the post-treatment period is centered around the concept of early detection and the potential for "salvage" surgery to provide a second chance for cure. There is evidence that tumor regression can occur for up to 6 months following the end of radiotherapy treatment. Close monitoring in the time following the conclusion of radiotherapy, typically starting 8–12 weeks following the last dose of radiation (when post-irradiation inflammation has lessened), is done via direct examination with digital rectal examination and anoscopy. Routine biopsy of residual, but shrinking, lesions in the anal canal is not generally indicated until the 6th month following radiotherapy, to allow time for tumor regression and healing. After that time, persistent ulcers or masses should be evaluated via biopsy [54]. However, a tumor that appears to be regrowing after chemoradiotherapy prior to the 6-month window should be biopsied at the time regrowth is suspected and treatment initiated if biopsies are positive.

Although chemoradiation is an effective initial treatment for anal canal SCCa, about 10–30% of patients will suffer from persistent/recurrent tumor, mostly in a locoregional pattern. The risk of persistence/recurrence parallels stage. Prior to initiating salvage therapy, patients should be restaged, typically with physical examination and biopsy confirming the presence of tumor, CT/PET, and pelvic MR in select cases of locally advanced disease. Contraindications to salvage surgery include very poor performance status combined with advanced age, incurable distant metastatic disease, and pelvic sidewall/levator or nerve root invasion. For those without these concerning features, APR is appropriate prior to administration of systemic chemotherapy. With APR, the 5-year survival rate is about 50–60%, better than with salvage chemotherapy or chemoradiotherapy where salvage rates in small series are only 30% [54, 55]. Positive margins, involved nodes, and distant metastatic disease are poor prognostic indicators postoperatively. En bloc resection of locally invaded resectable structures (vagina, prostate, distal sacrum) is possible and advisable with planning and involvement of a multidisciplinary team. Soft tissue flap reconstruction of the perineum is often necessary with or without additional organ involvement. Highly irradiated perineal tissue makes wound healing challenging, and these patients have a higher rate of perineal wound infection and dehiscence when compared to those undergoing APR for adenocarcinoma. Comparison of perineal wound closure with and without flap shows that those closed with flaps are also subject to infection or dehiscence, albeit at a lower rate, and wound healing progresses faster with flaps than with primary closure [56]. In other words, flap closure does not necessarily prevent wound infection from occurring but does reduce the size of the wound, and its presence speeds wound healing if infection or superficial dehiscence does occur. VRAM or vertical rectus abdominis myocutaneous flaps are most effective for closing large perineal wounds (Fig. 20.4a, b) [57, 58]. Perineal wound complications are more likely in patients with bulkier tumors and larger perineal defects.

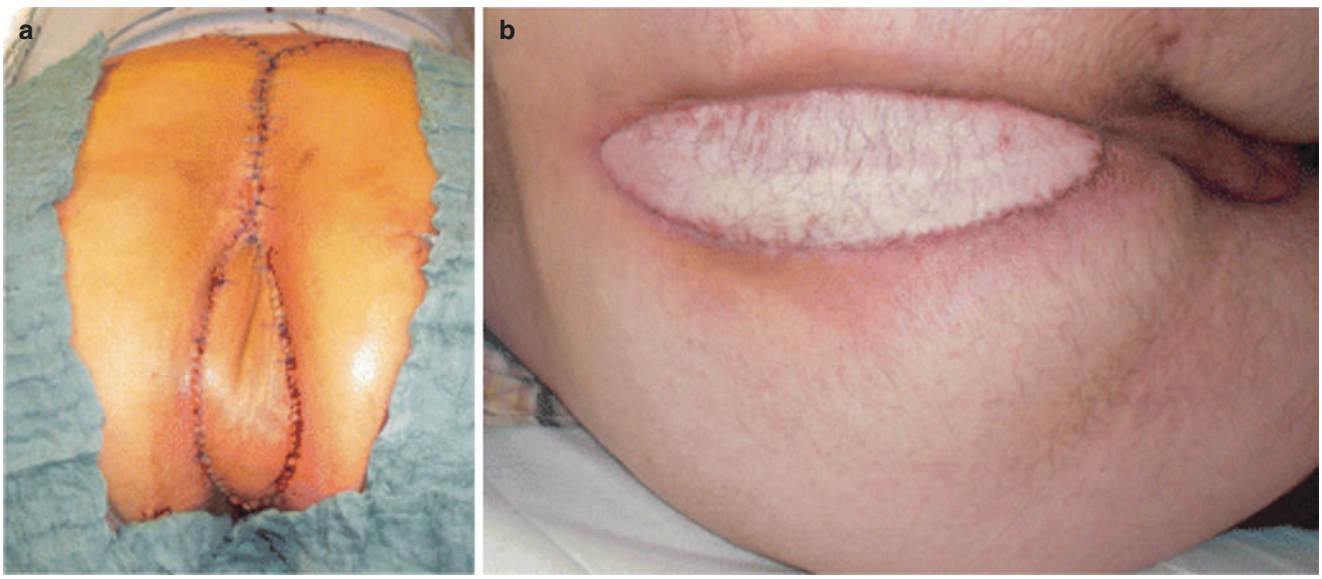

Fig. 20.4 (**a**) VRAM flap with bilateral gluteus advancements. (**b**) VRAM flap, early postoperative phase. (Reused with permission Horch et al. [126]. Copyright Springer Nature)

Those patients with isolated inguinal nodal recurrence represent a distinct subset of metastatic disease that may be considered for resection with intent to cure. It is possible to have a complete clinical response at the primary site with an isolated inguinal metastasis amenable to superficial inguinal groin dissection. If there is no evidence of additional distant or regional disease on re-staging studies (contrast CT of the chest, abdomen, and pelvis and/or PET-CT), patients with isolated inguinal metastases can be considered for superficial inguinal lymph node dissection, typically followed by systemic therapy. FNA of the area to confirm the diagnosis of SCCa is important, as morbidity of groin dissection can be substantial. Although complication rates for groin dissection following radiation are fairly high (wound dehiscence, surgical site infection, edema), long-term outcomes from smaller studies suggest that it is reasonably effective in treating isolated locoregional recurrent disease. 5-year DFS rates of 55% have been observed in select patients meeting criteria for resection [48].

Anal Cancer and HIV

Patients living with HIV (PLWH) have a higher incidence of anal cancer and comprise a known high-risk group. Comparisons of the PLWH population with HIV-negative cohorts have been mostly from larger database studies but have confirmed that 5-year OS and rates of complete response are similar [59, 60]. Other studies examining treatment course and tolerance between PLWH and HIV-negative patients found that treatment paradigms used were the same and there was no difference in tolerance or toxicity of chemoradiation. Some small retrospective studies seem to indicate that radiation-related morbidity in the form of skin inflammation and pain may be greater in the immunocompromised [60]. NCCN Guidelines for Cancer in PLWH state that PLWH who have anal cancer should be treated as per guidelines used for HIV-negative patients and that modifications to treatment should not be made solely on the basis of HIV status [49]. Use of normal tissue-sparing radiation techniques (IMRT) and consideration of nonmalignant causes for lymphadenopathy may deserve more attention in this cohort along with the need for more frequent post-treatment surveillance anal examinations.

Surveillance

Follow-up of patients after treatment of primary anal canal or perianal cancer is essential. Initial physical examination is typically done 8–12 weeks following the last dose of radiation. Examination of the anal canal or perianal area by digital rectal exam and direct visual inspection of the area by anoscopy (if the lesion originally extended into the anal canal) should be performed. Careful documentation of the extent of the response should be made. It is often helpful to include a digital photograph of the tumor/tumor treatment site in the electronic medical record, both at initial diagnosis and at surveillance examinations, as subtle changes in the tumor treatment site may be the first sign of persistence/recurrence, and examiners may change with time. The rationale for waiting for 6 months to perform biopsy in patients whose tumors are stable or regressing is that the ionizing effect of radiation on tumor cells extends well into the post-treatment period. The data to support this strategy comes from observational studies and the ACT II trial. The ACT II study compared the use of either mitomycin or cisplatin for anal cancer and showed that there was no difference in either OS or PFS between the two drugs. It did show, however, that up to 72% of patients who failed to show a complete response at 11 weeks did respond completely by 26 weeks with no evidence of residual visual evidence of tumor, ulceration, or mass present [35]. Routine biopsy is not indicated in the absence of a mass or ulcer. However, as noted above, patients who have an enlarging mass or other evidence of progression on physical examination should have a biopsy at the time that progression is noted and the histologic results interpreted in the context of the clinical situation.

It is recommended that contrast CT scan of the chest, abdomen, and pelvis be performed annually for 3 years for those with large or clinically node-positive tumors. Digital rectal examination with anoscopy and inguinal nodal palpation should be done every 3–6 months for 4–5 years [49].

Anal Adenocarcinoma

Anal adenocarcinoma differs from rectal adenocarcinoma in location and prognosis. It is often difficult to differentiate between a distal rectal tumor invading the anal canal and a primary anal adenocarcinoma (Fig. 20.5). The latter typically present with a mass in the anal canal with a minimal mucosal component. Mucoid discharge is a frequent complaint. Anal adenocarcinoma can arise directly from an anal gland or can be found in proximity to chronic fistula tracts, particularly in patients with Crohn's disease, which can present diagnostic challenges leading to delays in diagnosis [61]. Anal adenocarcinoma accounts for approximately 20% of all anal cancers [62]. They may appear morphologically similar to rectal adenocarcinoma but will have an increased risk of inguinal lymph node metastasis [63].

Anal adenocarcinomas are both staged and treated similarly to rectal cancers. Large prospective series are lacking due to the rarity of the disease, but neoadjuvant radiotherapy or chemoradiotherapy prior to APR has been associated with

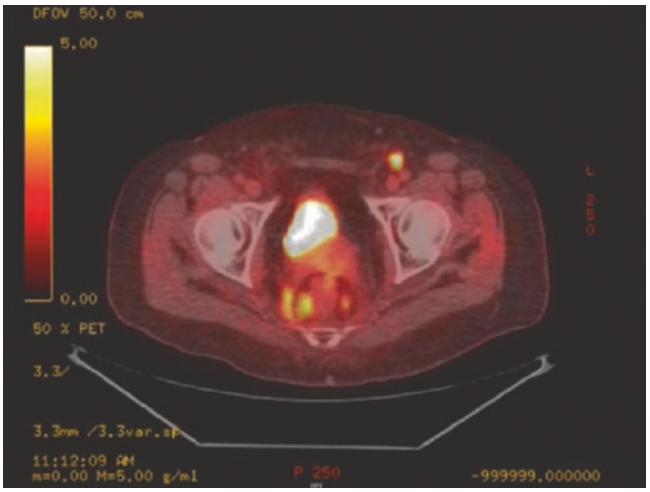

Fig. 20.5 Anal adenocarcinoma with left inguinal lymph node positivity

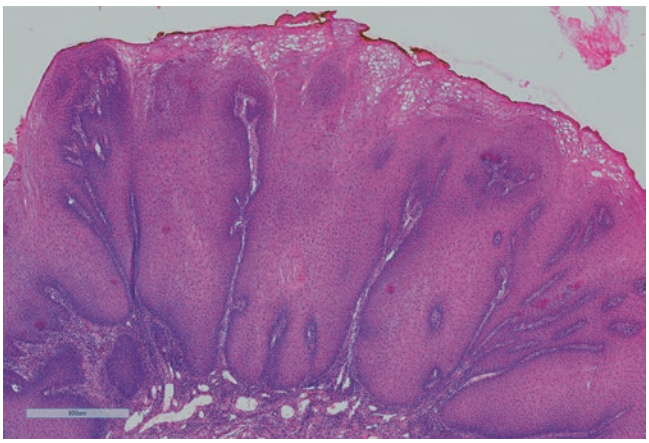

Fig. 20.6 Verrucous anal carcinoma with locally invasive histologic features. (Reused with permission from Pathology Outlines. © Copyright PathologyOutlines.com, Inc. www.PathologyOutlines.com)

improved disease-free survival and local control as compared to upfront surgery [64, 65].

Comparing the frequency and survival of anal adenocarcinoma to that of rectal adenocarcinoma and anal squamous cell carcinoma, it is noted that both the frequency and overall survival for anal adenocarcinoma are lowest. Comparisons of survival (all stages) in 57,369 cases of anorectal cancer revealed that anal adenocarcinoma represented only 0.8% of cases with a mean survival of 33 months, compared to rectal adenocarcinoma representing 87.8% of cases with a mean survival of 68 months and SCCa representing 11.4% of cases with a mean survival of 118 months [66]. A study using the National Cancer Database revealed that patients with anal adenocarcinoma had statistically worse survival when compared to both rectal adenocarcinoma and anal squamous carcinoma. Decreased survival in the anal adenocarcinoma group was associated with proctectomy and the use of chemotherapy, most likely reflecting more advanced disease at diagnosis [67]. It should be remembered, however, that studies of anal adenocarcinoma are hampered by accuracy of diagnosis, as it is often extremely difficult to distinguish whether a patient has true anal versus distal rectal adenocarcinoma.

Verrucous Carcinoma

Verrucous carcinomas of the anus are also known as Buschke-Lowenstein tumors. It was first described by Buschke and Lowenstein in 1925 and is also known as giant condylomata [68]. It presents as a large exophytic cauliflower-like lesion on the perianal skin. These lesions are characterized by their large size and their ability to infiltrate surrounding tissues (Fig. 20.6). There has been controversy as to whether a true Buschke-Lowenstein tumor should be considered benign and defined by its lack of invasion of the basement membrane (giant condylomata) or should be considered a slowly growing squamous cell carcinoma with tendency toward local invasion [69]. The lack of clarity in the definition has hampered scientific study. These tumors are often associated with HPV types 6 and 11 [70]. Following excision, substantial local recurrence rates of over 50% have been reported in meta-analysis [71]. Malignant transformation has been reported in 40–60% of cases [72]. The average time to transformation to malignancy is approximately 5 years following initial diagnosis [71].

Wide surgical excision is the mainstay of treatment. Chemoradiation, laser therapy, photodynamic therapy, antiretroviral therapy, and intralesional injection have all been reported with less success than local excision [73–76]. If mesorectal lymph node metastasis is suspected or there is local destruction of the anal canal, a more aggressive approach to treatment that may include chemoradiotherapy and/or abdominoperineal resection may be indicated.

Melanoma

Melanoma of the anus is a rare and aggressive tumor. First described in 1857 by Moore [77], the reported incidence of mucosal melanoma is between 1% and 2% of all melanomas affecting approximately 2 per million persons per year [78]. It has been estimated that anal melanoma accounts for 0.05% of all colorectal malignancies diagnosed each year [79].

Anal melanoma is most commonly seen in the sixth decade of life, with a female predominance [80]. It is unclear if the poor prognosis is related to biologic factors or simply late stage at diagnosis. As with other tumors of the anal region, patients will often attribute their symptoms of bleed-

ing and pain to hemorrhoids, thereby delaying diagnosis. A pigmented ulcerated mass in the region enhances the suspicion of melanoma (Fig. 20.7); however, it is recognized that up to 30% of anal melanomas are amelanotic [81]. These tumors can be found incidentally in hemorrhoidectomy specimens, and this scenario is one of the rare times when the tumor may be curable.

The extent of disease is assessed with pelvic MRI, PET-CT scan, colonoscopy, and complete dermatologic and ophthalmologic examination. The use of sentinel lymph node mapping is controversial with unproven survival benefit. The nodal basin is variable in the inguinal region and can be either unilateral or bilateral. While hematologic spread occurs, lymphatic spread to mesorectal nodes is not uncommon [82].

There is no TNM staging system specifically for anorectal melanoma. The staging for anorectal lesions has historically been based on clinical findings: stage I and II, local disease; stage III, regional lymph node involvement; and stage IV, distant metastatic disease [83]. Based on the findings that depth of muscle penetration impacts survival, a newer staging classification was proposed by Falch et al. (Table 20.5) [84].

The treatment for anorectal melanoma has historically been abdominoperineal resection. However, many studies have shown no survival benefit for this procedure compared to wide local excision, and it is recognized that most, but not all, treatment failures are from distant metastatic disease [85–87]. There is, however, improved local control with APR compared to wide local excision in some studies, and the use of APR for larger lesions or for salvage and palliation can be considered in select cases. The addition of radiotherapy has been proposed to augment local control after wide local excision, but it is not routinely used, as melanomas are not considered radiosensitive tumors [88, 89]. A study of 570 patients who underwent surgical resection (67% wide local excision vs 33% APR) showed that the 5-year overall survival was 21% in both groups regardless of the ability to achieve an R0 resection [90]. Similarly, a review of 653 patients with anal melanoma found comparable overall survival in both the radical and local excision groups [91]. These dismal statistics speak to the fact that death from anal melanoma is most frequently caused by the presence of distant metastatic disease, not from failure of local control.

Molecular diagnostic testing has gained importance in the characterization and management of anal melanoma. The mutations which are most commonly tested are BRAF and c-KIT. BRAF mutations may direct therapy with BRAF inhibitors in cutaneous melanomas [92]. Tyrosine kinase inhibitors such as imatinib have been targeted for treatment of patients with c-KIT (+) mutations [93].

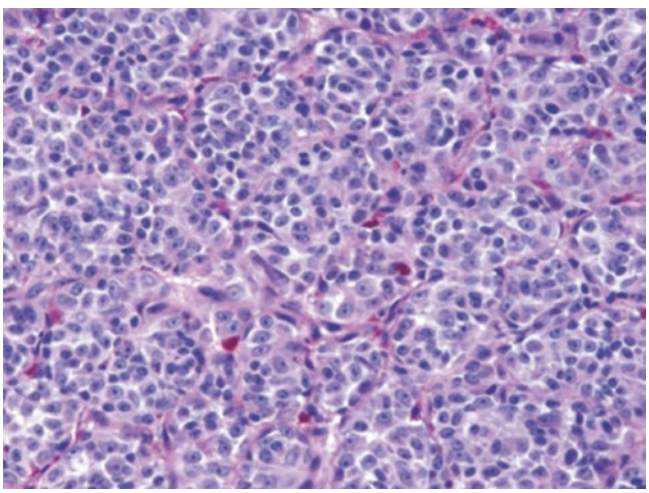

Fig. 20.7 Histology of anal melanoma

Table 20.5 Staging classification of primary anorectal malignant melanomas

Stage	Tumor spread
I	Local tumor spread without infiltration of the muscular layer
II	Local tumor spread with infiltration of the muscular layer
III	Regional tumor spread and/or positive lymph node metastasis
IV	Disseminated tumor spread

Perianal Paget's Disease (Intraepithelial Adenocarcinoma)

Extramammary perianal Paget's disease, or intraepithelial adenocarcinoma, was first reported in 1889 [94]. It is a rare skin condition arising from the apocrine glands, frequently presenting as a scaly lesion on the perianal skin (Fig. 20.8). It is estimated that 6% to 20% of all cases of extramammary Paget's disease occur in the perianal region [95–97]. It is more common in women with incidence rising starting in the fifth decade [98]. The lesion can be weeping and ulcerative and accompanied by bleeding pruritus or pain. Misdiagnosis as other more common skin conditions is not unusual, with biopsy prompted only after failure of topical steroid treatment [99]. Three types of extramammary Paget's disease have been described: those with no associated malignancy, those associated with an apocrine tumor in proximity, and those associated with internal gastrointestinal or genitourinary malignancy. This underscores the importance of a thorough search for associated malignancies [100]. In a recent review of 108 patients with anal Paget's disease, the rate of colorectal adenocarcinoma was 18.5% [101].

Histopathologic diagnosis is confirmed with the findings of classic Paget's cells with abundant cytoplasm, prominent nucleoli, and pleomorphic nuclei (Fig. 20.9) [102]. The surrounding keratinized cells are compressed. Immunohistochemical staining for cytokeratins, mucins,

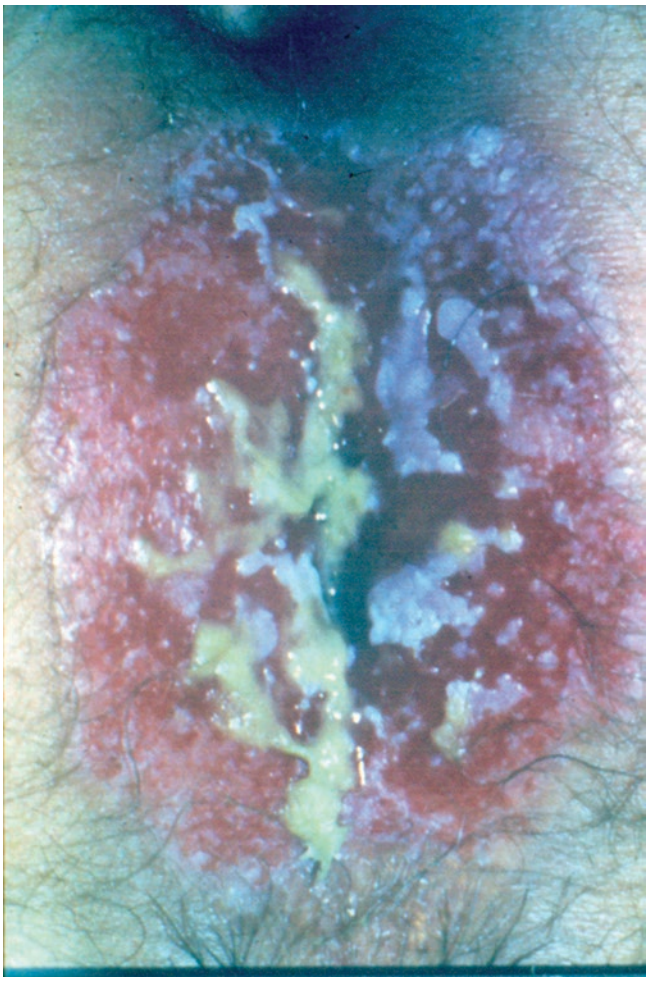

Fig. 20.8 Paget's disease of the anus. (Reuse with permission from Kann [127])

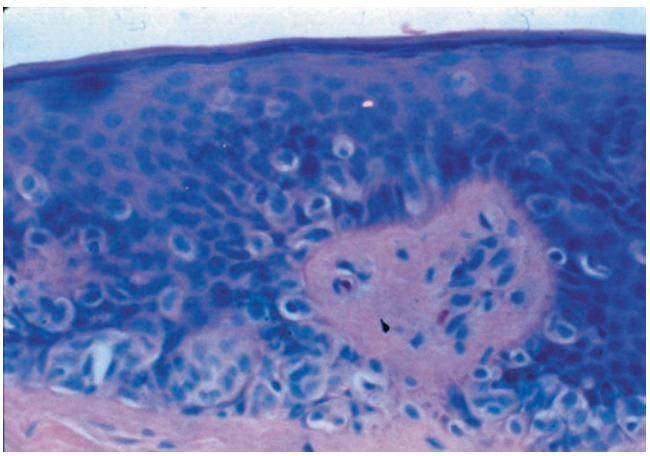

Fig. 20.9 Histology of anal Paget's disease

gross cystic disease fluid protein, and carcinoembryonic antigen has all been utilized in the diagnosis. Epidermal disease does not invade the dermis, while intradermal

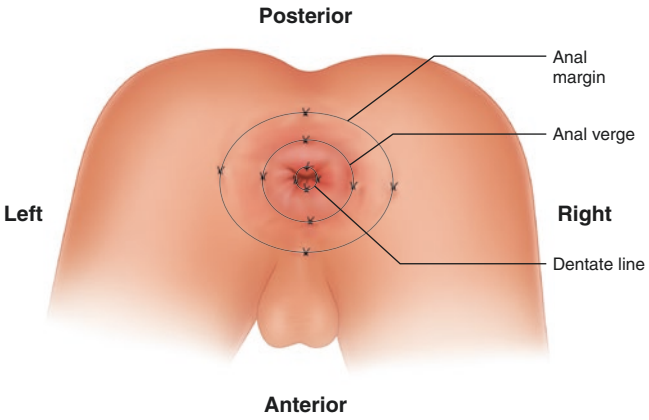

Fig. 20.10 Biopsy mapping chart of anal Paget's disease

growth pattern is less common [99]. Primary extramammary Paget's disease is thought to result from carcinoma in situ of the apocrine gland ducts, whereas secondary Paget's is thought to arise from intraepithelial spread of underlying carcinoma [103]. Because the incidence of extramammary perianal Paget's disease is so low, the majority of the literature is comprised of case reports or retrospective reviews of small series ranging from 20 to 108 cases reported sporadically over a span of decades [99, 101, 104–106]. This haphazard reporting has created dilemmas in treatment because of lack of standardization or contribution of prospective studies.

Achieving adequate surgical margins is a challenge in perianal Paget's disease because it is hard to detect grossly. Histologically, the disease can be present in normal-appearing surrounding tissues due to the multifocal or projection like growth pattern. The anatomic constraints of the anal canal can preclude adequate local excision of lesions that extend proximally. Mapping biopsies of the perianal region have been shown to be useful in avoiding overtreatment and achieving clear margins (Fig. 20.10) [102, 107]. Depending on the extent of excision, reconstruction may be necessary with skin grafts or flaps and may require a temporary diversion for proper healing. Mohs surgery with repeated frozen section analysis at a single setting has been used as a tool to tailor the excision with appropriate pathologic margins, but exposure is challenging, and the length of time it takes to perform the surgery in the prone or lithotomy position may limit the utilization of this technique [102]. The central focus of treatment is wide local excision with clear margins. However, if clear margins cannot be obtained in the anal canal with preservation of sphincter integrity or there is an associated malignancy in the anus or rectum, an abdominoperineal resection may be necessary.

Table 20.6 Classification and treatment of extramammary Paget's disease

Stage	Description	Management
I	Epidermal/intradermal Paget's cells found in perineal, scrotal, or vulvar area	WLE/MMS/TSE; if not amenable to resection or patient refusal of surgical treatment, consider 5% imiquimod
IIA	Epidermal/intradermal Paget's disease with involvement of anal canal	WLE plus transanal resection
IIB	Epidermal/intradermal Paget's with synchronous malignancies	Treat malignancy accordingly (e.g., abdominoperineal resection for rectal malignancy)
III	Epidermal/intradermal Paget's with node involvement (inguinal, iliac)	Chemotherapy
IV	Paget's disease with distant metastases of associated carcinoma	Chemotherapy, radiotherapy, local palliative management

WLE wide local excision, *MMS* Mohs micrographic surgery, *TSE* traditional surgical excision

Due to the morbidity associated with local excision and/or abdominoperineal resection, other strategies have been employed in the management of extramammary perianal Paget's disease with variable success. The use of topical imiquimod has been reported [100, 108]. Treatment with radiation therapy has been reported for primary and recurrent disease. The majority of the published studies are case reports or very small series precluding guiding conclusions as to efficacy. While there is no standardized treatment algorithm, nonsurgical treatments avoiding disfiguring surgical excision may be effective in select cases [109–111]. Photodynamic therapy has been utilized to avoid surgical resection [112]. In one of the largest series of patients with Paget's disease reported, however, recurrence rates were substantial. Half of the patients with invasive and one fourth of those with noninvasive Paget's disease recurred after complete resection, underscoring the rationale for exploring other nonsurgical treatments for this disease [106]. Moller et al. proposed a classification and treatment scheme based on stage of disease (Table 20.6) [113].

Basal Cell Carcinoma

Basal cell carcinoma is the most frequent malignant neoplasia of the skin, compromising 75% of nonmelanocytic tumors [114]. Tumors arising in non-sun-exposed areas are rare. As one might expect, perianal basal cell carcinoma is very rare, representing 0.1% of all basal cell tumors and 0.2% of all perianal tumors [115]. There has been association of these tumors with synchronous lesions in other locations in the body [116]. Therefore, a thorough examination of the entire skin surface should be performed. These tumors have no association with HPV. Treatment is local surgical excision with negative margins.

Gastrointestinal Stromal Tumor (GIST)

Gastrointestinal stromal tumors are the most common mesenchymal tumors of the GI tract, most often located in the stomach and small bowel [117]. The interstitial cells of Cajal are the cells of origin for these tumors [118]. Anorectal GISTs account for only 5% of all GISTs, with those located in the anal canal comprising only 2% of this subgroup [119]. There is a male predominance, with diagnosis typically in the sixth to seventh decade [119]. The tumor presents as a well-circumscribed hypoechoic mass in the intersphincteric space, as seen on endoanal ultrasound [117]. On physical exam, these lesions can present as entirely submucosal or as an ulcerated mass with a large non-luminal, submucosal component. Evaluation of proximity to adjacent structures like the vagina or prostate should be done. Biopsy is appropriate if the mass is larger and ulcerated as a chemotherapy neoadjuvant approach may be beneficial. Diagnosis with endoanal ultrasound or, more commonly, MRI for locoregional staging is appropriate, with a CT scan of the chest, abdomen, or pelvis or a PET-CT providing distant staging information. Because spread of these mesenchymal tumors is mostly hematogenous, GISTs rarely spread to locoregional lymph nodes [120]. Surgical excision is the mainstay of treatment for smaller tumors. Targeted therapy with tyrosine kinase inhibitors such as imatinib (Gleevec©) is often performed to reduce the size of larger, ulcerated, or high mitotic GIST tumors to facilitate local resection in those tumors that are proto-oncogene c-KIT (CD117) positive [121]. It has been suggested that low-risk GISTs with a diameter <2 cm and mitosis <5 per 50 per high-powered field may be considered for local excision if sphincter-saving surgery is technically feasible with or without preoperative tyrosine kinase inhibitor treatment (Fig. 20.11a, b). There are few large case series analyzing treatment for anal GIST. One of the larger reports of 18 patients noted local recurrence in 6 of 10 patients treated with local excision compared to none of the 8 patients treated with radical surgery. There was, however, no difference in survival in the two groups [122]. Evidence suggests that GISTs that are more aggressive should be treated with radical excision as well as chemotherapy [123]. Long periods of latency, exceeding 10 years, between initial treatment and development of recurrence, either local or distant, have been reported [119, 123, 124]. This underscores the potential benefit of extended surveillance of these patients.

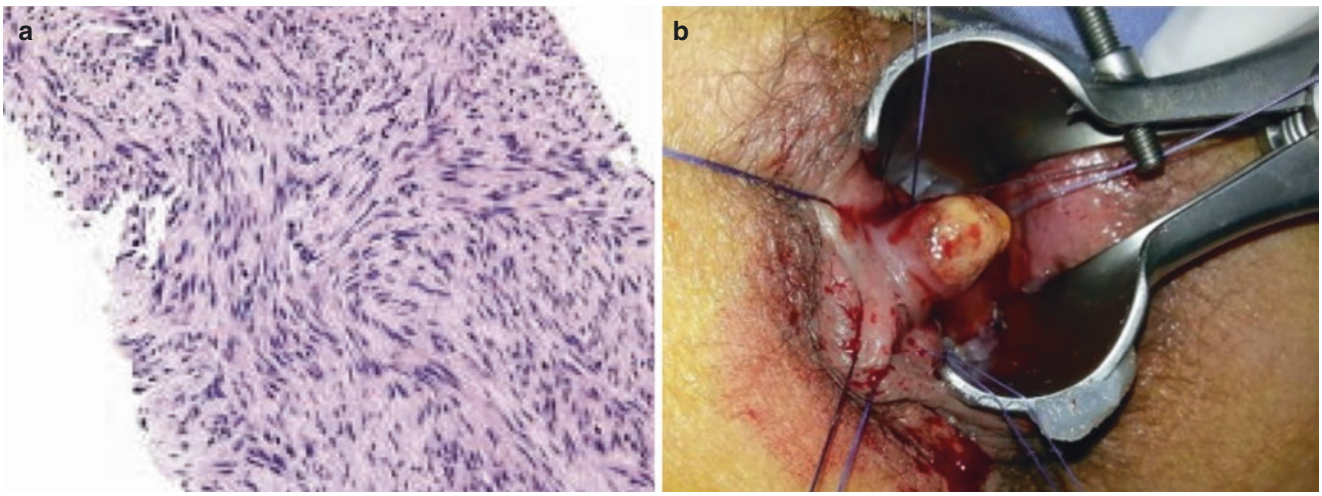

Fig. 20.11 Gastrointestinal stromal tumor (GIST) of the anus. (**a**) Histologic appearance of GIST tumor. (**b**) Small submucosal non-ulcerated GIST tumor. (Reused with permission from Author Azzaza et al. [117]. Copyright Elsevier)

Conclusion

In conclusion, malignancies of the anus are diverse and relatively rare, but the overwhelming majority of cancers are squamous cell carcinomas. These cancers are increasing in incidence but are imminently curable at early stages and amenable to early detection. Most, but not all, are HPV mediated and thus may be preventable. Protocols for treatment of anal squamous cell carcinoma, both in the anal canal and perianal region, are well-studied, and patients typically enjoy favorable outcomes. A high index of suspicion for anal cancer when persistent anorectal symptoms occur and a willingness to quickly examine and biopsy suspicious lesions may limit morbidity and mortality from both anal squamous cell carcinoma and in those anal cancers that are less common and more lethal.

References

1. Islami F, Ferlay J, Lortet-Tieulent J, et al. International trends in anal cancer incidence rates. Int J Epidemiol. 2017;46(3):924–38.
2. Deshmukh AA, Suk R, et al. Recent trends in squamous cell carcinoma of the anus incidence and mortality in the United States, 2001–2015. J Natl Cancer Inst. 2020;112(8):829–38.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7.
4. Johnson LG, Madeleine MM, Newcomer LM, Schwartz SM, Daling JR. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973–2000. Cancer. 2004;101(2):281–8.
5. Nelson RA, Levine AM, Bernstein L, Smith DD, Lai LL. Changing patterns of anal canal carcinoma in the United States. J Clin Oncol. 2013;31:1569–75.
6. Cheung ANY. WHO classification of tumours, Digestive system. 5th ed. Geneva: World Health Organization; 2018.
7. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: anal carcinoma, version 1.2019. 2019. https://www.nccn.org/professionals/physician_gls/default.aspx.
8. de Winton E, Heriot AG, Ng M, et al. The impact of 18-fluorodeoxyglucose positron emission tomography on the staging, management and outcome of anal cancer. Br J Cancer. 2009;100(5):693–700.
9. Mahmud A, Poon R, et al. PET imaging in anal canal cancer: a systematic review and meta-analysis. Br J Radiol. 2017;90:20170370.
10. Jones M, Hruby G, et al. The role of FDG-PET in the initial staging and response assessment of anal cancer: a systematic review and meta-analysis. Ann Surg Oncol. 2015;22:3574–81.
11. Teagle A, Gilbert D, Jones J, et al. Negative FDG-PET-CT may exclude residual or recurrent disease in anal cancer. Nucl Med Commun. 2016;37(10):1038–45.
12. Welton ML, Steele SR, Goodman KA, et al. Anus. In: Amin MB, editor in-chief. AJCC cancer staging manual. 8th ed. New York: Springer; 2017. p. 275–84.
13. Moore HG, Guillem JG. Anal neoplasms. Surg Clin North Am. 2002;82(6):1233–51.
14. Cummings BJ, Brierley JD. Principles and practice of radiation oncology. 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2008. p. 1383–96.
15. Schlienger M, Touboul E. Anal margin tumours. In: Belkacémi Y, Mirimanoff RO, Ozsahin M, editors. Management of rare adult tumours. Paris: Springer; 2009.
16. Behrendt GC, Hansmann ML. Carcinomas of the anal canal and anal margin differ in their expression of cadherin, cytokeratins and p53. Virchows Arch. 2001;439(6):782–6.
17. Klencke BJ, Palefsky JM. Anal cancer: an HIV-associated cancer. Hematol Oncol Clin North Am. 2003;12:859–72.
18. Jiang Y, Ajani JA. Anal margin cancer: current situation and ongoing trials. Curr Opin Oncol. 2012;24(4):448–53.
19. Papillon J, Chassard JL. Respective roles of radiotherapy and surgery in the management of epidermoid carcinoma of the anal margin: series of 57 patients. Dis Colon Rectum. 1992;35:422–9.
20. Jensen SL, Hagen K, Harling H, et al. Long-term prognosis after radical treatment of squamous-cell carcinoma of the anal canal and anal margin. Dis Colon Rectum. 1988;31:273–8.
21. Shridhar R, Shibata D, Chan E, Thomas CR. Anal cancer: current standards in care and recent changes in practice. CA Cancer J Clin. 2015;65:139–62.

22. Glynne-Jones R, Nilsson PJ, Aschele C, et al. Anal cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii10–20.
23. Newlin HE, Zlotecki RA, Morris CG, Hochwald SN, Riggs CE, Mendenhall WM. Squamous cell carcinoma of the anal margin. J Surg Oncol. 2004;86(2):55–63.
24. Chawla AK, Willett CG. Squamous cell carcinoma of the anal canal and anal margin. Hematol Oncol Clin North Am. 2001;15(2):321–44, vi.
25. Nigro ND, Vaitkevicius VK, et al. Combined therapy for cancer of the anal canal: a preliminary report. Dis Colon Rectum. 1974;17(3):354–6.
26. Nigro ND, Vaitkevicius VK, et al. Classic article – combined therapy for cancer of the anal-canal – a preliminary-report (Reprinted from Dis Colon Rectum, Vol 17, Pg 354–356, 1974). Dis Colon Rectum. 1993;36(7):709–11.
27. Bartelink H, Roelofsen F, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol. 1997;15:2040–9.
28. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on cancer research epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. Lancet. 1996;348:1049–54.
29. Flam M, John M, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. J Clin Oncol. 1996;14:2527–39.
30. Glynne-Jones R, Meadows H, et al. EXTRA--a multicenter phase II study of chemoradiation using a 5 day per week oral regimen of capecitabine and intravenous mitomycin C in anal cancer. Int J Radiat Oncol Biol Phys. 2008;72:119–26.
31. Meulendijks D, Dewit L, et al. Chemoradiotherapy with capecitabine for locally advanced anal carcinoma: an alternative treatment option. Br J Cancer. 2014;111:1726–33.
32. Goodman K, Rothenstein D, et al. Capecitabine plus mitomycin in patients undergoing definitive chemoradiation for anal squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2014;90:S32–3.
33. Thind G, Johal B, et al. Chemoradiation with capecitabine and mitomycin-C for stage I–III anal squamous cell carcinoma. Radiat Oncol. 2014;9:124.
34. Oliveira S, Moniz C, et al. Phase II study of capecitabine in substitution of 5-FU in the chemoradiotherapy regimen for patients with localized squamous cell carcinoma of the anal canal. J Gastrointest Cancer. 2016;47:75–81.
35. James R, Glynne-Jones R, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 x 2 factorial trial. Lancet Oncol. 2013;14:516–24.
36. Gunderson L, Winter K, et al. Long-term update of US GI Intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol. 2012;30:4344–51.
37. Moureau-Zabotto L, Viret F, et al. Is neoadjuvant chemotherapy prior to radio-chemotherapy beneficial in T4 anal carcinoma? J Surg Oncol. 2011;104:66–71.
38. Peiffert D, Tournier-Rangeard L, Gérard JP, et al. Induction chemotherapy and dose intensification of the radiation boost in locally advanced anal canal carcinoma: final analysis of the randomized UNICANCER ACCORD 03 trial [published correction appears in J Clin Oncol. 2012 Nov 1;30(31):3903]. J Clin Oncol. 2012;30(16):1941–8. https://doi.org/10.1200/JCO.2011.35.4837.
39. Deutsch E, Lemanski C, et al. Unexpected toxicity of cetuximab combined with conventional chemoradiotherapy in patients with locally advanced anal cancer: results of the UNICANCER ACCORD 16 phase II trial. Ann Oncol. 2013;24:2834–8.
40. Olivatto L, Vieira F, et al. Phase 1 study of cetuximab in combination with 5-fluorouracil, cisplatin, and radiotherapy in patients with locally advanced anal canal carcinoma. Cancer. 2013;119:2973–80.
41. Garg M, Zhao F, et al. Cetuximab plus chemoradiotherapy in immunocompetent patients with anal carcinoma: a phase II Eastern Cooperative Oncology Group-American College of Radiology Imaging Network Cancer Research Group trial (E3205). J Clin Oncol. 2017;35:718–26.
42. Sparano J, Lee J, et al. Cetuximab plus chemoradiotherapy for HIV-associated anal carcinoma: a phase II AIDS Malignancy Consortium trial. J Clin Oncol. 2017;35:727–33.
43. John M, Pajak T, et al. Dose escalation in chemoradiation for anal cancer: preliminary results of RTOG 92-08. Cancer J Sci Am. 1996;2:205–11.
44. Ferrigno R, Nakamura R, et al. Radiochemotherapy in the conservative treatment of anal canal carcinoma: retrospective analysis of results and radiation dose effectiveness. Int J Radiat Oncol Biol Phys. 2005;61:1136–42.
45. Konski A, Garcia M, et al. Evaluation of planned treatment breaks during radiation therapy for anal cancer: update of RTOG 92-08. Int J Radiat Oncol Biol Phys. 2008;72:114–8.
46. Ajani J, Winter K, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. JAMA. 2008;299:1914–21.
47. Ortholan C, Resbeut M, et al. Anal canal cancer: management of inguinal nodes and benefit of prophylactic inguinal irradiation (CORS-03 Study). Int J Radiat Oncol Biol Phys. 2012;82(5):1988–95.
48. Tanabe T, Shida D, et al. Long-term outcomes after surgical dissection of inguinal lymph node metastasis from rectal or anal canal adenocarcinoma. BMC Cancer. 2019;19(1):733.
49. Benson AB, Venook AP, et al. Anal carcinoma, version 2.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2018;16(7):852–71.
50. Darragh T, Colgan T, et al. The lower anogenital squamous terminology standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Arch Pathol Lab Med. 2012;136:1266–97.
51. Arana R, Flejou J, et al. Clinicopathological and virological characteristics of superficially invasive squamous-cell carcinoma of the anus. Colorectal Dis. 2015;17:965–72.
52. Chai C, Tran Cao H, et al. Management of stage I squamous cell carcinoma of the anal canal. JAMA Surg. 2018;153:209–15.
53. Klas JV, Rothenberger DA, et al. Malignant tumors of the anal canal: the spectrum of disease, treatment, and outcomes. Cancer. 1999;85(8):1686–93.
54. Rousseau DL Jr, Petrelli NJ, et al. Overview of anal cancer for the surgeon. Surg Oncol Clin N Am. 2004;13(2):249–62.
55. Pocard M, Tiret E, et al. Results of salvage abdominoperineal resection for anal cancer after radiotherapy. Dis Colon Rectum. 1998;41(12):1488–93.
56. Hardt J, Mai S, et al. Abdominoperineal resection and perineal wound healing in recurrent, persistent, or primary anal carcinoma. Int J Colorectal Dis. 2016;31(6):1197–203.
57. Chessin D, Hartley J, et al. Rectus flap reconstruction decreases perineal wound complications after pelvic chemoradiation and surgery: a cohort study. Ann Surg Oncol. 2005;12:104–10.

58. Devulapalli C, Jia Wei A, et al. Primary versus flap closure of perineal defects following oncologic resection: a systematic review and meta-analysis. Plast Reconstr Surg. 2016;137:1602–13.
59. Chiao E, Giordano T, et al. Human immunodeficiency virus-associated squamous cell cancer of the anus: epidemiology and outcomes in the highly active antiretroviral therapy era. J Clin Oncol. 2008;26:474–9.
60. Seo Y, Kinsella M, et al. Outcomes of chemoradiotherapy with 5-Fluorouracil and mitomycin C for anal cancer in immunocompetent versus immunodeficient patients. Int J Radiat Oncol Biol Phys. 2009;75:143–9.
61. Chan DK, Tan KK. Anal adenocarcinoma presenting as a non-healing ischiorectal wound. J Gastrointest Surg. 2017;21(3):604–5. https://doi.org/10.1007/s11605-016-3238-4.
62. AFIP. Atlas of tumor pathology. 3rd series. Fascicle 32. Washington: AFIP; 2003.
63. Kulkarni MP, Momin YA, Pandav AB, Sulhyan KR. Adenocarcinoma of the anal canal: a report of two cases with review of literature. Indian J Pathol Microbiol. 2016;59:404–6.
64. Hongo K, Kazama S, Sunami E, Kitayama J, Watanabe T. Perianal adenocarcinoma associated with anal fistula: a report of 11 cases in a single institution focusing on treatment and literature review. Hepatogastroenterology. 2013;60(124):720–6.
65. Díaz-Vico T, Fernández-Martínez D, García-Gutiérrez C, et al. Mucinous adenocarcinoma arising from chronic perianal fistula-a multidisciplinary approach. J Gastrointest Oncol. 2019;10(3):589–96. https://doi.org/10.21037/jgo.2019.01.11.
66. Franklin R, Giri S, Valasareddy P, et al. Comparative survival of patients with anal adenocarcinoma, squamous cell carcinoma of the anus and rectal adenocarcinoma. Clin Colorectal Cancer. 2016;3:48–53.
67. McKenna NP, Bergquist JR, Habermann EB, Chua HK, Kelley SR, Mathis KL. Surgery and chemotherapy are associated with improved overall survival in anal adenocarcinoma: results of a national cohort study. Int J Colorectal Dis. 2019;34(4):607–12. https://doi.org/10.1007/s00384-018-03232-8.
68. Buschke A, Lowenstein L. Uber carcinomahnliche condylomata Acuminata des penis. Kiln Wochenschr. 1925;4:726–8.
69. Knoblich R, Failing J. Giant condyloma acuminatum (Buschke Lowenstein tumor) of the rectum. Am J Clin Pathol. 1967;48(4):398–5.
70. Braga JC, Nadal SR, Stiepcich M, Framil VM, Muller H. Buschke-Loewenstein tumor: identification of HPV type 6 and 11. An Bras Dermatol. 2012;87(1):131–4.
71. Chu Q, Vezeridis M, Libbey N, et al. Giant condyloma acuminatum (Buschke-Lowenstein tumor) of the anorectal and perianal regions. Analysis of 42 cases. Dis Colon Rectum. 1994;37(9):950–7.
72. Papiu HS, Dumnici A, Olariu T, et al. Perianal giant condyloma acuminatum (Buschke-Löwenstein tumor). Case report and review of the literature. Chirurgia. 2011;106(4):535–9.
73. Nambudiri VE, Mutyambizi K, Walls AC, Fisher DC, Bleday R, Saavedra AP. Successful treatment of perianal giant condyloma acuminatum in an immunocompromised host with systemic interleukin 2 and topical cidofovir. JAMA Dermatol. 2013;149(9):1068–70.
74. Grodner C, Henn A, Lelièvre JD, Gallien S. Successful improvement of Buschke-Löwenstein tumour in an HIV-infected patient with antiretroviral therapy alone. BMJ Case Rep. 2016;2016:bcr2016217753.
75. Indinnimeo M, Impagnatiello A, D'Ettorre G, et al. Buschke-Löwenstein tumor with squamous cell carcinoma treated with chemo-radiation therapy and local surgical excision: report of three cases. World J Surg Oncol. 2013;11:231. Published 16 Sept 2013. https://doi.org/10.1186/1477-7819-11-231.
76. Gholam P, Enk A, Hartschuh W. Successful surgical management of giant condyloma acuminatum (Buschke-Löwenstein tumor) in the genitoanal region: a case report and evaluation of current therapies. Dermatology. 2009;218(1):56–9.
77. Moore W. Recurrent melanosis of the rectum after previous removal from the verge of the anus in a man aged 65. Lancet. 1857;1:290–4.
78. Schaefer T, Satzger I, Guzmer R. Clinical prognosis and new therapeutic options in patients with mucosal melanoma. A retrospective analysis of 75 patients. Medicine. 2017;96:1–7.
79. Cagir B, Whiteford MH, Topham A, et al. Changing epidemiology of anorectal melanoma. Dis Colon Rectum. 1999;42:1203–8.
80. Pessaux P, Pocard M, Elias D, Duvillard P, Avril MF, Zimmerman P, et al. Surgical management of primary anorectal melanoma. Br J Surg. 2004;91:1183–7.
81. Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer. 1998;83:1664–78.
82. Iddings DM, Fleisig AJ, Chen SL, et al. Practice patterns and outcomes for anorectal melanoma in the USA, reviewing three decades of treatment: is more extensive surgical resection beneficial in all patients? Ann Surg Oncol. 2010;17:40–4.
83. Singer M, Mutch MG. Anal melanoma. Clin Colon Rectal Surg. 2006;19(2):78–87. https://doi.org/10.1055/s-2006-942348.
84. Falch C, et al. Anorectal malignant melanoma: extensive 45-year review and proposal for a novel staging classification. J Am Coll Surg. 2013;217(2):324–35.
85. Nusrath S, Thammineedi SR, Patnaik SC, et al. Anorectal malignant melanoma-defining the optimal surgical treatment and prognostic factors. Indian J Surg Oncol. 2018;9(4):519–23. https://doi.org/10.1007/s13193-018-0791-1.
86. Zhang S, Gao F, Wan D. Abdominoperineal resection or local excision? A survival analysis of anorectal malignant melanoma with surgical management. Melanoma Res. 2010;20(4):338–41. https://doi.org/10.1097/CMR.0b013e328339b159.
87. Matsuda A, Miyashita M, Matsumoto S, Takahashi G, Matsutani T, Yamada T, Kishi T, Uchida E. Abdominoperineal resection provides better local control but equivalent overall survival to local excision of anorectal malignant melanoma: a systematic review. Ann Surg. 2015;261(4):670–7.
88. Ramakrishnan AS, Mahajan V, Kannan R. Optimizing local control in anorectal melanoma. Indian J Cancer. 2008;45:13–9.
89. Ballo MT, Gershenwald JE, Zagars GK, et al. Sphincter-sparing local excision and adjuvant radiation for anal-rectal melanoma. J Clin Oncol. 2002;20:4555–8.
90. Ford MM, Kauffmann RM, Geiger TM, Hopkins MB, Muldoon RL, Hawkins AT. Resection for anal melanoma: is there an optimal approach? Surgery. 2018;164(3):466–72. https://doi.org/10.1016/j.surg.2018.05.026.
91. Fields AC, Goldberg J, Senturk J, et al. Contemporary surgical management and outcomes for anal melanoma: a national cancer database analysis. Ann Surg Oncol. 2018;25(13):3883–8. https://doi.org/10.1245/s10434-018-6769-y.
92. Davis H, Bignell G, Cox C, et al. Nature. 2002;417:949–54.
93. Knowles J, Lynch A, Warrier S, et al. A case series of anal melanoma including the resulte of treatment with imatinib in selected patients. Colorectal Dis. 2015;18:877–82.
94. Marchesa P, FazioVW OS, GoldblumJR LIC, Milsom JW. Long-term outcome of patients with perianal Paget's disease. Ann Surg Oncol. 1997;4:475–80.
95. Lian P, Gu WL, Zhang Z, et al. Retrospective analysis of perianal Paget's disease with underlying anorectal carcinoma. World J Gastroenterol. 2010;16:2943–8.
96. Lopes Filho LL, Lopes IM, Lopes LR, Enokihara MM, Michalany AO, Matsunaga N. Mammary and extramammary Paget's disease. An Bras Dermatol. 2015;90:225–31.

97. Lo O, Li G, Law W. Management of extramammary Paget's disease involving the dentate line without abdominoperineal resection. Tech Coloproctol. 2015;20:419–22.
98. Amin R. Perianal Paget's disease. Br J Radiol. 1999;72(858):610–2.
99. Boehringer A, Leiter U, Metzler G, et al. Extramammary Paget's disease: extended subclinical growth detected using three dimensional histology in routine paraffin procedure and course of the disease. Dermatol Surg. 2011;37:1417–26.
100. Vereecken P, Awada A, Chanem G, et al. A therapeutic approach to perianal extramammary Paget's disease: topical imiquimod can be useful to prevent or defer surgery. Med Sci Monit. 2007;13(6):CS75–7.
101. Lee G, Kunitake H, Stafford C, et al. High risk of proximal and local neoplasms in 2206 patients with anogenital extramammary Paget's disease. Dis Colon Rectum. 2019;62:1283–93.
102. King B, Park S, Chang H. The effectiveness of mapping biopsy in patients with extramammary Paget's disease. Arch Plast Surg. 2014;41:753–8.
103. Wagner G, Sachse MM. Extramammary Paget disease: clinical appearance, pathogenesis, management. J Dtsch Dermatol Ges. 2011;9:448–54.
104. Isik O, Aytac E, Brainard J, et al. Perianal Paget's disease: three decades of experience. Int J Colorectal Dis. 2015;31:29–34.
105. McCarter MD, Quan SH, Busam K, Paty PP, Wong D, Guillem JG. Long-term outcome of perianal Paget's disease. Dis Colon Rectum. 2003;46:612–6.
106. Perez DR, Trakarnsanga A, Shia J, et al. Management and outcome of perianal Paget's disease: a 6-decade institutional experience. Dis Colon Rectum. 2014;57(6):747–51.
107. Nagai Y, Kazama S, Yamada D, et al. Perianal and vulvar extramammary Paget's disease: a report of six cases and mapping biopsy of the anal canal. Ann Dermatol. 2016;28:624–8.
108. Ho SJ, Aw DC. Extramammary Paget's disease treated with topical imiquimod 5% cream. Dermatol Ther. 2010;23:423–7.
109. Mann J, Lavaf A, Tejwani A, Ross P, Ashamalla H. Perianal Paget disease treated definitively with radiotherapy. Curr Oncol. 2012;19(6):e496–500. https://doi.org/10.3747/co.19.1144.
110. Brown R, Lankester K, McCormack M, Power D, Spittle M. Radiotherapy for perianal Paget's disease. Clin Oncol. 2002;14:272–84. 21.
111. Besa P, Rich TA, Delclos L, Edwards CL, Ota DM, Wharton JT. Extramammary Paget's disease of the perineal skin: role of radiotherapy. Int J Radiat Oncol Biol Phys. 1992;24:73–8.
112. Wollina U, Goldman A, Bieneck A, Abdel-Naser MB, Petersen S. Surgical treatment for extramammary Paget's disease. Curr Treat Options Oncol. 2018;19:27.
113. Moller MG, Lugo-Baruqui JA, Milikowski C, Salgado CJ. Staged marginal contoured and central excision technique in the surgical management of perianal Paget's disease. Am J Surg. 2014;207:485–49.
114. Bulur I, Boyuk E, Saracoglu ZN, et al. Perianal basal cell carcinoma. Case Rep Dermatol. 2015;7:25–8.
115. Espino-Urbina LA, Espinosa-de-los-Monteros A, Domínguez-Cherit J, et al. Basal cell carcinoma of the perianal region: a case report and literature review. Rev Gastroenterol Mex. 2013;78:52–4.
116. Paterson CA, Young-Fadok TM, Dozois RR. Basal cell carcinoma of the perianal region. Dis Colon Rectum. 1999;42:1200–2. https://doi.org/10.1007/BF02238575.
117. Azzaza M, Ammar H, Abdessayed N, et al. Wide local excision for anal GIST: a case report and review of literature. Int J Surg Case Rep. 2017;30:97–100. https://doi.org/10.1016/j.ijscr.2016.11.046.
118. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH, Weiss SW. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol. 2002;33(5):459–65.
119. Miettinen M, Furlong M, Sarlomo-Rikala M, Burke A, Sobin LH, Lasota J. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the rectum and anus: a clinicopathologic, immunohistochemical, and molecular genetic study of 144 cases. Am J Surg Pathol. 2001;25:1121–33.
120. Paramythiotis D, Bangeas P, Karakatsanis A, Karayannopoulou G, Michalopoulos A. Anal canal gastrointestinal stromal tumors – report of a rare case and review of the literature. Hippokratia. 2016;20(4):313–6.
121. Gold JS, Dematteo RP. Combined surgical and molecular therapy: the gastrointestinal stromal tumor model. Ann Surg. 2006;244(2):176–84.
122. Tworek JA, Goldblum JR, Weiss SW, Greenson JK, Appelman HD. Stromal tumors of the anorectum: a clinicopathologic study of 22 cases. Am J Surg Pathol. 1999;23:946–54.
123. Li JC, Ng SS, Lo AW, Lee JF, Yiu RY, Leung KL. Outcome of radical excision of anorectal gastrointestinal stromal tumors in Hong Kong Chinese patients. Indian J Gastroenterol. 2007;26(1):33–5.
124. Carvalho N, Albergaria D, Lebre R, et al. Anal canal gastrointestinal stromal tumors: case report and literature review. World J Gastroenterol. 2014;20(1):319–22.
125. Beck DE. Perianal and anal canal neoplasms. In: Beck DE, Wexner SD, Rafferty JF, editors. Gordon and Nivatvongs' principles and practice of surgery for the colon, rectum, and anus. 4th ed. New York: Thieme Medical Publishers Inc.; 2019.
126. Horch RE, Hohenberger W, Eweida A, et al. A hundred patients with vertical rectus abdominis myocutaneous (VRAM) flap for pelvic reconstruction after total pelvic exenteration. Int J Colorectal Dis. 2014;29:813–23.
127. Kann BR. Anal neoplasms. In: Beck DE, Steele SR, Wexner SD, editors. Fundamentals of anorectal surgery. 3rd ed. Cham: Springer Nature; 2018. https://doi.org/10.1007/978-3-319-65966-4

Presacral Tumors

21

Scott R. Kelley and Eric J. Dozois

Key Concepts

- The presacral (retrorectal) space is the location of a wide range of rare tumors with incidence as low as 1 in 40,000–60,000 hospital admissions. Discovery in asymptomatic patients is increasing due to expanded use of cross-sectional imaging.
- Advances in cross-sectional imaging and understanding of tumor biology have led to better outcomes for these challenging patients.
- MRI is the best imaging study to assist in diagnosis and operative planning.
- Most benign lesions have malignant potential and observation alone in some patients is acceptable when a dedicated surveillance protocol is in place.
- When performed appropriately and selectively, a CT-guided biopsy of the lesion may assist in management of solid and heterogeneous cystic lesions.
- The surgical principles that should guide a surgeon who manages these lesions are a function-sparing approach for benign lesions and an en bloc approach for malignant lesions.

Introduction

The presacral (retrorectal) space is a potential space and the location of a wide range of rare tumors. Reports from referral centers have indicated the incidence may be as low as 1 in 40,000–60,000 hospital admissions [1–4]. Detection is frequently delayed since patients are often asymptomatic until tumors reach considerable size. Advances in cross-sectional imaging and understanding of tumor biology have led to better outcomes for these challenging patients. Although most surgeons will encounter a patient with a presacral tumor in their career, few will have the opportunity to treat a large volume of these complex lesions. The care of these patients can be greatly optimized by an experienced multidisciplinary team (MDT).

Anatomic Considerations

Evaluation and management of presacral tumors require a thorough understanding of the anatomic relationships of the pelvic viscera, the bony confines of the pelvis, and the neuromuscular structures. Anteriorly the presacral space is bordered by the mesorectum, posteriorly by the anterior table of the sacrum, inferiorly by the levator muscles, and laterally by the lumbosacral plexus, ureters, and iliac vessels (Fig. 21.1).

Several important vascular and neural structures are located where presacral tumors occur. Injury to these may have important physiological, neurologic, and musculoskeletal consequences. Knowledge of anatomy of the thigh and lower extremity is also necessary in complex cases utilizing muscle or other soft tissue flap coverage. When sacrectomy is required, a multidisciplinary surgical team familiar with the anatomy of the sacrotuberous and sacrospinous ligaments, sciatic nerve, piriformis muscle, the thecal (dural) sac, and sacral nerve roots is necessary (Fig. 21.2a and b). Knowledge of sacral nerve root function is important in order to be able to counsel patients on potential functional sequelae that can influence their quality of life. Todd and colleagues evaluated bowel and bladder function in a group of patients following sacral resection. They found that if bilateral S2–S5 nerve roots were removed patients had complete loss of bladder and bowel function. If bilateral S3–S5 were removed, 40% had normal bowel function and 25% had nor-

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mal bladder function. If bilateral S4–S5 were taken, 100% had normal bowel function and 69% had normal bladder function. If unilateral S1–S5 were taken, 87% had normal bowel function and 89% had normal bladder function [5]. If the S1 nerve root or sciatic nerve is resected foot drop can occur, severely impairing ambulatory function [6]. In addition to functional consequences, when high sacrectomy is performed, pelvic stability can be compromised if more than half of the S1 vertebral body is resected. Moreover, preoperative radiotherapy can increase the risk of stress fractures destabilizing the pelvic ring. When spinopelvic stability is a concern, patients undergo sacropelvic reconstruction with metallic fixation, bone grafting, or 3D printed titanium prostheses [7].

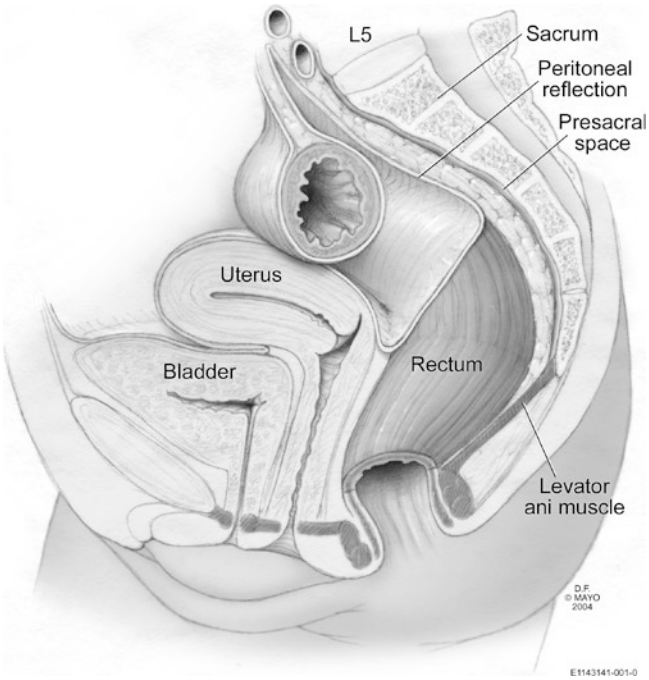

Fig. 21.1 Relationship of pelvic structures to presacral space. (Reused with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

Clinical Presentations

Presacral tumors are often discovered incidentally during routine pelvic/rectal examination, or on imaging for other purposes [8]. If symptoms are present, pain is typically vague, of long duration, and in the pelvis, perineum, and/or low back. The vague nature of pain can make diagnosis difficult, and at times patients are referred to a psychiatrist when no obvious etiology is found on routine physical examination. Typically, pain is heightened by sitting and improved by standing or walking. Pain is more often associated with malignant lesions and can be an ominous sign [2]. Constipation, urinary and fecal incontinence, and sexual dysfunction are typically seen with sacral nerve involvement from advanced tumors. Leg and gluteal symptoms are often associated with extension and mass effect.

Occasionally patients complain of longstanding perineal/sacrococcygeal discharge and their symptoms may be confused with perianal fistulas or pilonidal disease. Singer and colleagues reported on seven patients with presacral cysts (six females, one male). All patients had previously been misdiagnosed and treated for pilonidal cysts, perirectal abscesses, fistula in ano, psychogenic disorder, proctalgia fugax, and posttraumatic or postpartum pain before the correct diagnosis was made. Patients underwent an average of

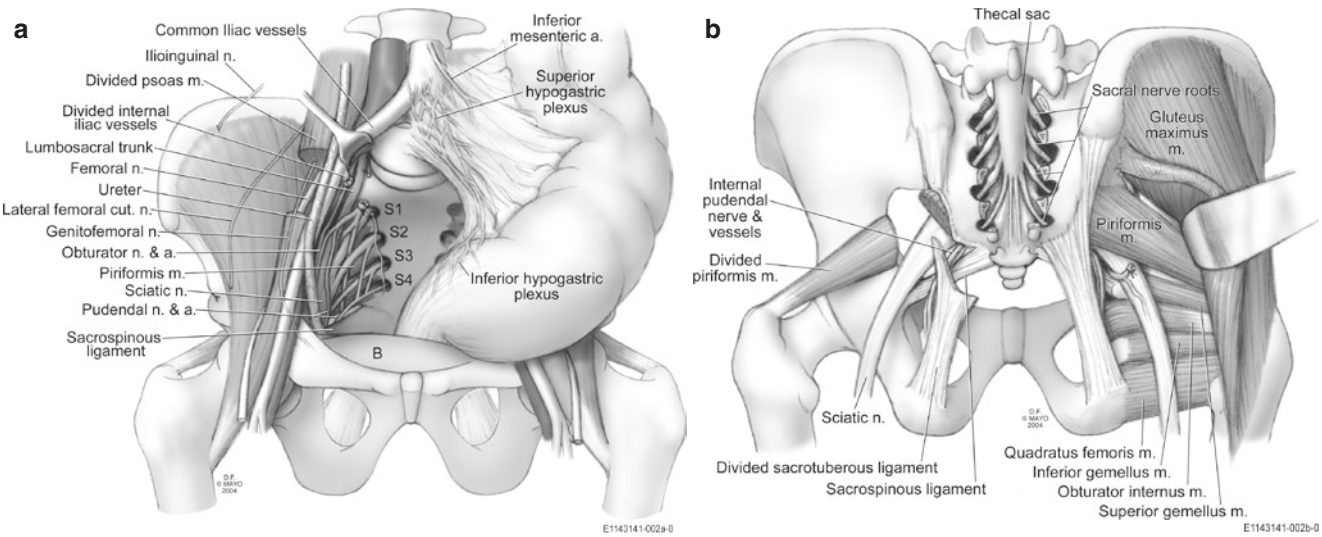

Fig. 21.2 (**a**) Anterior view of the pelvic anatomy. (**b**) Posterior view of the pelvic anatomy. (Reused with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

4.1 prior operative procedures. All patients were successfully treated with resection through a parasacrococcygeal approach after the correct diagnosis was made [9]. Multiple unsuccessful attempts at treatment of anal fistula or pilonidal disease should alert the surgeon to the possibility of a presacral cystic lesion.

Physical Examination

Physical examination should focus on the perineum and rectum. In all but a very small percentage of patients' digital rectal examination will reveal the presence of an extra-rectal mass displacing the rectum anteriorly [2]. It also allows one to determine fixation to the rectal wall and relation to surrounding structures such as the prostate, vagina, and coccyx/sacrum. Evaluation for a post-anal dimple should also be performed. A rigid or flexible proctosigmoidoscopy should be completed to evaluate the mucosa and potentially the upper and lower extent of the tumor. The most common endoscopic appearance is normal mucosa with extrarectal mass effect. The presence of abnormal and/or inflamed mucosa is often suggestive of infection/prior infection or erosion into the rectal wall. Neurologic evaluation of musculoskeletal reflexes and sacral nerve function should be performed if clinically indicated.

Imaging Studies

Anterior/posterior and lateral radiographs are of limited utility, but if obtained can identify osseous expansion, destruction, and/or calcifications of soft tissue occupying masses. In patients with an anterior meningocele, the characteristic "scimitar sign" can often be seen on sacral views. Endorectal ultrasound can be performed at the same time as flexible sigmoidoscopy to assess for invasion of the rectal wall or anal sphincter complex.

Computed tomography (CT) and magnetic resonance imaging (MRI) have dramatically changed the way presacral tumors are evaluated. Both CT and MRI can distinguish between cystic, solid, or mixed (cystic and solid) tumors, and can determine if other pelvic structures (rectum, bladder, ureters, etc.) are involved. Each modality can also define the anatomic extent of the mass, facilitate an accurate diagnosis, and establish the optimal surgical approach (anterior, posterior, or combination). Given the high soft tissue resolution, MRI has become the gold standard imaging modality for evaluating presacral tumors [10, 11]. Magnetic resonance imaging is more sensitive than CT for determining associated cord abnormalities such as sacral nerve root involvement, foraminal encroachment, and dural sac compression [12]. The improved resolution of MRI more clearly defines bony involvement, pelvic sidewall invasion, arterial and venous anatomy, and invasion of surrounding structures (rectum, bladder, ureters, etc.) [11, 13]. Contrast enhanced MRI with gadolinium can also detect meningoceles, thus avoiding the risks associated with myelogram. CT or MR angiography/venography may provide additional information regarding vascular involvement. Preoperative diagnostic accuracy of MRI has been reported to be as high as 100%, with 50–88% sensitivity and 92–97% specificity for differentiating benign from malignant [14, 15]. Low T1 and high T2 signal, gadolinium enhancement, irregular or infiltrative margins, and lesions with heterogeneous and/or solid components are more often associated with malignancy [10, 14, 16].

Hosseini-Nik and colleagues developed an algorithmic approach for MR imaging of presacral tumors. They subdivided fat-containing masses into solid, cystic, or complex lesions. Solid lesions were further subdivided into well and ill defined. Non-fat containing masses were classified as solid or complex, and cystic. Cystic lesions were sub classified as unilocular or multilocular, and solid lesions were differentiated based on the presence or absence of sacral destruction. In addition, they also outlined an optimal MR imaging protocol. They recommend imaging of the pelvis utilizing 1.5 T or 3 T systems with multi-channel phased array torso coils. Multiplanar 2D or high spatial-resolution 3D T2-weighted (T2-W) pulse sequences, together with obliquely oriented 2D T2-W sequences along the long axis of the sacrum helps assess the relationship of the mass to the rectum, sacrum, sacral foramina, and nerve roots. Frequency-selective or inversion recovery fat-suppressed T2-weighted pulse sequences improves the dynamic range for T2-weighting and tissue contrast and also confirms the presence of macroscopic fat. Routine T1-weighted (T1-W) sequences with and without fat saturation examines for macroscopic fat and multiphasic contrast-enhanced acquisitions must be acquired for appropriate characterization. In-phase (IP) and out of phase (OP) T1 gradient-echo imaging is helpful in identifying intracellular lipid [11].

For patients with a presacral cystic lesion thought to be the source of a chronically draining sinus, a fistulogram may help clarify the diagnosis. Our study of choice in this situation is an MRI using fistula-protocol sequences similar to evaluations done in patients with perianal Crohn's disease or suspected occult cryptoglandular fistula-in-ano.

Preoperative Biopsy

Preoperative biopsies have been an ongoing topic of debate [8, 17–20]. Advances in high-resolution imaging have increased the ability to accurately diagnose presacral tumors without tissue [10, 14, 21]. The need for biopsy is predicated on whether the result will change preoperative or operative management. For example, the surgical approach and necessary margins differ significantly for neurofibroma as com-

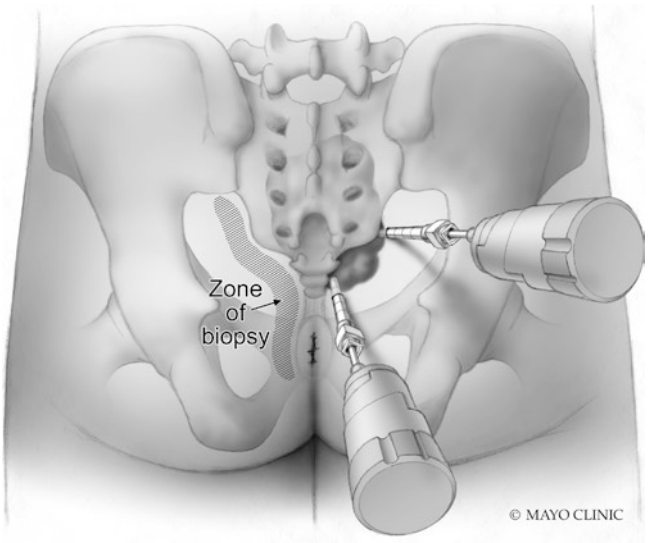

Fig. 21.3 Preoperative biopsy technique using CT guidance. (Reused with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

pared to neurofibrosarcoma. If biopsy is necessary, the intended operative approach should be discussed with the interventional radiologist performing the procedure. Either transperineal or parasacral approaches may be considered depending on the anticipated field of resection (parasacral for planned sacral resection). Needle biopsies should be performed within the field of the proposed area of resection so the needle tract can be resected en bloc with the specimen to decrease the risk of seeding and local recurrence (Fig. 21.3). The external needle entry site can be spot tattooed to aid in future identification. Transperitoneal, transrectal, and transvaginal biopsies should be avoided. If histopathology reveals malignancy, en bloc complete or partial excision of the rectum or vagina with the presacral mass becomes necessary if the biopsy tract traversed one of these organs. In addition, biopsies of tumors in this area can result in bowel perforation, bleeding, and fistulas. Biopsy of cystic lesions increases the risk of secondary infection, and recurrence after resection. Inadvertent biopsy of a meningocele may lead to disastrous sequel such as meningitis and death.

Although historically surgeons have recommended complete excision of any biopsy tract, recently there has been discussion on leaving the biopsy tract in situ. Messick and colleagues reported on 87 presacral tumors, of which preoperative tissue biopsies were obtained in 24/87 (28%). Only 4/24 (17%) underwent excision of the biopsy site to evaluate the tissue (all negative for malignancy). The remaining 20 did not undergo surgical excision of the biopsy site and were followed clinically (or by radiographic imaging) with no reported tumor recurrences in the tract site [4]. Further investigation and evidence is needed before any definitive recommendations can be made on avoidance of biopsy site excision for malignant tumors.

Some patients benefit from neoadjuvant chemotherapy, radiation, hormonal, or immunotherapy, and a tissue diagnosis is often required to make that determination. Large pelvic desmoids can be removed more easily after reducing their size with neoadjuvant radiotherapy. Preoperative chemotherapy and radiotherapy improves outcomes with osseous tumors such as Ewing's sarcoma, osteogenic sarcoma, and neurofibrosarcoma. Hormonal therapy has shown benefit in reducing the size of giant aggressive angiomyxomas, and immunotherapy is showing promise for treating advanced chordomas [22–24]. Thus, when performed safely, a preoperative biopsy can optimize overall management [4, 19].

Classification

The presacral space is primarily composed of connective tissue, nerves, fat, and blood vessels. Totipotential cells that differentiate into three germ cell layers (endoderm, ectoderm, mesoderm) make up the complex embryologic potential space, which can lead to the development of a multitude of tumor types. The original classification described by Uhlig and Johnson divided tumors into congenital, neurogenic, osseous, and miscellaneous [29]. We have modified and updated the classification scheme to subcategorize tumors as malignant or benign, as this greatly impacts therapeutic approaches (Table 21.1).

Lesions found in the presacral space can be broadly classified as congenital or acquired and benign or malignant. Congenital lesions result from abnormalities in embryological processes (fusion of hindgut and proctodeum, degeneration of the notochord, etc.), whereas acquired tumors develop from remnant embryonic or other differentiated tissues found in the presacral space. In general, two-thirds are congenital, of which two-thirds are developmental cysts, with the next most common masses being neurogenic tumors [30]. Around 45–50% are malignant or have malignant change within them [2, 31]. Understanding the various subtypes, disease behavior, and malignant potential is essential to tailor treatment [16].

Epidermoid and Dermoid Cysts

Epidermoid and dermoid cysts (Fig. 21.4) are more common in females, tend to be well circumscribed, have a thin outer layer, result from defects during closure of the ectodermal layer, and are typically benign. They occasionally communicate with the skin surface creating a characteristic postanal dimple and are histologically composed of keratinized stratified squamous epithelium. The cysts are often misdiagnosed

Table 21.1 Mayo classification of presacral tumors

	Benign	Malignant
Congenital	Adrenal rest tumor	Chordoma
	Anterior sacral meningocele	Germ cell tumor
	Developmental cysts (dermoid, epidermoid [aka epidermal], enterogenous [aka rectal duplication], tailgut [aka cystic hamartomas/mucous secreting], teratoma)	Malignant developmental cysts
		Teratocarcinoma
Neurogenic	Ganglioneuroma	Ependymoma
	Neurofibroma	Ganglioneuroblastoma
	Schwannoma (aka neurilemoma)	Malignant schwannoma
		Neuroblastoma
		Peripheral nerve sheath tumors (aka neurofibrosarcoma)
		Primitive neuroectodermal
Osseous	Aneurysmal bone cyst	Chondrosarcoma
	Giant cell tumor	Ewing's sarcoma
	Osteoblastoma	Giant cell tumor
	Osteoma	Myeloma
	Simple bone cyst	Osteogenic sarcoma
		Plasmacytoma
		Reticulum cell sarcoma
		Spindle cell sarcoma
Miscellaneous	Aggressive angiomyxoma	Angiosarcoma
	Benign GIST	Carcinomasarcoma
	Benign hemagiopericytoma	Degenerated hamartoma
	Desmoid (aka fibromatosis)	Epithelioid sarcoma
	Ectopic kidney	Fibrosarcoma
	Endothelioma	Fibromyxoid sarcoma
	Fibroma	Histiosarcoma
	Hamartoma	Hydatid cyst
	Hemangioma	Leiomyosarcoma
	Leiomyoma	Liposarcoma
	Lipoma	Lymphoma
	Lipofibroma	Malignant desmoid
	Myelolipoma	Malignant hemagiopericytoma
	Pecoma	Malignant GIST
	Solitary fibrous tumor	Malignant solitary fibrous tumor
	Tuberculosis	Metastatic carcinoma
		Myeloliposarcoma
		Neuroendocrine tumors
		Rhabdomyosarcoma
		Small cell tumor
		Spindle cell tumor
		Squamous cell carcinoma
		Undifferentiated sarcoma

GIST gastrointestinal stromal tumor

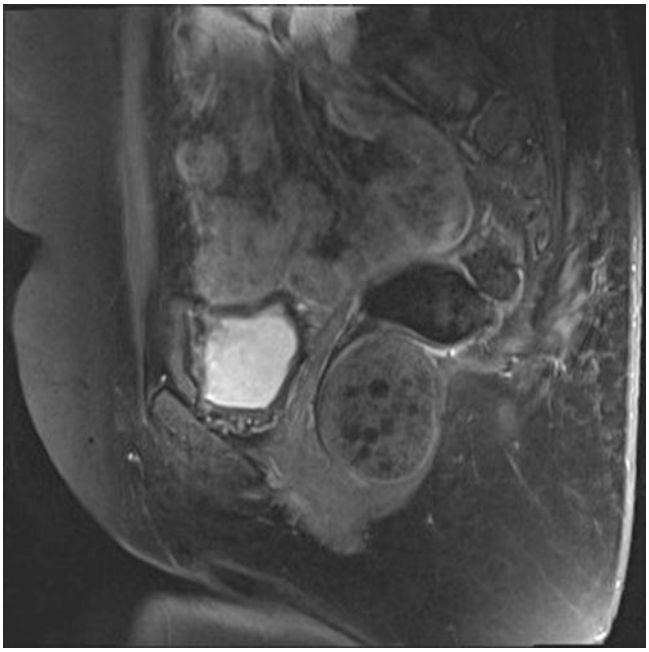

Fig. 21.4 MRI of dermoid cyst. (Reused with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

as perirectal abscesses and can become infected with manipulation. Recurrently infected cysts have been associated with the development of squamous cell carcinoma [1]. Dermoid cysts may contain skin appendages (sweat glands, hair follicles, sebaceous cysts) whereas epidermoid cysts do not [9].

Tailgut Cysts

Tailgut cysts (cystic hamartomas/mucous secreting cysts) are congenital lesions arising from remnants of normally regressing postanal primitive hindgut and are more common in females. The cysts are lined with columnar epithelium and can morphologically resemble the adult or fetal intestinal tract [32]. They do not communicate with the rectal lumen and are often multiloculated or biloculated, and well defined and homogenous (Fig. 21.5). The presence of glandular or transitional epithelium differentiates them from epidermoid and dermoid cysts. Malignant transformation has been reported in some series [27, 33–35].

Enterogenous Cysts

Enterogenous cysts (rectal duplication cysts) are more common in women, often in communication with the rectum, and are thought to derive from the developing hindgut. Since they originate from endodermal tissue they can be lined with squamous, cuboidal, columnar, or transitional

epithelium. Unlike epidermoid, dermoid, and tailgut cysts they have a well-defined muscular wall with a myenteric plexus. The lesions tend to be multi-lobular with one dominant and smaller satellite cysts. In order to be classified as a rectal duplication cysts three anatomic criteria must be met: the cyst must be attached to the alimentary tract; it must be lined by a mucous membrane similar to that part of the gastrointestinal tract; and it must possess a smooth muscular coat. Enterogenous cysts are generally benign, but there are case reports describing malignant transformation [25, 36].

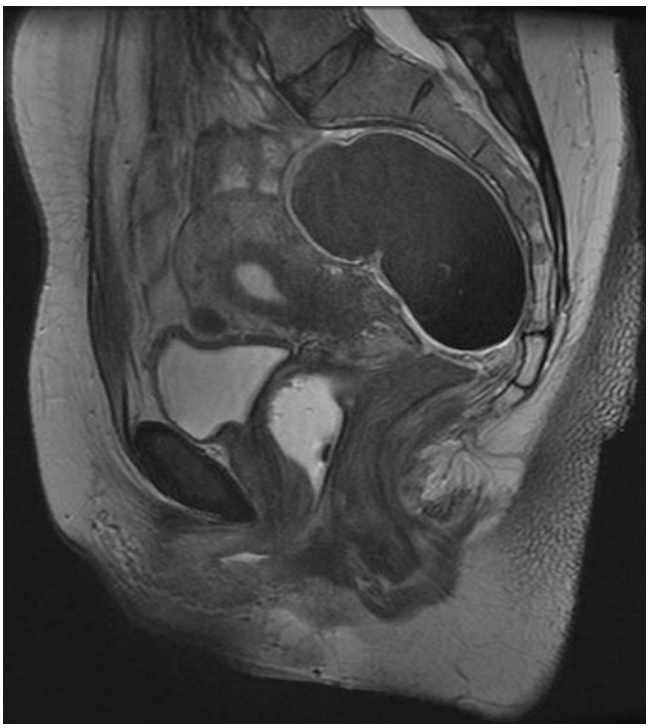

Fig. 21.5 MRI of tailgut cyst. (Reused with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

Teratomas

Sacrococcygeal teratomas are neoplasms that may include all three germ layers (totipotential cells), can contain both solid and cystic components, and are more common in the pediatric age group and females. These tumors can contain tissues from almost any organ system including digestive, nervous, respiratory, and skeletal [37]. Histologically, tumors are referred to as either mature or immature, which reflects the degree of cellular differentiation. The more recognizable the elements (hair, bone, teeth) the more likely the tumor is to be benign, although all should be viewed as potentially malignant. Cystic components are typically benign whereas solid components are more often associated with malignant degeneration. The tumors can reach considerable size and diagnosis is often delayed (Fig. 21.6a–c). Teratomas are often associated with anomalies of the vertebra, urinary tract, and anorectum [38]. The rate of malignancy correlates strongly with age, being much less common beyond the second decade [20, 39]. In infants only 7% of girls and 10% of boys presented with malignancy prior to 2 months, whereas the rates can be as high as 48% and 67%, respectively, after 2 months of age [40]. Malignant degeneration can occur in adults, and incomplete or intralesional resection increases the likelihood of malignant degeneration [41–43]. Because of the diverse germ cell layers these lesions can transform into squamous cell carcinoma (ectodermal origin), rhabdomyosarcoma (mesenchymal origin), or anaplastic (indeterminate cell of origin) tumors [3].

Chordomas

Sacrococcygeal chordomas are the most common malignant tumor of the presacral space. The lesions are more common in male patients and rarely encountered in those less than 30 years of age [2, 44]. They are thought to arise from vesti-

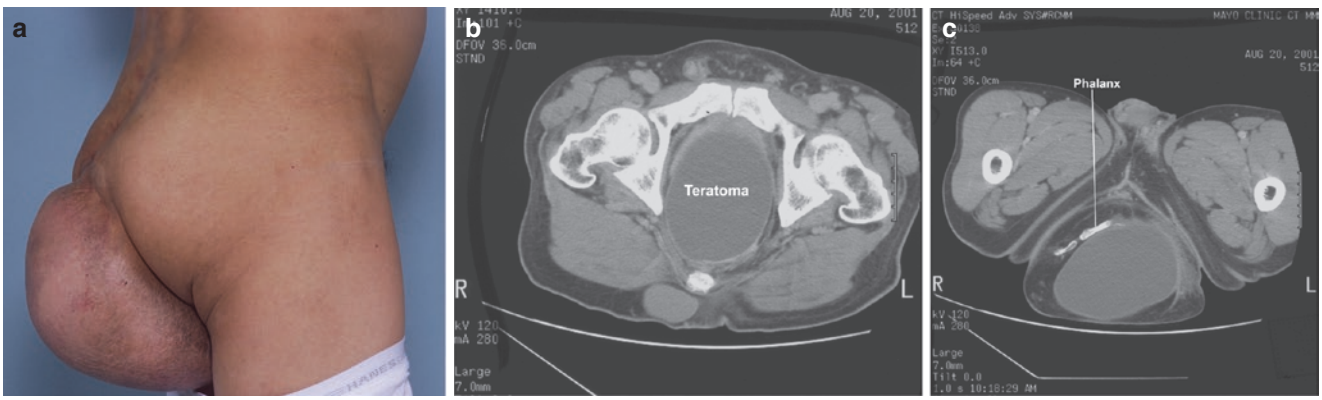

Fig. 21.6 (**a**) Massive cystic teratoma with sacral appendage. (**b**) CT of intrapelvic portion. (**c**) CT of extrapelvic portion with fully developed phalanx. (Reused with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

gial notochord tissue, which embryologically extends from the base of the occiput to the caudal limit in the embryo. The lesions can occur almost anywhere on the spinal cord but are most commonly found in the pheno-occipital region at the base of the skull and the sacrococcygeal region in the pelvis [45, 46]. Symptoms are often vague and include low back, pelvic, and buttock pain, which is aggravated by sitting and alleviated by standing. As a result of the vague symptomology diagnosis is often delayed and the tumors can reach considerable size and result in constipation, fecal and urinary incontinence, and sexual dysfunction. Centrally chordomas contain extracellular mucin and can be soft, firm, or gelatinous. The tumors often contain areas of hemorrhage and can invade or destroy bone and soft tissues and distend into adjacent regions. Local and distant recurrence rates have been documented as 43% and 22%, respectively, and 5- and 10-year survival rates are 67% and 40% [47]. Resection with negative margins is the treatment of choice [47–50].

Meningoceles

Anterior sacral meningoceles arise from protrusions of the thecal sac through a defect in the sacrum, contain cerebrospinal fluid, and can be seen in conjunction with presacral cysts and lipomas. The classic radiographic finding is the "scimitar sign" (sickle-shaped sacrum/hemisacral agenesis), which is a unilateral well-marginated, crescent-shaped defect in the lateral sacrum (Fig. 21.7). Symptoms can include headaches related to postural changes and the Valsalva maneuver (straining/coughing), low back and pelvic pain, constipation/defecatory dysfunction, dyspareunia, and urinary urgency, retention, or incontinence [51]. Anterior sacral meningoceles can be associated with other congenital anomalies including urinary tract and/or anal malformations, uterine and/or vaginal duplication, tethered spinal cord, and spina bifida. These lesions should not be biopsied due to the risk of bacterial contamination of the cerebrospinal fluid and development of iatrogenic meningitis [52]. Surgical treatment consists of obliterating the communication between the subarachnoid space and herniated sac, detethering the spinal cord, and resecting the congenital tumor [53].

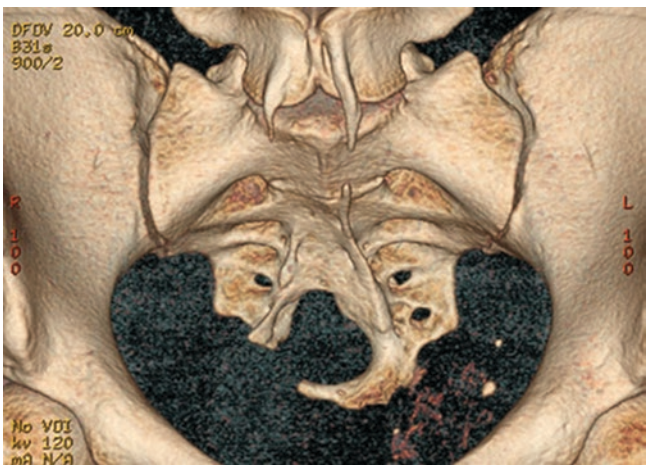

Fig. 21.7 CT pelvis scimitar sign. (Reused with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

Neurogenic Tumors

Neurogenic tumors arise from the peripheral pelvic nerve plexus (Fig. 21.8a and b), make up approximately 10–15% of all presacral masses, and typically affect younger patients (median age 38). Although the vast majority (>90%) are benign, at times differentiating benign from malignant tumors can be difficult without a tissue biopsy. Schwannomas and ependymomas are the two most commonly encountered lesions [2, 26, 48]. Presenting symptoms can include neuropathies and low back and pelvic pain. Benign and malignant tumors have a high local recurrence rate, and survival for malignant tumors is poor. Early detection and aggressive surgical intervention are necessary to improve outcomes. With the use of a nerve-sparing technique a function-preserving resection can be safely completed with an overall improvement in symptoms [54, 55]. The goal is sacral nerve root preservation, but sacrifice may be required for extended resections for malignant tumors.

Osseous Tumors

Osseous lesions that grow into the presacral space make up less than 10% of presacral tumors and can arise from bone, cartilage, fibrous tissue, and marrow. They are more commonly found in males and half are malignant at the time of diagnosis [18]. Osseous tumors can reach considerable size and cause significant local destruction. They have pronounced metastatic potential, with pulmonary being the most common [56]. Although benign, giant cell tumors of the sacrum can metastasize to the lung and transform to a fulminate malignant variant, which has a very poor prognosis [57].

Miscellaneous Lesions

Miscellaneous masses in the presacral space can include heterogeneous pathologies including carcinoids, gastrointestinal stromal tumors, dermoids, angiomyxomas, metastatic deposits, ectopic kidneys, and hematomas [58].

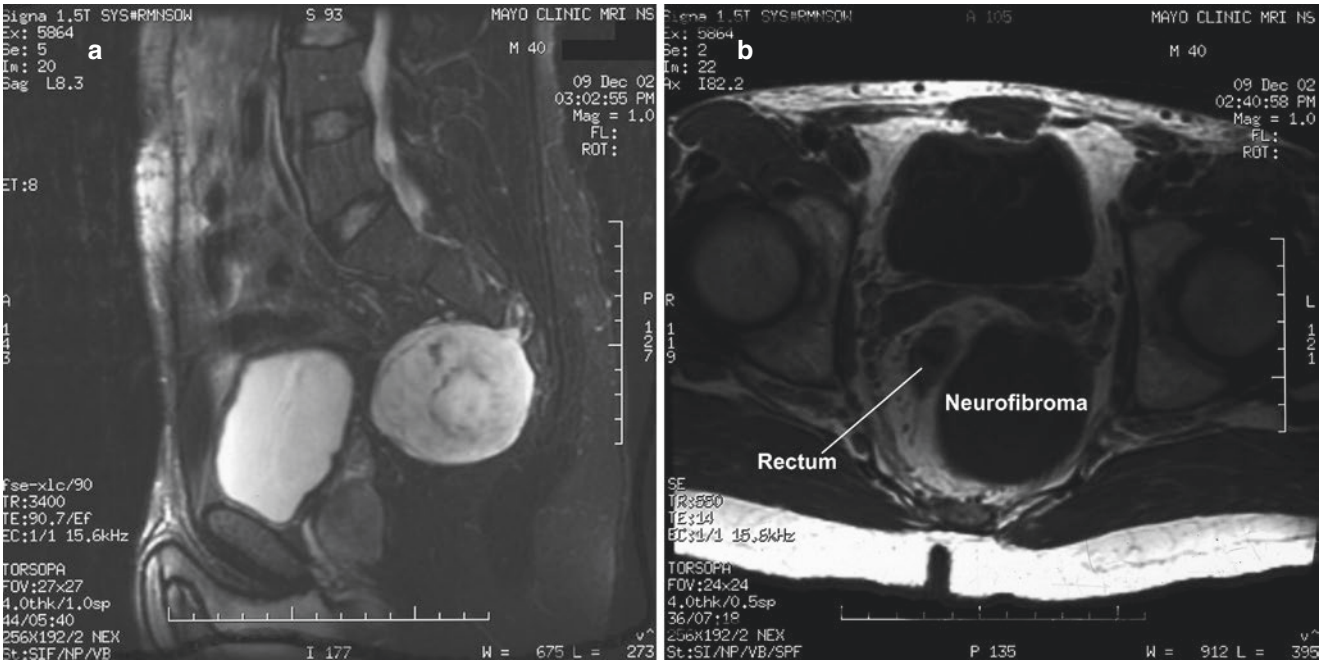

Fig. 21.8 (**a**) T2 weighted pelvic MRI of neurofibroma extending from the third sacral foramina. (**b**) T1 weighted pelvic MRI of neurofibroma. (Reused with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

Currarino Syndrome

Surgeons seeing patients with presacral tumors should be familiar with Currarino syndrome. Currarino syndrome, described in 1981 is a rare congenital malformation associated with three main features: sacral malformation (agenesis or sickle shape), hindgut anomaly, and presacral tumor [59]. It is an autosomal dominant disorder linked to mutations in the HLXB9 gene, although sporadic cases have been described [59, 60]. To date, 43 heterozygous mutations have been reported [61]. As a result, patients can present with variable phenotypes including spinal cord anomalies (tethered cord, thickened filum, syrinx), genitourinary malformations, anorectal and gynecological anomalies, and presacral lesions. More than one presacral lesion can occur in the same patient [62]. The most commonly associated presacral mass is dermoid cyst, although teratomas have been identified in 25–40% of cases. Malignancy in Currarino syndrome is rare and only a small number of adult (19–45 years old) patients with malignant teratoma have been described [39, 63]. An abnormal looking sacrum on imaging is often the tip off that a patient has Currarino syndrome.

Management

The recommendation for treating presacral tumors has historically been surgical resection. Operative indications include known malignancy, concern for future malignant transformation, alleviation of symptoms, and a consistent increase in size (which may make future resection more risky). Small tumors can be addressed independently by colon and rectal surgeons specifically trained to manage these lesions. Larger lesions, or those associated with neuromusculoskeletal structures, are best managed by a multidisciplinary team that can bring specialty expertise to decision-making and assist in a safe surgical approach. For locally adherent malignant tumors, en bloc removal of adjacent organs, soft tissue, and bone is the goal of oncologic resection. At our institution, we have established a decision-making algorithm to guide the management of presacral tumors (Fig. 21.9a and b). The principles that should guide the surgical team include a function-sparing approach for benign lesions and an en bloc oncologic approach for malignant lesions.

There is recent literature supporting nonoperative surveillance (serial imaging) for small cystic lesions without symptoms or suspicious radiologic features [28], although the proof for advisability of this approach needs further investigation. Hopper and colleagues followed six cystic lesions with serial imaging for a median of 20 months (range, 5–66). Interval imaging ranged from every 6 months to every 2 years. At last follow-up, four (67%) were noted to be stable in size [28]. In our own practice, we consider an observational approach for small (<5 cm), asymptomatic neurogenic tumors.

Multidisciplinary Team

An experienced multidisciplinary team is critical for optimal outcomes in patients with complex presacral tumors

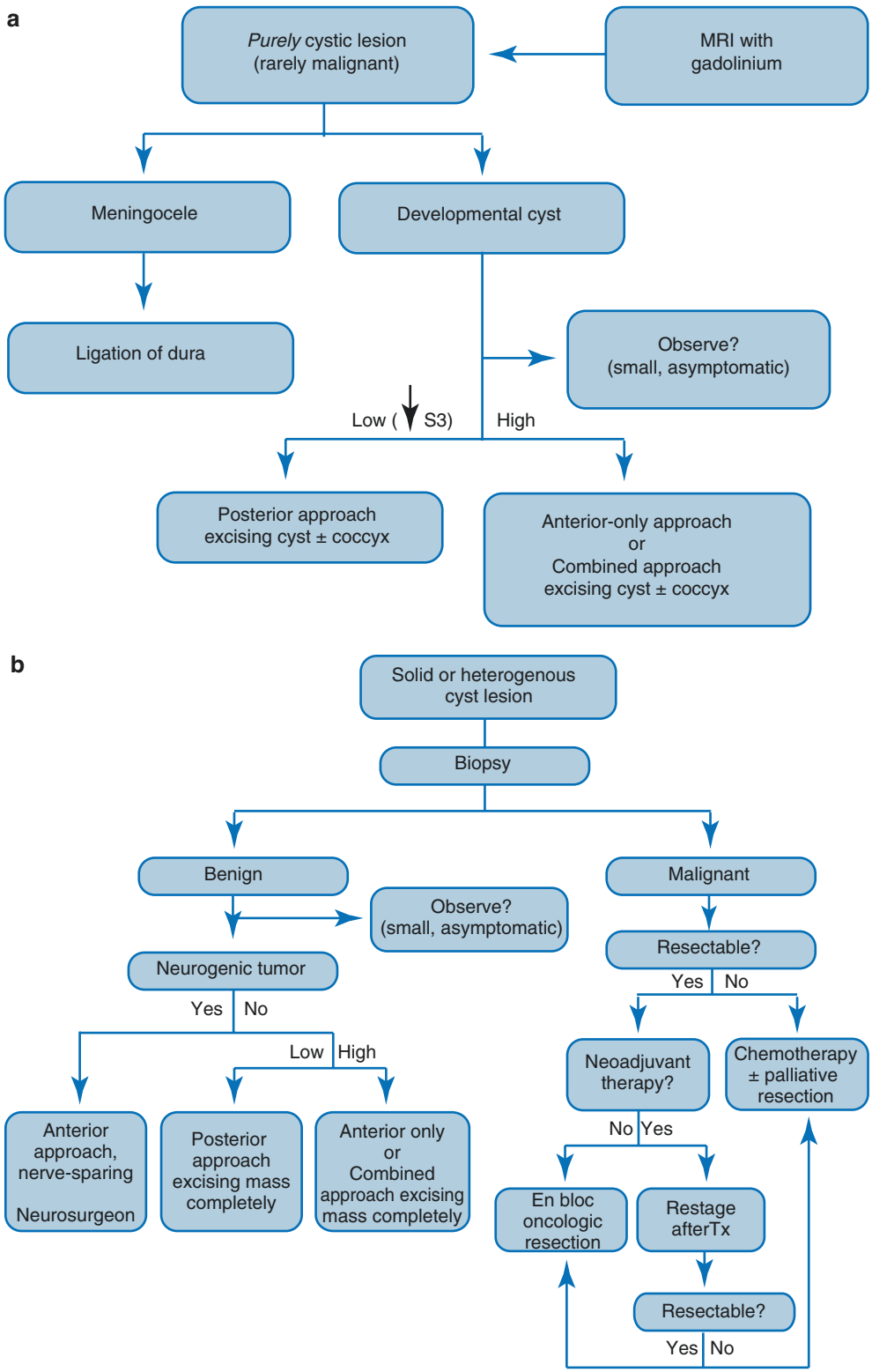

Fig. 21.9 (**a**) Proposed treatment algorithm for purely cystic lesions. (**b**) Proposed treatment algorithm for solid or heterogenous cystic lesions. (Reused with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

[64]. The team may consist of surgeons from colorectal, orthopedic oncology, spine, neurosurgery, urology, vascular, and plastic surgery, as well as medical oncology, radiation oncology, musculoskeletal radiologists, and anesthesiologists with special expertise in complex presacral tumors [26, 65]. A formal discussion at multidisciplinary team conferences is essential for perioperative planning and treatment.

Neoadjuvant Therapy

Although many malignant presacral tumors, such as chondrosarcomas and chordomas, are poorly responsive to radiotherapy and chemotherapy, there are a number which are responsive. The addition of neoadjuvant therapy can decrease tumor size, increase resectability, and potentially decrease the rate of local recurrence. Compared to postoperative administration, the irradiation treatment field in the preoperative setting is smaller and results in less morbidity. Ewing's and osteogenic sarcomas are often associated with metastasis and neoadjuvant chemotherapy is a cornerstone of therapy. Providing chemotherapy in a neoadjuvant setting allows for treatment of micrometastatic disease prior to surgery, as well as decreases delays in chemotherapy treatment that may occur should the patient suffer postoperative complications.

The use of neoadjuvant therapy for presacral sarcomas has been extrapolated from protocols for treating soft tissue sarcomas. Radiation therapy has been shown to decrease local recurrence following resection of both retroperitoneal and extremity sarcomas [66, 67]. Others have shown chemotherapy, with and without radiation, trends toward an improved survival and decreases local and distant relapses for extremity and retroperitoneal sarcomas [26, 68–70].

Due to small case series and heterogeneity in patient populations, it is unclear if patients with malignant cysts benefit from neoadjuvant chemoradiotherapy. We have used this approach in patients with malignant cysts that have either squamous cell carcinomas or adenocarcinomas within them, with the rationale that chemoradiotherapy works well in patients with adenocarcinomas of the rectum and squamous cancers of the anus.

Preoperative Considerations

Optimizing patients for surgery is of paramount importance. When possible, anemia should be improved, protein calorie malnutrition enhanced, and debility reduced. For patients presenting in a debilitated state, social work consultation prior to surgery is important for postoperative rehabilitation and care planning. To decrease intraoperative bleeding, preoperative selective coil embolization of feeding vessels may be useful in some patients with large vascular tumors like hemangiopericytomas (Fig. 21.10a–c) [71].

For complex tumors, the multidisciplinary team should review films and operative planning together before surgery. Significant bleeding can occur with complex resections, and the blood bank should be alerted ahead of time to make sure adequate product is available. An operating room team (anesthesiologists, nurses, assistants, etc.) comfortable with complex pelvic surgery is needed for these procedures.

Surgical Approach

The location, involvement of other pelvic structures, and surgeon experience dictates the operative approach. For tumors superior to the S3–4 sacral bodies, a purely abdominal (anterior) approach should be pursued, while lesions entirely inferior to the S3–4 sacral bodies can be approached through a posterior sacral incision. For tumors extending both proximal and distal to the S3–4 sacral bodies, a combined anterior and posterior approach is often utilized (Fig. 21.11) [10, 21, 65].

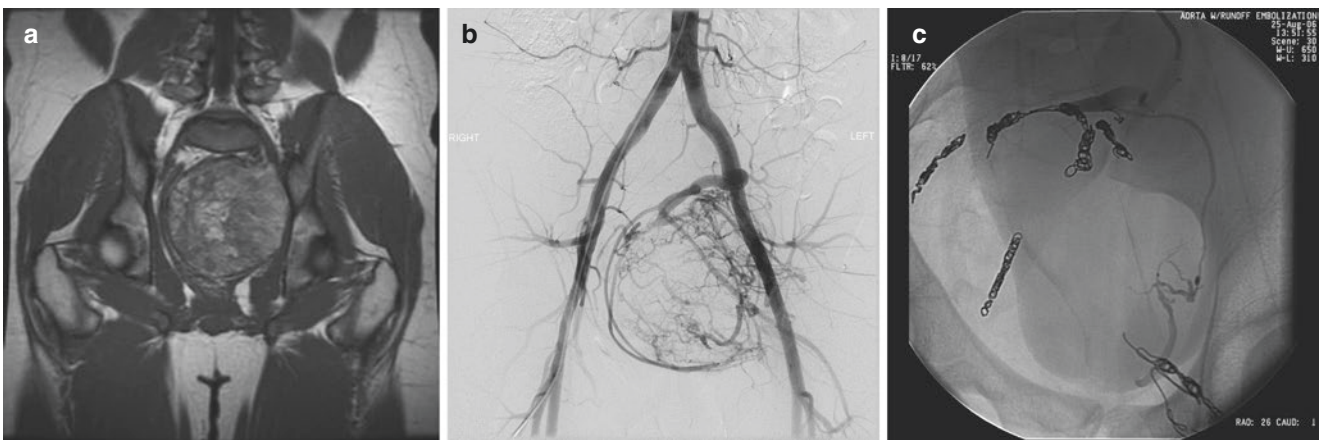

Fig. 21.10 (**a**) MRI of hemangiopericytoma. (**b**) Angiogram of hemangiopericytoma. (**c**) Post-coil embolization of hemangiopericytoma. (Reused with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

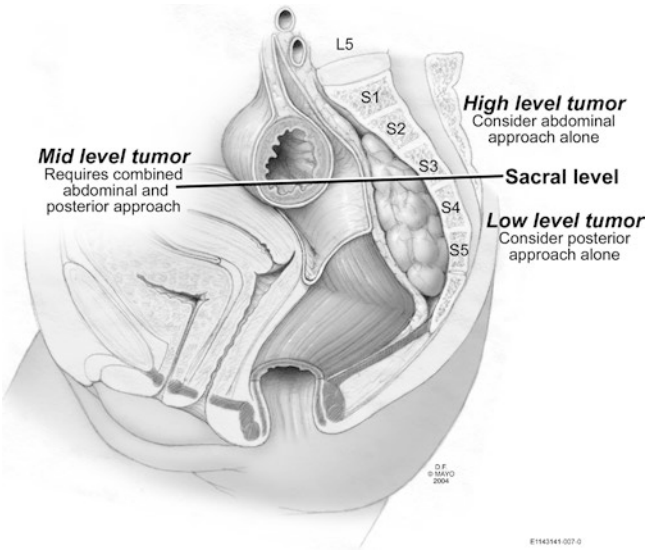

Fig. 21.11 Relationship of tumor to sacral level and proposed approach. (Reused with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

Posterior Approach

The patient is placed in a prone jackknife position and the buttocks are taped apart (Fig. 21.12a). Depending on surgeon experience and preference, an incision (midline, parasacral, paracoccygeal, transverse, and curvilinear to the left of the lower sacrum/coccyx and into the intergluteal fold) is created. The dissection is carried down to the distal sacrum/coccyx and through the anococcygeal ligament, taking care to avoid damage to the sphincter complex. The centrally decussating muscle fibers of the levator muscle (levator plate region) are removed from the tip of the coccyx allowing entry into the presacral space. A pseudocapsule is often encountered and helps facilitate a safe dissection from surrounding tissues including the rectum. A coccygectomy can be performed to facilitate exposure and resection of larger tumors or ones tethered to the coccyx (Fig. 21.12b). The surgeon may double-glove the non-dominant hand, and with the index finger in the anal canal and lower rectum, push the lesion outward to assist with dissection of the tumor from the posterior wall of the rectum (Fig. 21.12c). If necessary, the lower sacrum and/or coccyx can also be excised en bloc with the tumor. If there is concern for local invasion a portion of the rectal wall may need to be excised and the defect closed in layers, otherwise the rectum should be left intact. Rectal integrity can be evaluated with a rigid or flexible endoscope and an air leak test performed by submerging the open operative field with irrigation.

There has been ongoing debate regarding the utility of coccygectomy for every low presacral tumor. Some authors advocate that coccygectomy improves exposure and decreases the risk of recurrence, as the coccyx may harbor a nidus of totipotential cellular remnants that may later evolve into a recurrent cyst [31, 38, 42]. However, multiple studies demonstrating low recurrence rates without coccygectomy support the idea that routine coccygectomy is unnecessary and potentially adds morbidity to patients. Singer et al. did not perform a coccygectomy in six of the seven patients (86%) with benign lesions in their study and saw no difference in recurrence [9]. Mathis and colleagues performed a coccygectomy in 7/28 patients, all of whom underwent resection of presacral tailgut cysts, and reported only a single recurrence (4%) [27]. Messick et al. performed a coccygectomy in 51% of the patients in their series (44/87) and did not appreciate a difference in recurrence for those who did (14%) and did not (20%) undergo resection of the coccyx [4]. We favor coccygectomy in patients with sacrococcygeal teratomas which are uniformly adherent to the coccyx and likely have the highest risk of recurrence if any cyst components are left behind.

Abdominal and Combined Anterior and Posterior Approach

For tumors completely above S3–S4 with no sacral involvement a transabdominal approach can be utilized. If the upper pole of the tumor extends above S3 a combined anterior and posterior approach is usually indicated. Patients can be placed in a variety of positions including supine, synchronous (modified dorsal lithotomy), and modified "sloppy" lateral (Fig. 21.13a–c). For larger tumors bilateral ureteral stents can be placed after induction.

Depending on tumor characteristics (benign/malignant, local invasion) and surgeon experience and comfort either an open or minimally invasive approach is utilized. The abdomen is carefully explored to rule out disseminated disease and other pathology. The lateral attachments of the sigmoid colon are mobilized and the presacral space entered. Ureters and superior hypogastric nerves are identified and preserved. The mesorectum is dissected off the presacral fascia to the level of the upper extension of the tumor. The rectum is mobilized to facilitate identification and exposure of the pathologic area of interest. If the tumor can be safely separated circumferentially from the rectum, presacral fascia, and lateral pelvic sidewalls the dissection can proceed until the mass is removed. Bulky tumors make visualization difficult and may preclude safe dissection between the lesion and rectum. In this event the rectum can be excised en bloc with the tumor, and intestinal continuity reestablished following removal. If the tumor invades both S2 or S3 nerve roots excision of the rectum en bloc with the mass and creation of a permanent colostomy is appropriate since the patient will be rendered incontinent. During mobilization of malignant tumors, no structures attached to the specimen should be

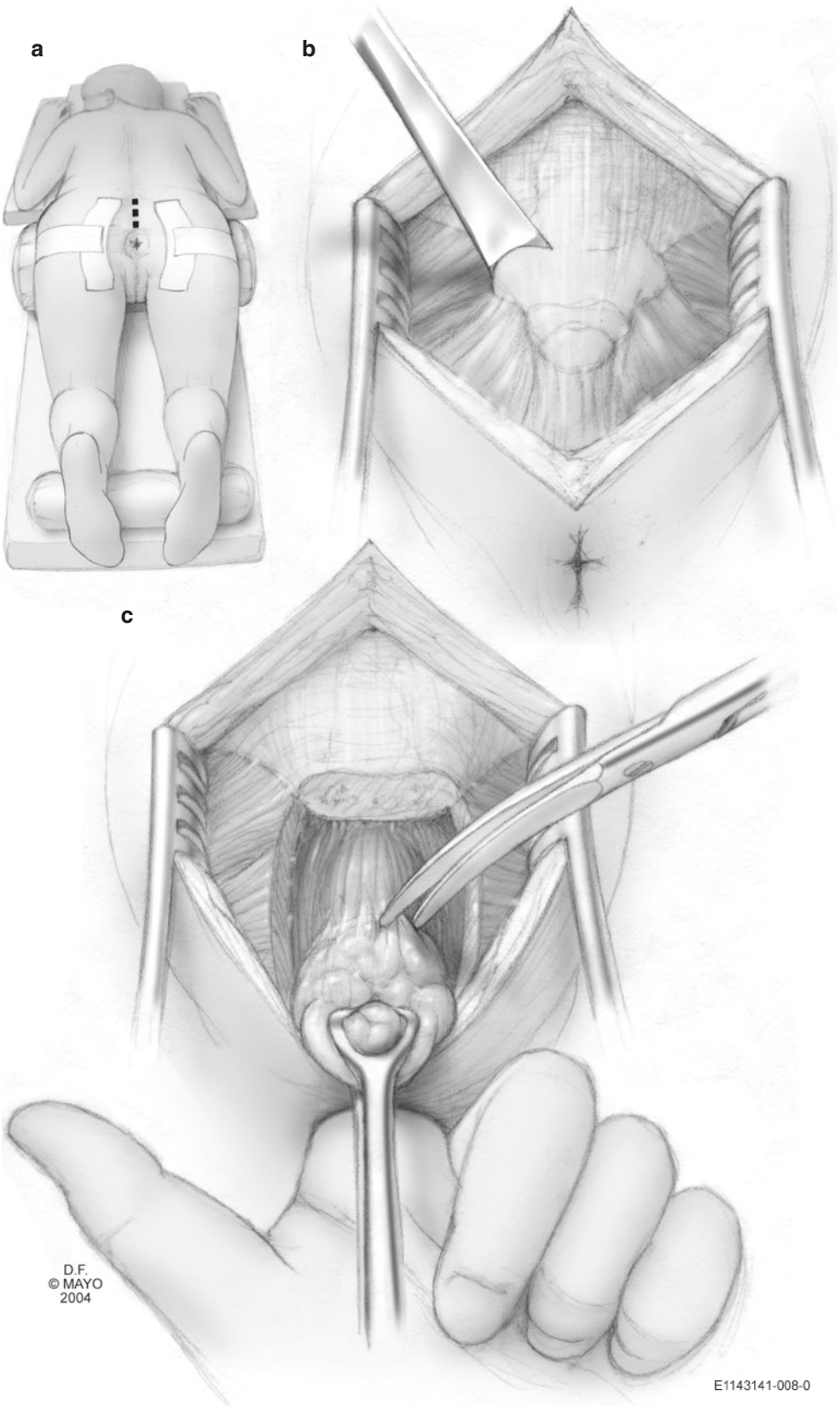

Fig. 21.12 (**a**) Positioning for posterior approach. (**b**) Coccygectomy. (**c**) Index finger in anal canal to "push" tumor outward facilitating dissection. (Reused with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

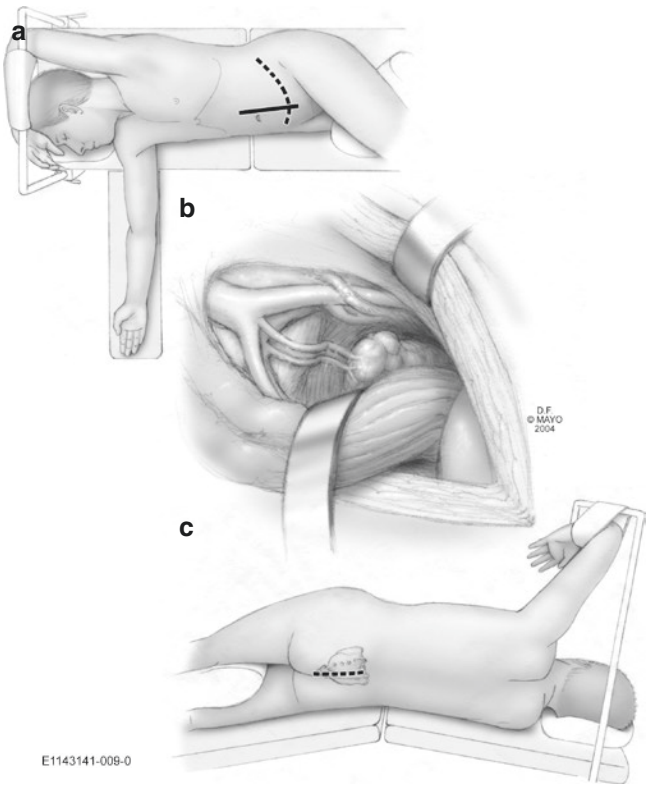

Fig. 21.13 (**a**) Modified lateral position for anterior exposure vis a midline (solid line) or ilioinguinal (dotted line) incision. (**b**) Anterior exposure of vessels and tumor. (**c**) Posterior approach to the sacrum. (Reused with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

separated (ureter, bone, vasculature, nerve, etc.), instead they should be removed en bloc with the tumor.

Substantial blood loss can occur during resection of large presacral tumors, especially in those requiring en bloc sacrectomy. Middle sacral vessels are often significantly enlarged. Selective ligation of the middle sacral artery and in some cases, the internal iliac vessels and their branches, can reduce blood loss (Fig. 21.14). Preoperative catheter based venous and/or arterial embolization can be considered when significant bleeding is anticipated. Preservation of the anterior division of the internal iliac artery and internal gluteal branches reduces the risk of perineal and gluteal necrosis. Multidisciplinary planning with vascular surgery is prudent for cases where significant vascular dissection is anticipated, especially for patients with prior irradiation or anticipated distorted vascular anatomy.

For expected large pelvic or postsacral defects, a plastic surgeon should be involved for tissue interposition/reconstruction. Multiple options are available such as vertical rectus abdominis myocutaneous (VRAM) flap, transverse rectus abdominis (TRAM) flap, omental pedicle flap, gracilis flaps, and gluteus myocutaneous flap (local or V–Y advancement) closures.

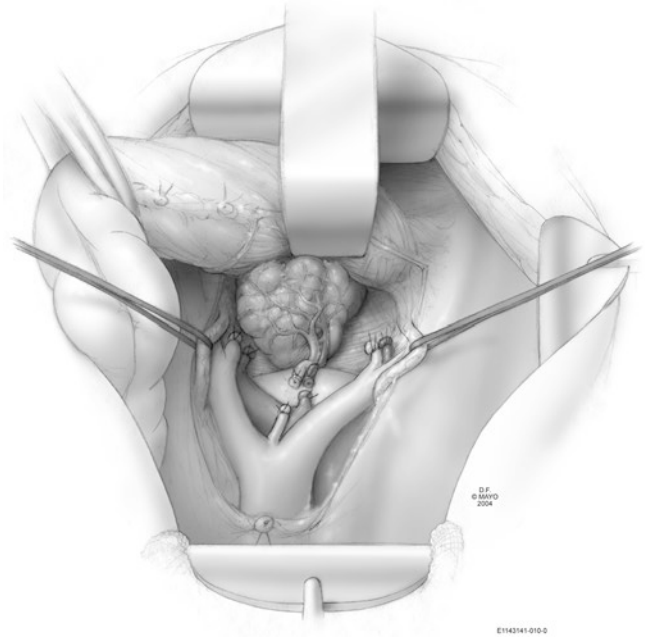

Fig. 21.14 Ligation of middle sacral and internal iliac vessel. (Reused with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

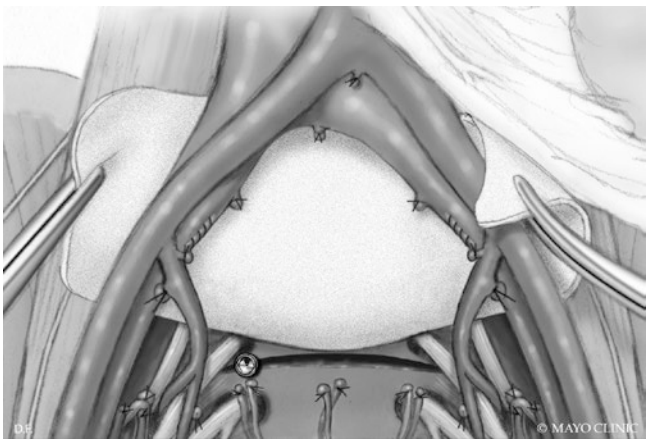

Fig. 21.15 Placement of silastic mesh to protect pelvic vasculature during posterior osteotomies. (Reused with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

For extended sacral involvement it is often necessary to change patient positioning. After the anterior dissection is completed, the abdomen closed, and colostomy matured, the patient is placed in a prone position for the posterior dissection. To reduce injury to vital structures (arteries/veins/ureters) when performing the posterior sacral transection a protective barrier (thick piece of silastic mesh or plastic sheeting, laparotomy pads, etc.) can be placed directly anterior to the sacrum (Fig. 21.15). The mesh will also help protect a pedicled flap that has been placed in the pelvis in preparation for later extraction for perineal reconstruction once the sacrum has been removed. After placing in a prone

position, a midline incision is made over the sacrum and coccyx down to the anus. The anococcygeal ligament is ligated and levator muscles retracted bilaterally. Orthopedic surgery can then continue with dissection of the gluteus maximus muscles bilaterally, transection of the sacrotuberous and sacrospinous ligaments (Fig. 21.16a), and division of the piriformis muscles to expose the sciatic nerves (Fig. 21.16b). An osteotomy is then performed at the desired level exposing and preserving uninvolved sacral nerve roots. For sacral resection in the region of S2–S3 or higher, the thecal sac should be closed with an absorbable suture to decrease issues with cerebrospinal fluid leak or life threatening intra-dural infection (Fig. 21.16c). The tumor is then removed en bloc with the sacrum, coccyx, and involved sacral nerve roots, with or without the rectum. If both S3 nerve roots are sacrificed a permanent colostomy is often necessary.

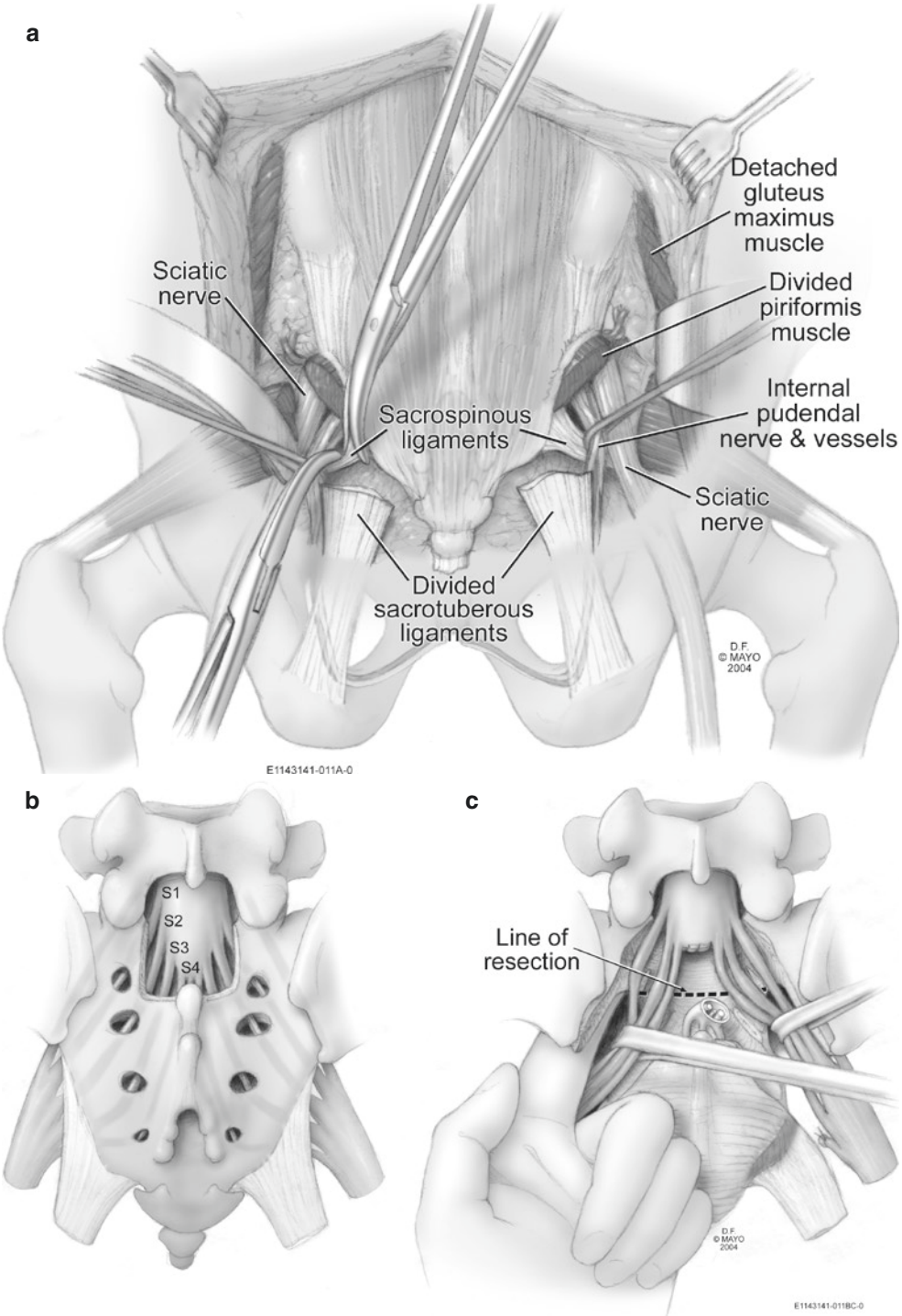

Fig. 21.16 (**a**) Posterior approach exposure of sciatic nerve. (**b**) Sacral nerve roots. (**c**) Ligation of thecal sac. (Reused with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

Minimally Invasive Approaches

Minimally invasive surgery (MIS) has the potential to minimize morbidity and enhance recovery. Laparoscopic and robotic techniques are being more commonly described as safe and feasible means for removing presacral tumors in selected patients (Figs. 21.17 and 21.18) [23, 72–78]. Conditions in which a MIS only approach may not be feasible are very large tumors or malignant tumors that involve the pelvic sidewall, sacrum, or multiple viscera. The overall goals of the surgery must be kept in mind when making a decision on the approach and include complete tumor resection, avoiding disruption of the tumor, and avoidance of injury to surrounding anatomical structures.

Mullaney and colleagues at Mayo Clinic recently performed a systematic review of the literature to determine the feasibility and surgical outcomes of presacral tumors approached using MIS techniques [79]. A total of 82 patients were found that met inclusion criteria. The majority of patients were female (n = 65; 79.2%), with a mean age of 41.7 years (range, 18–89 years). Seventy-three patients (89.0%) underwent laparoscopic or combined laparoscopic-perineal resection, and nine (10.8%) a robotic approach. The conversion rate was 5.5%. The overall 30-day morbidity rate was 15.7%, including one intraoperative rectal injury (1.2%). Ninety-five percent (n = 78) of the tumors were benign. Median length of stay was 4 days for both laparoscopic and robotic groups. No tumor recurrence was noted during follow-up [median 28 months (range, 5–71 months)]. They compared their data from select patients to historical controls from a systematic review of 1064 patients having an open operation. Patients who undergo a minimally invasive approach had a similar mean operating time (155 ± 63 vs. 175 ± 126 min), shorter hospital length of stay (4 vs. 9 days) and comparable 30-day postoperative complications (16% vs. 12.2%) [58]. Selection bias is obviously inherent to the study design, and thus one technique cannot be considered to be superior to another. However, these data suggest that MIS approaches to presacral tumors are reasonably safe and efficacious in select patients when undergoing operation by highly experienced surgeons.

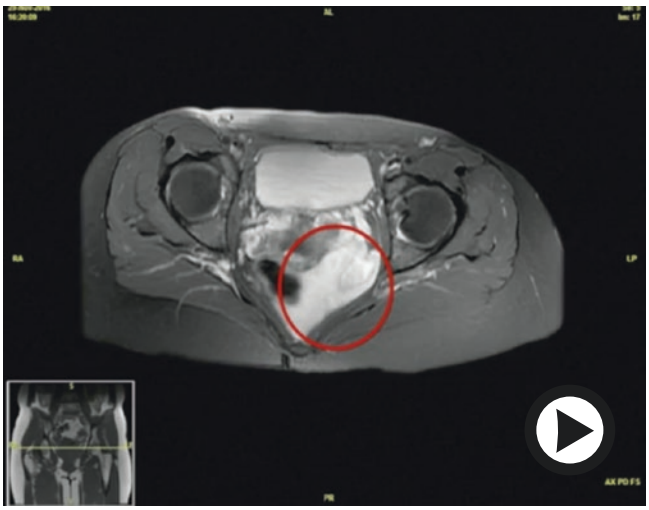

Fig. 21.17 Robotic excision of a giant aggressive angiomyxoma traversing through the levator muscle into the ischioanal space. (Reused with permission of Mayo Foundation for Medical Education and Research, all rights reserved). (https://doi.org/10.1007/000-33b)

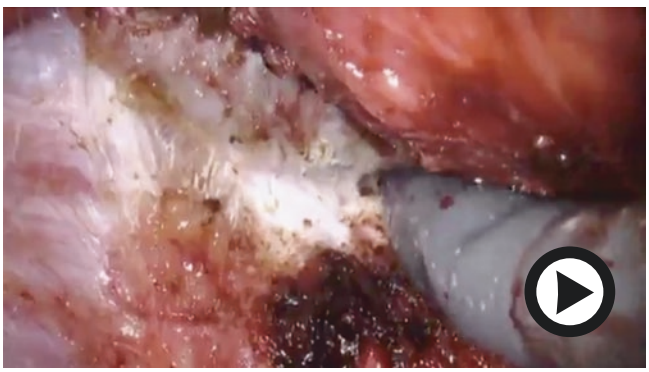

Fig. 21.18 Robotic excision of a presacral cyst below S3 with transvaginal extraction. (Reused with permission of Mayo Foundation for Medical Education and Research, all rights reserved). (https://doi.org/10.1007/000-33a)

Outcomes

Due to the heterogeneity and rarity of presacral tumors, it is difficult to draw any firm conclusions regarding outcomes following treatment from the published literature. Most reported series come from tertiary/quaternary referral centers, with cases accumulated over many years, or decades. As one might expect, there is great variability in follow-up regimens. This fact, and the absence of time-to-event (Kaplan–Meier) calculation of recurrence rates in many series, renders it impossible for the reader to gain more than a general impression of outcomes.

The largest series published since 1975, when Uhlig and Johnson updated the presacral tumor classification system, are outlined in Tables 21.2 and 21.3 [2, 4, 8, 10, 14, 17, 18, 20, 26, 27, 29, 46, 47, 49, 50, 65, 80–82]. For ease of interpretability the tables are separated into benign (Table 21.2) and malignant (Table 21.3), and provide a high-level overview of the numbers and types of tumors presented. Series of both benign and malignant tumors present data ranging from 8 to 48 years. Recurrence rates for benign masses range from 0% to 35%, with the highest recurrences noted for neurogenic tumors. Recurrence rates for malignant lesions range from 0% to 48%, and it is uniformly noted that a R0 resection with wide surgical margins is associated with lower rates of local recurrence.

Table 21.2 Benign tumors

Date	Author	Institution	Cases	Classification	Tumor types	(*n*)
1975	Uhlig et al. [29]	Portland Surgical Center	38	Congenital	Mucus secreting cyst	16
					Indeterminate cyst	7
					Teratoma	2
					Adrenal rest tumor	1
					Epidermoid cyst	1
				Neurogenic	Ganglioneuroma	2
					Neurolemmoma	1
					Neurofibroma	1
				Osseous	Osteoma	1
					Simple bone cyst	1
				Inflammatory	Abscess	2
					Foreign body granuloma	1
				Miscellaneous	Lymphangioma	1
					Desmoid	1
1985	Jao et al. [2]	Mayo Clinic	69	Congenital	Mucus-secreting cyst	16
					Epidermoid cyst	15
					Teratoma	15
					Meningocele	2
				Neurogenic	Neurilemoma	7
					Neurofibroma	3
				Osseous	Giant cell tumor	5
					Aneurysmal bone cyst	1
					Osteochondroma	1
				Miscellaneous	Lipoma	3
					Leiomyoma	1
1993	Bohm et al. [80]	Cleveland Clinic	20	Congenital	Teratoma	9
					Tailgut cyst	6
					Epidermoid cyst	5
1995	Wang et al. [17]	Chang Gung Hosp.	23	Congenital	Epidermal cyst	10
					Teratoma	3
					Dermal cyst	2
				Neurogenic	Neurilemoma	2
				Osseous	Giant cell tumor	4
				Miscellaneous	Leiomyoma	1
					Granuloma	1
2003	Lev-Chelouche et al. [18]	Tel Aviv Univ.	21	Congenital	Tailgut cyst	12
				Neurogenic	Schwanoma	3
				Miscellaneous	Leiomyoma	3
					Fibroma	2
					Angiomyxoma	1
2005	Glasgow et al. [8]	Washington Univ.	27	Congenital	Teratoma	8
					Dermoid/epidermoid cyst	5
					Rectal duplication cyst	2
				Neurogenic	Schwannoma/neurofibroma	5
				Miscellaneous	Leiomyoma	3
				Other	Not described	4
2009	Dozois et al. [26]	Mayo Clinic	46	Neurogenic	Schwannoma	28
					Neurofibroma	17
					Ganglioneuroma	1
2010	Mathis et al. [27]	Mayo Clinic	31	Congenital	Tailgut cyst	31

Table 21.2 (continued)

Date	Author	Institution	Cases	Classification	Tumor types	(*n*)
2012	Macafee et al. [10]	General Infirmary	39	Congenital	Tailgut cyst	13
					Epidermoid cyst	3
					Teratoma	2
				Neurogenic	Schwannoma	11
					Ganglioneuroma	NR
				Miscellaneous	Myelolipoma	NR
					Lipoma	NR
					Mucinous cyst	NR
					Mucin secreting tumor	NR
					Solitary fibrous tumor	NR
2013	Chereau et al. [14]	Hôpital Saint-Antoine	38	Congenital	Tailgut cyst	28
					Dermoid/epidermoid cyst	7
					Teratoma	2
					Rectal duplication cyst	1
2013	Messick et al. [4]	Cleveland Clinic	65	Congenital	Tailgut cyst	28
					Epidermoid cyst	10
					Teratoma	9
					Dermoid	4
					Rectal duplication cyst	2
				Neurogenic	Schwannoma	7
					Ganglioneuroma	1
					Neurofibroma	1
				Miscellaneous	Pecoma	1
					Myelolipoma	1
					Hemangiopericytoma	1
2014	Simpson et al. [20]	Mayo Clinic	21	Congenital	Teratoma	21
2016	Maddah et al. [82]	Mashhad Univ.	23	Congenital	Dermoid/epidermoid cyst	8
					Tailgut cyst	3
					Anterior meningocele	1
					Teratoma	1
					Duplication cyst	1
				Neurogenic	Schwannoma	2
				Osseous	Intra-osseous ganglion cyst	1
				Miscellaneous	Fibromatosis	2
					Hydatid cyst	2
					Lipofibroma	1
					Unknown	1

n number, *NR* not recorded

Table 21.3 Malignant tumors

Date	Author	Institution	Cases	Classification	Tumor types	(*n*)
1975	Uhlig et al. [29]	Portland Surgical Center	25	Congenital Neurogenic	Chordoma	6
					Teratocarcinoma	2
					Neurofibrosarcoma	1
					Ependymoma	1
				Osseous	Osteogenic sarcoma	1
				Miscellaneous	Local & Metastatic cancers	9
					Liposarcoma	2
					Hemangioendothelial sarcoma	1
					Undetermined tumor	1
					Plasma cell myeloma	1

(continued)

Table 21.3 (continued)

Date	Author	Institution	Cases	Classification	Tumor types	(*n*)
1981	Cody et al. [81]	MSKCC	39	Congenital	Chordoma	15
					Epidermoid carcinoma	1
				Neurogenic	Neuroblastoma	4
					Schwannoma	1
					Ganglioneuroblastoma	1
				Osseous	Chrondrosarcoma	3
					Reticulum cell sarcoma	2
					Ewing's sarcoma	1
					Plasmacytoma	1
				Miscellaneous	Unclassified tumor	3
					Hemangiopericytoma	3
					Adenocarcinoma	3
					Carcinoid	1
1985	Jao et al. [2]	Mayo Clinic	51	Congenital	Chordoma	30
					Teratocarcinoma	3
				Neurogenic	Neurofibrosarcoma	2
					Ependymoma	1
					Neuroblastoma	1
				Osseous	Ewing's sarcoma	3
					Osteogenic sarcoma	1
				Miscellaneous	Lymphoma	6
					Myeloma	2
					Fibrosarcoma	1
					Undifferentiated sarcoma	1
1993	Bohm et al. [80]	Cleveland Clinic	4	Congenital	Chordoma	4
1995	Wang et al. [17]	Chang Gung Hosp.	22	Congenital	Chordoma	5
					Teratocardinoma	1
				Neurogenic	Neurofibrosarcoma	1
					Ganglioneuroblastoma	1
				Miscellaneous	Leiomyosarcoma	7
					Undifferentiated sarcoma	2
					Fibrosarcoma	1
					Liposarcoma	1
					Lymphoma	1
					Histiocytoma	1
					Unknown	1
2001	McMaster et al. [49]	NCI	117	Congenital	Chordoma	117
2003	Lev-Chelouche et al. [18]	Tel Aviv Univ.	21	Congenital	Chordoma	9
				Neurogenic	Malignant schwannoma	1
				Osseous	Chrondrosarcoma	2
					Osteosarcoma	1
				Miscellaneous	Desmoid	2
					Angiosarcoma	2
					Fibrosarcoma	1
					Epithelioid sarcoma	1
					Squamous cell carcinoma	1
					Lymphoma	1
2005	Fuchs et al. [50]	Mayo Clinic	52	Congenital	Chordoma	52
2005	Glasgow et al. [8]	Washington Univ.	7	Congenital	Chordoma	3
					Teratocarcinoma	1
				Neurogenic	Malignant schwannoma	1
				Miscellaneous	Radiation induced sarcoma	1
					Leiomyosarcoma	1
2009	Dozois et al. [26]	Mayo Clinic	43	Neurogenic	Neurofibrosarcoma	35
					Ependymoma	6
					Ganglioneuroblastoma	1
					Neuroblastoma	1

Table 21.3 (continued)

Date	Author	Institution	Cases	Classification	Tumor types	(*n*)
2011	Dozois et al. [65]	Mayo Clinic	37	Neurogenic	Neurofibrosarcoma	8
				Osseous	Chrondrosarcoma	7
					Osteosarcoma	3
				Miscellaneous	Undifferentiated sarcoma	6
					Liposarcoma	6
					Leiomyosarcoma	4
					Fibromyxoid sarcoma	1
					GIST	1
					Solitary fibrous tumor	1
2012	Macafee et al. [10]	General Infirmary	17	Congenital	Chordoma	9
				Miscellaneous	Multicystic Adenocarcinoma	2
					Rhabdomyosarcoma	1
					Leiomyosarcoma	1
					Angiomyxoma	1
					Liposarcoma	1
					GIST	1
					NET	1
2013	Chereau et al. [14]	Hôpital Saint-Antoine	9	Congenital	Chordoma	1
				Miscellaneous	Degenerated hamartoma	6
					Unknown sarcoma	2
2013	Messick et al. [4]	Cleveland Clinic	23	Congenital	Chordoma	7
					Teratoma	3
				Osseous	Ewing's sarcoma	1
					Chrondrosarcoma	1
				Miscellaneous	B-cell lymphoma	2
					GIST	2
					Neuroendocrine tumor	2
					Myeloliposarcoma	1
					Histiosarcoma	1
					Squamous cell cancer	1
					Liposarcoma	1
					Fibrosarcoma	1
2014	Simpson et al. [20]	Mayo Clinic	5	Congenital	Teratoma	5
2016	Maddah et al. [82]	Mashhad University	27	Congenital	Chordoma	8
					Germ cell tumor	1
				Neurogenic	Ependymoma	2
					Neuofibrosarcoma	2
					Neuroblastoma	1
					Primitive neuroectodermal	1
				Osseous	Ewing's sarcoma	2
					Chrondrosarcoma	2
					Plasmacytoma	1
					Giant cell tumor	1
				Miscellaneous	Locally invasive cancer	2
					Liposarcoma	2
					Carcinosarcoma	1
					Spindle cell tumor	1
2018	Pan et al. [46]	Xiangya Hospital	451	Congenital	Chordoma	451
2019	Kerekes et al. [47]	Johns Hopkins, Duke, and the Netherlands	1235	Congenital	Chordoma	1235

MSKCC Memorial Sloan Kettering Cancer Center, *n* number, *NCI* National Cancer Institute

The largest body of literature regarding outcomes following treatment of presacral masses is focused on chordomas. McMaster et al. from the National Cancer Institute used data from the Surveillance, Epidemiology and End Results (SEER) database, over a 22-year period (1973–1995). Of 400 cases 33% were spinal, 32% cranial, 29% sacral, and 6% were extra-axial. Fuchs et al. at Mayo Clinic reported on 52 patients who underwent surgical treatment for sacrococcygeal chordoma between 1980 and 2001 (21 years). They found the most important predictor of survival was a wide margin. All patients with a wide margin survived, and the survival rate was significantly different from that for patients who had either marginal or intra lesional excision. Lung metastasis developed in 16 (31%), and all but three of those patients also had a local recurrence [50]. Pan et al. from Xiangya Hospital, China used the SEER database to identify all patients diagnosed with primary spinal chordoma from 1973 to 2014. A total of 808 patients were identified and the overall rate of distant metastatic cases was 8%. Three hundred fifty-seven spinal chordomas (44%) were located in the vertebral column, while 451 (56%) were located in the sacrum or pelvis. Multivariate models showed age ≥60 years, distant metastasis, and non-surgical therapies were independently associated with reduced survival. Tumor site (vertebrae vs. sacrum/pelvis) was not associated with survival for primary spinal chordoma [46]. Kerekes and colleagues from Johns Hopkins, Duke, and the Netherlands completed a systematic review and pooled cohort analysis (1980–2016) of local and distant recurrence in patients undergoing resection of sacral chordomas. They found 57 studies and 1235 cases for review, and noted wide surgical margin was associated with a lower rate of local recurrence; and wide surgical margin, female sex, and patient age ≥65 years was associated with lower rates of distant recurrence [47].

Follow-Up and Observation-Only Patients

There are limited data on which to base any firm recommendations regarding follow-up. In our practice we typically recommend an annual visit with digital rectal examination to assess for recurrence in patients who had benign lesions resected. A pelvic MRI is obtained 1-year post-resection, and then again at 5 years. In the interim, if a mass is palpated, pelvic imaging is performed. For malignant tumors, patients typically undergo an annual physical examination, pelvic MRI, and CT of the chest and abdomen for 5 years. Collaboration with colleagues in medical and radiation oncology is critical as part of postoperative surveillance and need for adjuvant therapy. Recurrences, when they occur, are considered for re-resection if a complete resection is possible.

Patients with small, benign, asymptomatic tumors can safely be approached in a nonoperative fashion and followed if the patient is comfortable with this plan. For cystic lesions, we recommend pelvic MRI every 5 years for a period of 10 years to assess the natural history of the lesion. If little change to the size or morphology of the lesion is noted, longer intervals between imaging can be considered. Decision-making is on a case-by-case basis. Patients should be counseled that if any change in symptoms occur, it should prompt a clinical and radiographic evaluation. For patients with benign solid tumors such as schwannomas, we recommend a similar follow-up.

Conclusions

Presacral tumors represent a rare group of both benign and malignant lesions. Most benign lesions have malignant potential and must be followed carefully if nonoperative treatment is chosen. MRI is the best overall imaging study to assist in diagnosis and operative planning. When performed appropriately and selectively, a biopsy of the lesion may assist in management of solid and heterogeneous cystic lesions. The surgical principles that should guide a surgeon who manages these lesions are a function-sparing approach for benign lesions and an en bloc approach for malignant lesions. Observation alone in some patients is acceptable when a dedicated surveillance protocol is in place. As the discovery of these tumors increases, more surgeons will be asked to evaluate these patients. Given the broad differential and significant implications of mismanagement, presacral tumors should be evaluated and treated by surgeons at centers that have a large experience in managing these complex tumors.

References

1. Spencer RJ, Jackman RJ. Surgical management of precoccygeal cysts. Surg Gynecol Obstet. 1962;115:449–52.
2. Jao SW, Beart RW Jr, Spencer RJ, Reiman HM, Ilstrup DM. Retrorectal tumors. Mayo Clinic experience, 1960–1979. Dis Colon Rectum. 1985;28(9):644–52.
3. Hobson KG, Ghaemmaghami V, Roe JP, Goodnight JE, Khatri VP. Tumors of the retrorectal space. Dis Colon Rectum. 2005;48(10):1964–74.
4. Messick CA, Hull T, Rosselli G, Kiran RP. Lesions originating within the retrorectal space: a diverse group requiring individualized evaluation and surgery. J Gastrointest Surg. 2013;17(12):2143–52.
5. Todd LT Jr, Yaszemski MJ, Currier BL, Fuchs B, Kim CW, Sim FH. Bowel and bladder function after major sacral resection. Clin Orthop Relat Res. 2002;397:36–9.
6. Zoccali C, Skoch J, Patel AS, Walter CM, Maykowski P, Baaj AA. Residual neurological function after sacral root resection during en-bloc sacrectomy: a systematic review. Eur Spine J. 2016;25(12):3925–31.

7. Wei R, Guo W, Ji T, Zhang Y, Liang H. One-step reconstruction with a 3D-printed, custom-made prosthesis after total en bloc sacrectomy: a technical note. Eur Spine J. 2017;26(7):1902–9.
8. Glasgow SC, Birnbaum EH, Lowney JK, Fleshman JW, Kodner IJ, Mutch DG, Lewin S, Mutch MG, Dietz DW. Retrorectal tumors: a diagnostic and therapeutic challenge. Dis Colon Rectum. 2005;48(8):1581–7.
9. Singer MA, Cintron JR, Martz JE, Schoetz DJ, Abcarian H. Retrorectal cyst: a rare tumor frequently misdiagnosed. J Am Coll Surg. 2003;196(6):880–6.
10. Macafee DA, Sagar PM, El-Khoury T, Hyland R. Retrorectal tumours: optimization of surgical approach and outcome. Color Dis. 2012;14(11):1411–7.
11. Hosseini-Nik H, Hosseinzadeh K, Bhayana R, Jhaveri KS. MR imaging of the retrorectal-presacral tumors: an algorithmic approach. Abdom Imaging. 2015;40(7):2630–44.
12. Lee KS, Gower DJ, McWhorter JM, Albertson DA. The role of MR imaging in the diagnosis and treatment of anterior sacral meningocele. Report of two cases. J Neurosurg. 1988;69(4):628–31.
13. Sung MS, Lee GK, Kang HS, Kwon ST, Park JG, Suh JS, Cho GH, Lee SM, Chung MH, Resnick D. Sacrococcygeal chordoma: MR imaging in 30 patients. Skelet Radiol. 2005;34(2):87–94.
14. Chereau N, Lefevre JH, Meurette G, Mourra N, Shields C, Parc Y, Tiret E. Surgical resection of retrorectal tumours in adults: long-term results in 47 patients. Color Dis. 2013;15(8):e476–82.
15. Sagar AJ, Koshy A, Hyland R, Rotimi O, Sagar PM. Preoperative assessment of retrorectal tumours. Br J Surg. 2014;101(5):573–7.
16. Toh JW, Morgan M. Management approach and surgical strategies for retrorectal tumours: a systematic review. Color Dis. 2016;18(4):337–50.
17. Wang JY, Hsu CH, Changchien CR, Chen JS, Hsu KC, You YT, Tang R, Chiang JM. Presacral tumor: a review of forty-five cases. Am Surg. 1995;61(4):310–5.
18. Lev-Chelouche D, Gutman M, Goldman G, Even-Sapir E, Meller I, Issakov J, Klausner JM, Rabau M. Presacral tumors: a practical classification and treatment of a unique and heterogeneous group of diseases. Surgery. 2003;133(5):473–8.
19. Merchea A, Larson DW, Hubner M, Wenger DE, Rose PS, Dozois EJ. The value of preoperative biopsy in the management of solid presacral tumors. Dis Colon Rectum. 2013;56(6):756–60.
20. Simpson PJ, Wise KB, Merchea A, Cheville JC, Moir C, Larson DW, Dozois EJ. Surgical outcomes in adults with benign and malignant sacrococcygeal teratoma: a single-institution experience of 26 cases. Dis Colon Rectum. 2014;57(7):851–7.
21. Sagar AJ, Tan WS, Codd R, Fong SS, Sagar PM. Surgical strategies in the management of recurrent retrorectal tumours. Tech Coloproctol. 2014;18(11):1023–7.
22. Bai HM, Yang JX, Huang HF, Cao DY, Chen J, Yang N, Lang JH, Shen K. Individualized managing strategies of aggressive angiomyxoma of female genital tract and pelvis. Eur J Surg Oncol. 2013;39(10):1101–8.
23. Kelley SR. Robotic extralevator excision of a retrorectal giant aggressive angiomyxoma. Obstet Gynecol Sci. 2018;61(6):693–7.
24. Frezza AM, Botta L, Trama A, Dei Tos AP, Stacchiotti S. Chordoma: update on disease, epidemiology, biology and medical therapies. Curr Opin Oncol. 2019;31(2):114–20.
25. Springall RG, Griffiths JD. Malignant change in rectal duplication. J R Soc Med. 1990;83(3):185–7.
26. Dozois EJ, Wall JC, Spinner RJ, Jacofsky DJ, Yaszemski MJ, Sim FH, Moran SL, Cima RR, Larson DR, Haddock MG, Okuno SH, Larson DW. Neurogenic tumors of the pelvis: clinicopathologic features and surgical outcomes using a multidisciplinary team. Ann Surg Oncol. 2009;16(4):1010–6.
27. Mathis KL, Dozois EJ, Grewal MS, Metzger P, Larson DW, Devine RM. Malignant risk and surgical outcomes of presacral tailgut cysts. Br J Surg. 2010;97(4):575–9.
28. Hopper L, Eglinton TW, Wakeman C, Dobbs BR, Dixon L, Frizelle FA. Progress in the management of retrorectal tumours. Color Dis. 2016;18(4):410–7.
29. Uhlig BE, Johnson RL. Presacral tumors and cysts in adults. Dis Colon Rectum. 1975;18(7):581–9.
30. Dunn KB. Retrorectal tumors. Surg Clin North Am. 2010;90(1):163–71.
31. Wolpert A, Beer-Gabel M, Lifschitz O, Zbar AP. The management of presacral masses in the adult. Tech Coloproctol. 2002;6(1):43–9.
32. Yang DM, Park CH, Jin W, Chang SK, Kim JE, Choi SJ, Jung DH. Tailgut cyst: MRI evaluation. Am J Roentgenol. 2005;184(5):1519–23.
33. Caropreso PR, Wengert PA Jr, Milford HE. Tailgut cyst – a rare retrorectal tuor. Report of a case and review. Dis Colon Rectum. 1975;18(7):597–600.
34. Hjermstad BM, Helwig EB. Tailgut cysts. Report of 53 cases. Am J Clin Pathol. 1988;89(2):139–47.
35. Prasad AR, Amin MB, Randolph TL, Lee CS, Ma CK. Retrorectal cystic hamartoma: report of 5 cases with malignancy arising in 2. Arch Pathol Lab Med. 2000;124(5):725–9.
36. Michael D, Cohen CR, Northover JM. Adenocarcinoma within a rectal duplication cyst: case report and literature review. Ann R Coll Surg Engl. 1999;81(3):205–6.
37. Pantoja E, Rodriguez-Ibanez I. Sacrococcygeal dermoids and teratomas: historical review. Am J Surg. 1976;132(3):377–83.
38. Izant RJ Jr, Filston HC. Sacrococcygeal teratomas. Analysis of forty-three cases. Am J Surg. 1975;130(5):617–21.
39. Dirix M, van Becelaere T, Berkenbosch L, van Baren R, Wijnen RM, Wijnen MH, van der Zee DC, Heij HA, Derikx JP, van Heurn LW. Malignant transformation in sacrococcygeal teratoma and in presacral teratoma associated with Currarino syndrome: a comparative study. J Pediatr Surg. 2015;50(3):462–4.
40. Altman RP, Randolph JG, Lilly JR. Sacrococcygeal teratoma: American Academy of Pediatrics Surgical Section Survey-1973. J Pediatr Surg. 1974;9(3):389–98.
41. Waldhausen JA, Kolman JW, Vellios F, Battersby JS. Sacrococcygeal teratoma. Surgery. 1963;54:933–49.
42. Miles RM, Stewart GS Jr. Sacrococcygeal teratomas in adults. Ann Surg. 1974;179(5):676–83.
43. Hickey RC, Martin RG. Sacrococcygeal teratomas. Ann N Y Acad Sci. 1964;114:951–7.
44. Gray SW, Singhabhandhu B, Smith RA, Skandalakis JE. Sacrococcygeal chordoma: report of a case and review of the literature. Surgery. 1975;78(5):573–82.
45. Dahlin DC. Bone tumors. General aspects and data on 6,221 cases. 3rd ed. Springfield: Charles C. Thomas; 1978. p. 329. ISBN: 0398036926.
46. Pan Y, Lu L, Chen J, Zhong Y, Dai Z. Analysis of prognostic factors for survival in patients with primary spinal chordoma using the SEER Registry from 1973 to 2014. J Orthop Surg Res. 2018;13(1):76.
47. Kerekes D, Goodwin CR, Ahmed AK, Verlaan JJ, Bettegowda C, Abu-Bonsrah N, Sciubba DM. Local and distant recurrence in resected sacral chordomas: a systematic review and pooled cohort analysis. Global Spine J. 2019;9(2):191–201.
48. Stewart RJ, Humphreys WG, Parks TG. The presentation and management of presacral tumours. Br J Surg. 1986;73(2):153–5.
49. McMaster ML, Goldstein AM, Bromley CM, Ishibe N, Parry DM. Chordoma: incidence and survival patterns in the United States, 1973-1995. Cancer Causes Control. 2001;12(1):1–11.
50. Fuchs B, Dickey ID, Yaszemski MJ, Inwards CY, Sim FH. Operative management of sacral chordoma. J Bone Joint Surg Am. 2005;87(10):2211–6.
51. Manson F, Comalli-Dillon K, Moriaux A. Anterior sacral meningocele: management in gynecological practice. Ultrasound Obstet Gynecol. 2007;30(6):893–6.

52. Berstock JR, Bunni J, Thorpe PL. Caution: laparoscopic biopsy of a large pelvic mass may result in disaster. J Minim Invasive Gynecol. 2012;19(5):651–3.
53. Cheng C, Tao B, Bai S, Gao G, Li S, Shang A. Anterior sacral meningocele: a new classification and treatment using the dorsal transsacral approach. Spine. 2020;45(7):444–51.
54. Hébert-Blouin MN, Sullivan PS, Merchea A, Léonard D, Spinner RJ, Dozois EJ. Neurological outcome following resection of benign presacral neurogenic tumors using a nerve-sparing technique. Dis Colon Rectum. 2013;56(10):1185–93.
55. Alderete J, Novais EN, Dozois EJ, Rose PS, Sim FF. Morbidity and functional status of patients with pelvic neurogenic tumors after wide excision. Clin Orthop Relat Res. 2010;468(11):2948–53.
56. Freier DT, Stanley JC, Thompson NW. Retrorectal tumors in adults. Surg Gynecol Obstet. 1971;132(4):681–6.
57. Randall RL. Giant cell tumor of the sacrum. Neurosurg Focus. 2003;15(2):E13. Review.
58. Baek SK, Hwang GS, Vinci A, Jafari MD, Jafari F, Moghadamyeghaneh Z, Pigazzi A. Retrorectal tumors: a comprehensive literature review. World J Surg. 2016;40(8):2001–15.
59. Currarino G, Coln D, Votteler T. Triad of anorectal, sacral, and presacral anomalies. AJR Am J Roentgenol. 1981;137(2):395–8.
60. AbouZeid AA, Mohammad SA, Abolfotoh M, Radwan AB, Ismail MME, Hassan TA. The Currarino triad: what pediatric surgeons need to know. J Pediatr Surg. 2017;52(8):1260–8.
61. Crétolle C, Pelet A, Sanlaville D, Zérah M, Amiel J, Jaubert F, Révillon Y, Baala L, Munnich A, Nihoul-Fékété C, Lyonnet S. Spectrum of HLXB9 gene mutations in Currarino syndrome and genotype-phenotype correlation. Hum Mutat. 2008;29(7):903–10.
62. Leonard D, Pendlimari R, Larson DW, Dozois EJ. Currarino syndrome: typical images of a rare condition. Tech Coloproctol. 2010;14(3):289–90.
63. Pendlimari R, Leonard D, Dozois EJ. Rare malignant neuroendocrine transformation of a presacral teratoma in patient with Currarino syndrome. Int J Color Dis. 2010;25(11):1383–4.
64. MacCarty CS, Waugh JM, Coventry MB, Cope WF Jr. Surgical treatment of sacral and presacral tumors other than sacrococcygeal chordoma. J Neurosurg. 1965;22(5):458–64.
65. Dozois EJ, Jacofsky DJ, Billings BJ, Privitera A, Cima RR, Rose PS, Sim FH, Okuno SH, Haddock MG, Harmsen WS, Inwards CY, Larson DW. Surgical approach and oncologic outcomes following multidisciplinary management of retrorectal sarcomas. Ann Surg Oncol. 2011;18(4):983–8.
66. Yang JC, Chang AE, Baker AR, Sindelar WF, Danforth DN, Topalian SL, DeLaney T, Glatstein E, Steinberg SM, Merino MJ, Rosenberg SA. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol. 1998;16(1):197–203.
67. Feng M, Murphy J, Griffith KA, Baker LH, Sondak VK, Lucas DR, McGinn CJ, Ray ME. Long-term outcomes after radiotherapy for retroperitoneal and deep truncal sarcoma. Int J Radiat Oncol Biol Phys. 2007;69(1):103–10.
68. Rosenberg SA, Tepper J, Glatstein E, Costa J, Baker A, Brennan M, DeMoss EV, Seipp C, Sindelar WF, Sugarbaker P, Wesley R. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg. 1982;196(3):305–15.
69. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Sarcoma Meta-analysis Collaboration. Lancet. 1997;350(9092):1647–54.
70. Raut CP, Pisters PW. Retroperitoneal sarcomas: combined-modality treatment approaches. J Surg Oncol. 2006;94(1):81–7.
71. Dozois EJ, Malireddy KK, Bower TC, Stanson AW, Sim FH. Management of a retrorectal lipomatous hemangiopericytoma by preoperative vascular embolization and a multidisciplinary surgical team: report of a case. Dis Colon Rectum. 2009;52(5):1017–20.
72. Witherspoon P, Armitage J, Gatt M, Sagar PM. Laparoscopic excision of retrorectal schwannoma. Dis Colon Rectum. 2010;53(1):101–3.
73. Duclos J, Maggiori L, Zappa M, Ferron M, Panis Y. Laparoscopic resection of retrorectal tumors: a feasibility study in 12 consecutive patients. Surg Endosc. 2014;28(4):1223–9.
74. Fong SS, Codd R, Sagar PM. Laparoscopic excision of retrorectal tumours. Color Dis. 2014;16(11):O400–3.
75. Zhou JL, Wu B, Xiao Y, Lin GL, Wang WZ, Zhang GN, Qiu HZ. A laparoscopic approach to benign retrorectal tumors. Tech Coloproctol. 2014;18(9):825–33.
76. Manabe T, Koba R, Nagayoshi K, Sadakari Y, Fujita H, Nagai S, Ueki T, Nagai E, Nakamura M. Laparoscopic excision of neurogenic retrorectal tumors. Asian J Endosc Surg. 2017;10(2):223–6.
77. Cataneo J, Cataldo T, Poylin V. Robotic excision of retrorectal mass. J Gastrointest Surg. 2018;22(10):1811–3.
78. Hove MG, Gil JM, Rodríguez TS, Lomas ÁF, Casajús JP, López-Farré A, Guijarro JJ. Laparoscopic approach to tailgut cyst (retrorectal cystic hamartoma). J Minim Access Surg. 2019;15(3):262–4.
79. Mullaney TG, Lightner AL, Johnston M, Kelley SR, Larson DW, Dozois EJ. A systematic review of minimally invasive surgery for retrorectal tumors. Tech Coloproctol. 2018;22(4):255–63.
80. Bohm B, Milsom JW, Fazio VW, Lavery IC, Church JM, Oakley JR. Our approach to the management of congenital presacral tumors in adults. Int J Color Dis. 1993;8(3):134–8.
81. Cody HS 3rd, Marcove RC, Quan SH. Malignant retrorectal tumors: 28 years' experience at Memorial Sloan-Kettering Cancer Center. Dis Colon Rectum. 1981;24(7):501–6.
82. Maddah G, Abdollahi A, Etemadrezaie H, Ganjeifar B, Gohari B, Abdollahi M, Hassanpour M. Problems in diagnosis and treatment of retrorectal tumors: our experience in 50 patients. Acta Med Iran. 2016;54(10):644–50.

Sporadic and Inherited Colorectal Cancer: How Epidemiology and Molecular Biology Guide Screening and Treatment

22

Sean C. Glasgow and Karin M. Hardiman

Key Concepts

- Colorectal cancer is caused by the accumulation of a variety of genetic alterations in colonic mucosa.
- Colorectal cancer can be hereditary or sporadic (not inherited). Both forms share many of the same genetic alterations.
- Multiple hereditary forms of colorectal cancer have an expected phenotype due to the genetic alteration that increases the likelihood of the cancer.
- Screening algorithms for colorectal cancer differ between hereditary and sporadic cancer based on the time expected for an adenoma to become a carcinoma in that patient.
- Hereditary forms of colorectal cancer are more commonly seen in patients with young onset colorectal cancer.
- Treatment algorithms for hereditary colorectal cancer are directed towards removal of the cancer and decreasing future risk of additional cancers.

Introduction

This chapter outlines the basic molecular biology of both inherited and sporadic colorectal cancer (CRC). An understanding of the molecular mechanisms underlying CRC is important for clinicians, as it explains the epidemiology of the disease and often informs treatment decisions.

Sporadic Versus Inherited Colorectal Cancer

CRC is the third leading cause of cancer-related death worldwide [1]. Cancer can either be inherited, meaning that it is passed down genetically within the patient's family or sporadic, meaning that it was not inherited. This is somewhat simplified because there are clearly families with multiple members with CRC such that it is likely that they carry a genetic propensity for the disease, but no known genetic alteration can be identified on testing. The cause is likely either a genetic alteration that is yet to be identified or a collection in an individual of low-penetrance alterations that each increase risks to a lesser degree. This level of complexity is beyond the scope of this chapter. Most CRCs are considered sporadic, and the genetics of sporadic cancer, in many ways, mirrors that of inherited CRC.

Sporadic Colorectal Cancer

Approximately 80% of CRC is considered sporadic [2]. Sporadic cancers are caused by genetic alterations in the tissue that becomes the tumor, whereas inherited cancers are caused by genetic alterations within the entire patient (germline mutations) that then secondarily lead to further alterations within the tissue that becomes the tumor. These alterations are typically in the same genes and pathways, but the pace and age at which they occur differ.

Epidemiology of Sporadic CRC

CRC is the third most common cancer in the United States and globally [1, 3]. Approximately 47% of cases are in women [3]. Most new CRC cases are in those over age 65 (58%), but 39% of females and 45% of males are diagnosed under age 65. Mean age of colon diagnosis is 68 for men and 72 for women, whereas the mean age of diagnosis of rectal cancer is 63 for both men and women. CRC incidence and mortality vary by ethnicity, with the highest rate in Alaskan Natives (2010–2013 incidence of 91 per 100,000) and African Americans (49 per 100,000) and the lowest in Asian Americans (32 per 100,000). The accumulation of genetic alterations causing CRC is thought to progress over several

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years. CRC is most commonly located in the right colon (41%) or the rectum (28%) [3]. Right-sided lesions are more common in older patients, and distal tumors are more common in younger patients. Current endoscopic screening guidelines for average risk patients recommend starting at age 45 with repeat every 10 years if patients are not found to have adenomas. These are based on the typical time to progression from an adenoma to a carcinoma [4].

Risk Factors for Sporadic Colorectal Cancer

The underlying causes of CRC are not clear but likely are an interplay between predisposing genetic factors and lifestyle, dietary factors, and environmental and other exposures including the gut microbiome. Individual studies as well as multiple systematic reviews support the role of diet as a risk factor for the development of CRC. Vieira et al. performed a meta-analysis of 111 studies and showed that the risk of CRC increases by 12% for every 100 g/day increase in intake of red and processed meat and 7% for every 10 g/day of alcohol intake but decreases 17% for every 90 g/day of whole grains and 13% for every 400 g/day of dairy [5]. The particular mechanism whereby diet alters risk of CRC is not known but could, in part, be via changes in the microbiome. The gut microbiome differs significantly between patients with and without CRC [6]. The changes in the microbiome of patients with CRC are more similar to those in people who have a diet high in red meat. In addition to dietary factors, sedentary lifestyle and obesity have been associated with most types of cancer. Increased physical activity to levels concordant with national guidelines resulted in a deceased relative risk of CRC of approximately 19% in a recent meta-analysis [7]. The mechanism whereby sedentary lifestyle predisposes to CRC may be via altered metabolism and oxidative stress [8].

Molecular Biology of Sporadic Colorectal Cancer

Genetic mutations accumulate in the colon and rectum over time as cells replicate in the mucosa of the bowel due to a combination of exposure and somatic alterations. These alterations can be nucleotide changes in the coding region of genes causing the product of these genes to be dysfunctional (as in the case of tumor suppressors), increased function of oncogenes, copy number changes where chromosomes are amplified or deleted, or epigenetic alterations causing altered transcription of genes through promoter methylation (Table 22.1). In general, sporadic CRC can be split into hypermutated tumors, which often have over 1000 mutations and very few copy number changes, and non-hypermutated tumors with fewer mutations and more copy number changes [9]. Because cellular functions are caused not just by individual proteins but by groups of them working together in a pathway, alterations in individual genes can be assessed across known pathways to identify important pathways. In CRC, the recurrently altered pathways are in WNT, MAPK, PI3K, TGF-β, and p53 pathways. Genetic alterations are only clinically relevant if they are shown to be biomarkers of disease or if they can be targeted with treatment. Thus far, most alterations in CRC are neither.

Table 22.1 Sporadic colorectal cancer molecular genetics

Sporadic colorectal cancer	
Topic	Summary
Genetic alterations	CIN: Accumulation of CNV with varied karyotypes from cell to cell and LOH leading to loss of tumor suppressor genes and mutations in key driver genes CIMP: Tumors are hypermutated, BRAF mutation common, widespread epigenetic promoter methylation of DNA Gene point mutations, insertions, deletions: 60–1000's of mutations per tumor
Pathways/ genes	Wnt pathway; *APC*, *TP53*; TGF-β and EMT; *PI3K*
Consensus molecular subtypes	CMS1: MSI immune, 14%, hypermutated, more often right-sided
	CMS2: Canonical, 37%, Wnt and MYC activation, CNV high, more often left-sided
	CMS3: Metabolic, 13%, CNV and CIMP low
	CMS4: Mesenchymal, 23%, CNV high, EMT, worse survival

CIN chromosomal instability, *MSI* microsatellite instability, *CIMP* CpG island methylator phenotype, *EMT* epithelial-to-mesenchymal transition, *CNV* copy number variation

Adenoma to Carcinoma Pathway

In 1990, after in-depth studies of various stages of CRC, Fearon and Vogelstein outlined a model of CRC development that proposed that the progressive accumulation of alterations in the genome caused abnormal growth, starting with normal colonic mucosa, progressing to adenoma and then to adenocarcinoma. This early description described alterations in the genome that were found commonly in certain genes in CRC via mutation, copy number change, or hypomethylation [10]. They highlighted loss of tumor suppressors as well as alterations in oncogenes (Table 22.1). Since that time, our understanding of CRC progression has advanced, but many of the original concepts remain.

Mutations

With the advent of next-generation sequencing came the ability to know the genetic alterations in solid tumors. For any two patients with CRC, they likely share alterations in only one or two genes, as there is substantial inter-tumor heterogeneity in CRC. Because of the inherent genome instability found in tumors, many of the mutations identified in sequencing studies are not clinically consequential. Since so many mutations may occur and they differ from one tumor to another, predictive models are used to determine whether alterations in any one gene are important. These important mutations are called "driver mutations" meaning

that they promote tumorigenesis and tumor progression. The most common driver mutations in CRC have been described in a series of publications and include mutations in *APC*, *TP53*, *KRAS*, and *PIK3CA* [9, 11]. For example, *APC* is the most commonly mutated gene in CRC (72% mutation rate in The Cancer Genome Atlas) and is important as an early driver of adenoma formation. The APC protein acts as a tumor suppressor. Alteration in *APC* causes accumulation of beta-catenin which translocates to the nucleus and binds to LEF and TCF, causing transcription upregulating multiple pathways. In addition, loss or mutation of *APC* can lead to transcriptional activation independent of ß-catenin. *TP53* mutation is the second most common alteration in CRC. It is more commonly altered in patients with more advanced disease and is considered a late driver. It is a tumor suppressor gene because its normal function is to cause damaged cells to stop dividing until the DNA can be repaired and to undergo apoptosis if the DNA cannot be repaired. Mutation or loss of TP53 results in increased proliferation, decreased DNA repair, and decreased apoptosis. Mutations of clinical relevance include *RAS* mutations which occur in about half of patients with CRC including *KRAS* and *NRAS*. These are important because patients with RAS mutations do not benefit from treatment with anti-epidermal growth factor receptor (EGFR) agents [12]. Additionally, around 10% of patients have tumors containing mutations in *BRAF*, which is important because this is a biomarker of worse survival in stage 4 patients [13]. Although BRAF inhibitors can improve outcome in other tumor types with these mutations, in 95% of CRCs are resistant to BRAF inhibition via redundant alterations in the MAPK pathway [14]. Another key pathway in CRC that is especially important in metastasis is the epithelial-to-mesenchymal transition (EMT). [15] EMT is the process whereby epithelial cells acquire mesenchymal properties. This allows the cells to change their architecture, interact differently with their microenvironment, and become invasive. Proteins important in EMT in CRC are ZEB1 and ZEB2, TGF-β, SNAIL, and vimentin. EMT and ZEB2 specifically have such an important role in metastasis that small trials have shown that addition of nuclear ZEB2 staining in CRC to the staging system will improve patient stratification for prediction of outcome [16].

Most tumors contain 100–200 mutations, while about 15% of tumors contain 1000s of mutations. These hypermutated tumors typically harbor genetic or epigenetic alterations in the mismatch repair genes causing rapid accumulation of mutations; thus, they are called hypermutated tumors. The inherited form of this is called Lynch syndrome (LS) which is caused by somatic mutations in the mismatch repair pathway genes and will be covered later in the chapter. Stage for stage, these tumors have better outcome than CRCs without a high mutation burden, and studies have shown that these tumors are responsive to immunotherapy, whereas most non-Lynch tumors are not [17].

In addition to the inter-tumor genetic heterogeneity, there is also intra-tumor genetic heterogeneity whereby different areas of a tumor and its associated metastasis can harbor different mutations and copy number changes because tumors are made up of many genetically related sub-clones [18–20]. These sub-clones can have different abilities and drug resistance profiles with substantive clinical implications.

Chromosomal Alterations

About 85% of CRCs harbor substantial chromosomal alterations. This is called chromosome instability or CIN. Hypermutated tumors, which make up about 15% of tumors, are the exception and have few copy number changes. Common copy number variations in tumors affected by CIN include loss of 8p, 17p, and 18q and gains in chromosomes 8q, 13, and 20q [9, 21, 22]. These gains and losses affect the genes on these chromosomes which can have profound implications for tumors. For example, the tumor suppressor *TP53* is on 17p which is commonly lost.

Epigenetic Alterations in Colorectal Cancer

CpG islands are commonly found in the promoters of genes. When these islands are hypermethylated, the downstream gene can be silenced. This is the mechanism for many sporadic microsatellite unstable (MSI-high, or MSI-H) tumors whereby the promoter of the mismatch repair *MLH1* gene is silenced by hypermethylation [23]. These tumors then lack functional MLH1 protein and then accumulate genetic mutations quickly because they lack this form of DNA repair. This CpG island methylator phenotype (CIMP) is found in sessile serrated adenomas and the cancers that arise from them [24]. These tumors commonly harbor *BRAF* mutations.

Molecular Subtypes of CRC

Due to genetic heterogeneity and differences in the effects of genetic mutations, gene expression is critical in tumor phenotype. In 2015, an international group of researchers published the most comprehensive study to date of gene transcription data from 4151 patients [25]. Using multiple classification algorithms and network clustering, they categorized tumors into four consensus molecular subtypes. These subtypes, called consensus molecular subtype (CMS) 1–4, recognize the heterogeneity that makes up CRC (Table 22.1). CMS1 tumors are hypermutated, MSI-high tumors with a high immune infiltrate. Tumors with an increased number of copy number variations are CMS2–4. CMS2 tumors have alterations described as canonical with upregulation of WNT and MYC targets along with increased expression of EGFR and HER2. CMS3 tumors are classified by metabolic dysregulation and characterized by KRAS

mutations. CMS4 tumors have activated EMT with increased TGFβ, extracellular matrix, and integrins. These classifications have clinical relevance. CMS4 tumors have the worst outcome and CMS2 have the best. The full ramifications of these classifications are yet to come.

Right vs. Left CRC

The right and left colon have distinct embryologic origins as well as differences in their microbiome and exposure to toxins such as bile acids, and thus, it is not surprising that they would have somewhat different molecular phenotypes for tumors developing in the two areas [26]. Right-sided tumors are more likely to be hypermutated and are more common in older patients, whereas left-sided tumors are more likely to be found in younger patients. The sides have different distributions of the consensus molecular phenotypes with CMS1 and 3 subtypes being more common on the right and CMS2 and 4 more common on the left. This has therapeutic implications; whereby early, right-sided tumors have a better prognosis, but once metastatic, they have a worse outcome [27, 28]. This difference based on sidedness with metastasis may be because of the high rate of BRAF mutations in metastatic right-sided tumors which have a poor prognosis. Differences in survival between patients with right- and left-sided tumors may also be due to differences in response to treatment. A 2018 study of response to bevacizumab and cetuximab in metastatic CRC found that primary tumor site was associated with response to biologic therapy [29]. Right-sided primary tumor location was associated with higher mortality regardless of biologic therapy type. In patients with wild-type KRAS tumors, treatment with cetuximab benefited only those with left-sided primary tumors and was associated with significantly poorer survival among those with right-sided primary tumors. This study highlights the need for better understanding of prognostic factors to guide treatment.

Screening for Sporadic CRC

Screening guidelines for CRC directly relate to the time that it takes for a polyp to become an adenocarcinoma and at what age does the risk of developing CRC increase to the point where screening is more efficacious than harmful. If an average-risk patient has a low risk of CRC based on finding no polyps on their initial screening colonoscopy, then another intervention is likely not needed for 10 years. However, when patients are found to have polyps, particularly when there are multiple lesions or high-risk lesions, the patient has proven that for genetic or environmental reasons, they are at increased risk and their screening interval should be shorter.

Treatment for Sporadic CRC

As will be discussed to a greater extent elsewhere, the treatment of CRC is based upon the stage at which it is identified. Early stage intraperitoneal colon tumors (stages I–II) are typically treated with surgical resection alone, whereas later stage tumors, which have demonstrated the ability to move from where they started and invade nearby lymph nodes (stage III) or distant organs (stage IV), are typically treated with chemotherapy either as an adjunct to surgical resection or as a primary palliative treatment. The typical chemotherapeutic regimen used to treat CRC is the combination of 5-fleurouracil, oxaliplatin, and leucovorin (FOLFOX). This combination yields survival benefit for patients with stage III and IV disease. Together, these drugs have a high response rate in CRC. They are not molecularly targeted. Targeted therapies directed at VEGF, EGFR, and kinases are available for metastatic CRC. Many patients are resistant to these drugs, likely due to redundancies between different pathways in CRC such that tumors can increase untargeted pathways to become resistant to targeted therapies.

Young Onset CRC

Epidemiology

In many countries around the world, there is an increasing incidence of CRC in people under the age of 50, referred to as young-onset CRC (YO-CRC) [30, 31]. The incidence of YO-CRC has increased significantly over the past 20 years for unknown reasons. The increase is predominantly left-sided, especially rectal. These patients often present with symptomatic tumors due to the location, and the younger they are, the more likely they are to present at an advanced stage [32]. Due to the increased risk of CRC in young adults, the American Cancer Society has decreased its recommended age to start screening in average-risk patients to 45 years old, but the recommendation by the National Comprehensive Cancer Network (NCCN) to start screening at age 50 has not changed [33].

Management

The assessment and treatment of patients presenting with YO-CRC is similar to tumors in older patients except that they are more likely to need urgent intervention for obstruction [34, 35]. YO-CRC patients have a high prevalence of inherited CRC and should undergo testing. As little is known about differences in treatment response in YO-CRC patients, recommendations for management remain largely unchanged.

Genetics of YO-CRC

YO-CRC patients should undergo genetic testing, as heritable CRC will be found in 16–20% of YO-CRC patients [2, 36]. Many of these patients (75%) will not have a first-degree relative with CRC [2]. The increasing incidence of CRC in those under the age of 50 does not appear to be due to an

increase in inherited CRC, but this is difficult to distinguish given changes in testing and evolution of understanding of the causes of inherited CRC over time. The testing strategy will vary by institution, but testing should be directed by clinical phenotype and family history. If neither point to a particular genetic syndrome, then broader panel testing should be considered. Even for those patients where a heritable form of CRC is not found, the genetics of the tumor itself differ from tumors in older patients. YO-CRC that is sporadic typically has increased copy number change and is microsatellite stable [37]. Lieu and colleagues assessed the mutation rate across 403 cancer-related genes in 18,218 patients and found that those under the age of 50 had more alterations in *TP53* and *CTNNB1* but fewer mutations in *APC*, *KRAS*, *BRAF*, and *FAM123B*. How these and other genetic alterations change the biology of YO-CRC and its response to treatment is yet to be determined.

Inherited CRC

Inherited CRC is defined as CRC that is inherited through the transfer of an increased risk for CRC due to genetic alterations that have been passed on from one's parents. Each inherited genetic alteration causes a somewhat variable phenotype, and each has CRC as a part of the multiple phenotypic expressions of that genotype. Inherited CRC falls into two basic categories, those related to inherited polyposis and those that are not due to polyposis. Patients with polyposis develop polyps of the colon or rectum earlier and in greater number than patients with sporadic polyps. Patients with non-polyposis inherited CRC have an increased chance that a polyp will progress more rapidly to a cancer than a sporadic polyp does. The genetic alterations that cause inherited CRC have, in many cases, not been known before the phenotype of the disease was known, and so the syndromes are often defined by their phenotype rather than the mutation itself, as multiple different genetic alterations can lead to similar phenotypes. When thinking of treatment of these patients, it is important to remember to treat the phenotype of the patient and family rather than only their mutation status since a substantial percentage of patients with an apparently familial cancer will not have a known mutation identified [38]. This is likely due to our lack of knowledge of all the genetic mutations that produce an increased risk phenotype, rather than a true lack of a genetic alteration.

Lynch Syndrome (Hereditary Non-polyposis CRC)

LS is the most common inherited CRC syndrome, with Lynch-associated genetic defects identified in approximately 3% of CRC patients [39]. LS is inherited in an autosomal dominant manner. Family history plays an important role in identifying affected probands and prompting screening of at-risk family members, although establishing the diagnosis of LS requires testing for specific germline mutations in mismatch repair (MMR) genes. Once diagnosed with LS, recommendations for screening and treatment can be tailored for the patient and their at-risk relatives.

The designation of *hereditary non-polyposis CRC* (or HNPCC) denotes a familial CRC syndrome that meets certain criteria based on presenting factors and family history, while the "LS" designation is reserved for patients in whom germline genetic testing confirms specific mutations in MMR genes. The term "non-polyposis" may be misconstrued to mean that LS-associated CRCs do not follow a typical progression from adenoma to invasive carcinoma. On the contrary, most (but perhaps not all) CRCs in MMR-deficient patients do arise from adenomatous polyps. In fact, LS patients have a similar incidence of adenomas as patients with sporadic CRC [40]. However, LS-related carcinogenesis progresses more rapidly than sporadic carcinogenesis, some developing from seemingly normal mucosa in as quickly as a year [41].

Genetic Mutation

The genetic alteration causing malignancy in patients with LS is a defect in the mechanisms for repairing acquired genetic defects. During DNA replication, mistakes are made at a rate of about 1 in every 10,000 bases which is called mismatch. The four major genes responsible for mismatch repair (MMR) are *MLH1*, *MSH2*, *MSH6*, and *PMS2*. In addition, deletions in the 3′ end of *EPCAM* leads to methylation of the promoter region of *MSH2*, resulting in silencing of this gene and clinical presentation similar to genetic mutation of *MSH2* itself. Patients with LS have an inherited defect in a specific MMR gene and then acquire a "second hit" to their remaining functional copy. This leads to complete loss of function of MMR and subsequent accumulation of genetic errors throughout the genome, leading to cancers mostly in organs with a higher rate of cellular turnover such as the colon, endometrium, stomach, and urologic system.

Tumors with defective MMR often display high levels of microsatellite instability (MSI). Microsatellites are tandem base pair repeats in the DNA, typically 1–3 nucleotides in length. Impaired mismatch repair mechanisms allow these microsatellites to proliferate. MSI can be detected using polymerase chain reaction (PCR) assays. Cleaving of DNA during PCR leads to irregular strand lengths at specific intervals and the designation of instability. By definition, tumors that are high in instability measurements (MSI-H) have greater than 30% instability at common loci.

Overall, approximately 15% of CRCs are MSI-H, reflecting a possible deficiency in MMR [42]. However, not all MSI results from inherited mutations in MMR genes. Approximately 70% of MMR deficiency is caused by sporadic hypermethylation of MLH1, leading to suppressed

expression of this particular gene repair product and the subsequent accumulation of genetic damage. Hypermethylation is strongly associated with a specific somatic mutation in the BRAF oncogene (specifically, the V600E mutation) which is found in 69% of hypermethylated tumors; thus, loss of expression of MLH1 should prompt further investigation of the status of BRAF [43]. In general, if a patient has an MLH1-deficient tumor, and a BRAF mutation is found, it is unlikely the patient has Lynch. However, if BRAF is normal, the patient should be considered for germline mutational analysis to look for Lynch-associated mutations.

Clinically, MMR gene function is assessed either by MSI measurement using PCR or direct staining for specific gene products using immunohistochemistry (IHC for MMR). MSI and IHC testing has comparable sensitivity and specificity for defects in MMR gene function; the preferred testing approach is institution dependent, although IHC tends to be less expensive than MSI testing and has supplanted MSI testing in many areas [44]. It is important to note that MSI and IHC testing of the tumor is an evaluation of the phenotype of the tumor itself, and thus neither MSI nor IHC testing confirms the diagnosis of LS. LS is confirmed only by finding germline mutations on subsequent genetic testing.

Additionally, specific patterns of differential expression may be observed. For instance, MLH1 and PMS2 proteins function as a heterodimer; loss of expression of both indicates either an alteration in MLH1 due to somatic methylation (sporadic cancer) or MLH1 germline mutation (as in LS) [45]. For these reasons, loss of expression of MLH1 should lead to further tumor-specific genetic testing. Conversely, functional absences of MSH2, MSH6, or PMS2 typically arise from germline mutations.

Diagnosis and Histology

The initial identification of a "family cancer syndrome" by Henry Lynch and colleagues in 1966 described two Midwestern kindreds who exhibited multigenerational autosomal dominant inheritance of colorectal, endometrial, and other malignancies [46]. The authors noted that family members likely represented "carcinoma-susceptible genotypes." In 1991, the clinical context was further refined by the International Collaborative Group on HNPCC meeting in Amsterdam, with the development of guidelines for identifying potentially affected individuals. These definitions were broadened in 1999 by the Amsterdam II criteria to include non-colonic malignancies. The Bethesda criteria were subsequently developed to better refine which patients may benefit from additional workup with genetic testing. Over the last two decades, additional research has focused on improving the sensitivity and specificity of these parameters. Clinical online or downloadable risk prediction models exist for determining the likelihood a family member of a patient with CRC has LS. Both PREMM5 (premm.dfci.harvard.edu) and MMRpro (projects.iq.harvard.edu/bayesmendel/mmrpro) assess the risk in unaffected individuals. In the setting of a suggestive family history, use of these models may reduce unnecessary genetic testing [44]. Ultimately, routine MMR testing of biopsied or resected CRCs has largely supplanted reliance on family history for identifying potential LS. Figure 22.1 depicts one proposed pathway for reliably confirming LS while eliminating possible confounding conditions. When establishing the diagnosis of LS, it remains important to advise patients of the risk for other family members. Since LS is inherited in an autosomal dominant manner, offspring of the proband have a 50% chance of being affected. Genetic counseling and germline testing are recommended for all immediate family members of LS patients.

As previously mentioned, routine testing for MMR pathway function in resected colorectal and endometrial cancers has become standard in most facilities. The most recent guidelines from the NCCN and the American Gastroenterological Association recommend universal screening for MMR function in all resected CRC specimens [44, 47]. This may be accomplished either with determination of MSI status or IHC staining for MMR proteins. Rectal cancer biopsy specimens should also undergo routine screening, as rectal cancer patients are often treated with neoadjuvant therapy which may interfere with this analysis post hoc. An exciting near-term alternative to sequential MSI or IHC testing followed by germline evaluation is next-generation sequencing of the tumor biopsy itself. Compared to traditional multiple sequential evaluation for LS (e.g., MSI/IHC, followed by germline blood or buccal testing), up-front tumor sequencing demonstrated equivalent specificity and superior sensitivity for LS in a prospective cohort of CRC patients [43]. Next-generation tumor sequencing has the added benefit of off-target testing for other mutations such as *KRAS/NRAS* and *DPYD* that may influence chemotherapeutic decision-making, and it may shorten the time to final diagnosis of LS, thereby providing the surgeon and patient more complete information prior to surgery.

LS-related CRCs have certain phenotypic and histologic findings. MMR-deficient cancers may present at an earlier stage; deficient MMR is seen in 20% of stage II, 11% of stage III, and only 3.5% of stage IV CRCs [45, 48]. MMR-deficient colon cancers more commonly arise on the right side, although MMR-deficient cancers in the descending or sigmoid colon or rectal cancer may certainly occur. Compared to sporadic tumors, LS-associated CRC is more often poorly differentiated and presents with mucinous or signet ring cell features on histology. Tumor-infiltrating lymphocytes (TILs) are commonly observed as well [42]. The robust immune response by TILs relates to the greater expression of tumor-related antigens present in tumors with high mutational rates, particularly the accumulation of

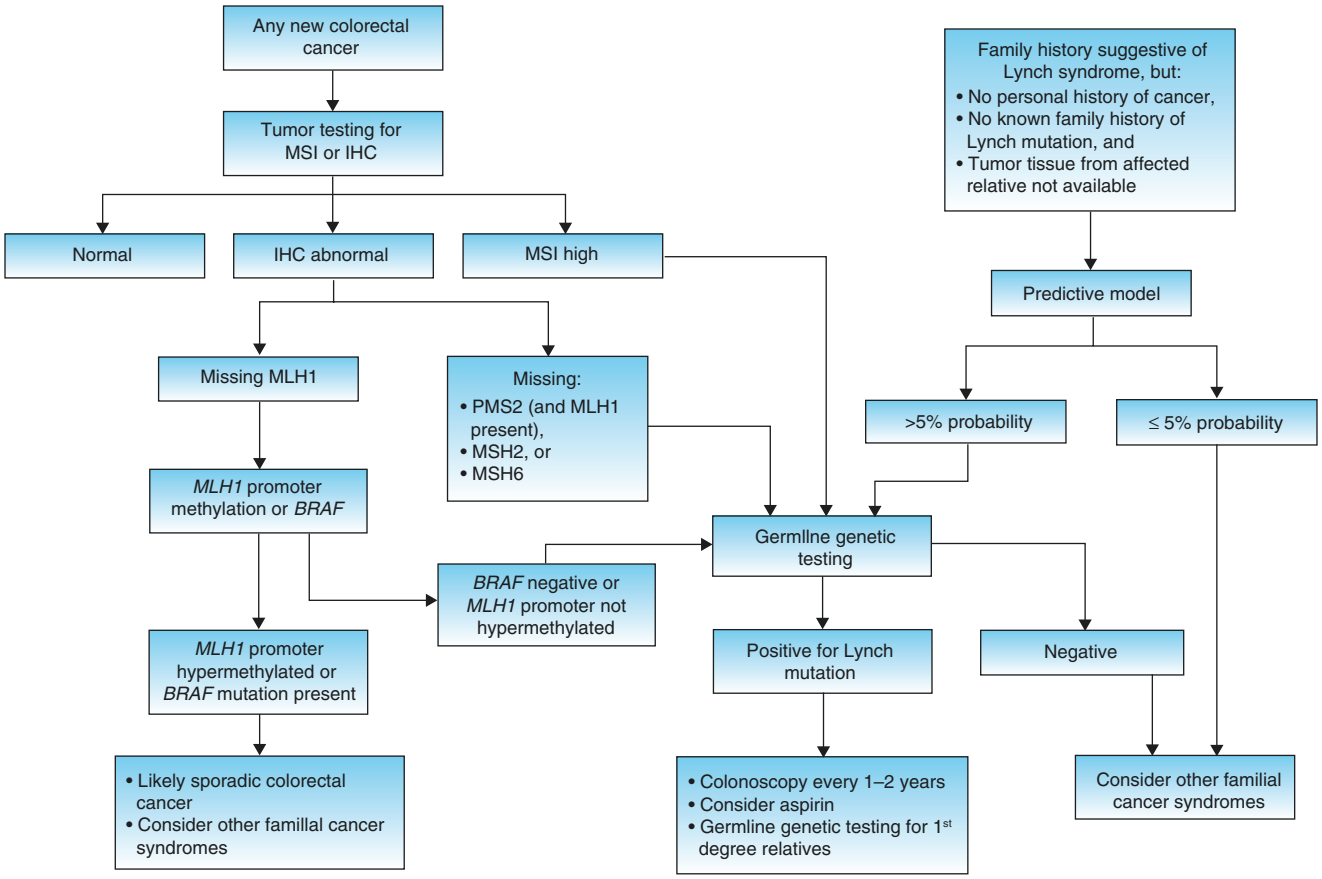

Fig. 22.1 A proposed algorithm for evaluating patients with newly diagnosed colorectal cancer for Lynch syndrome. (Used with permission from Rubenstein et al. [44]. Copyright © 2015 Elsevier)

frameshift mutations that lead to synthesis of neoantigens recognized by CD8+ T cells [42, 49].

Lynch Syndrome Variants

Turcot Syndrome

In addition to CRC, patients with Turcot syndrome develop tumors of the central nervous system. Also termed "brain tumor polyposis syndrome" or BTPS, Turcot syndrome can be due to mismatch repair deficiencies as seen in Lynch (type 1) or related to biallelic loss of the APC gene as seen with familial adenomatous polyposis (FAP) (type 2) [50]. Glioblastoma multiforme is the most common neurological cancer in type 1, while patients with type 2 may develop medulloblastomas.

Muir-Torre Syndrome

Patients with Muir-Torre syndrome (MTS) present with skin structure-related neoplasms, predominantly sebaceous gland tumors. While most commonly caused by loss of genes involved in LS, approximately one-third of MTS may be related to MUTYH-associated polyposis [51]. Sebaceous adenomas and carcinomas are rarely seen outside of MTS, and genetic counseling should be considered for any patient diagnosed with a sebaceous tumor [51]. Use of immunosuppressant medications may unmask MTS as an underlying condition.

Familial CRC X

Patients who meet clinical guidelines for HNPCC based on family history and age at presentation (e.g., Bethesda criteria) but have microsatellite-stable (MSS) tumors are designated as having familial CRC X syndrome. Such patients tend to present at a later age than those with LS, colon cancers occur distally more often, and they seemingly do not have similar risk for extra-colonic malignancies [52, 53]. While the exact genetic mechanism is unknown, unlike LS cancers which tend to have stable chromosomal length, familial CRC X-related cancers demonstrate a high degree of chromosomal instability more similar to sporadic cancers.

Screening Recommendations

Large population-based retrospective studies suggest that while routine biannual colonoscopy reduces the incidence of CRC in LS patients, such surveillance still fails to prevent a substantial number of cancers [39, 41, 54–56]. Conversely, others have shown that high compliance with recommended

screening in LS patients yields cancer-specific survival rates similar to non-affected family members [55]. A recent meta-analysis found that surveillance colonoscopy was associated with a decreased incidence of CRC (OR 0.23) and decreased CRC mortality (OR 0.06) compared to no screening [44]. On average, the simple act of screening increased life expectancy by 7 years. Specifically, for people with mutations in *MLH1* or *MSH2*, the estimated risk of developing CRC over the subsequent 5 years increases from 1 in 71 for males (1 in 102 for females) in their 20s to 1 in 7 for males (1 in 12 for females) by age 50 years [57]. In light of these findings, most experts recommend surveillance colonoscopy every 1–2 years in patients diagnosed with LS. Carriers of MLH1 or MSH2 mutations should undergo screening colonoscopy starting at age 20–25 years; colonoscopy should commence at age 30 for those with MSH6 and no later than age 35 for PMS2 [58, 59].

Women with LS are at increased risk for developing endometrial and ovarian cancers, and after CRC, endometrial cancer is the most common malignancy in LS. MSH6 in particular conveys elevated risk, with a lifetime incidence of over 40% [58]. Based on these risks, female LS patients should undergo annual bimanual exams with endometrial sampling and transvaginal ultrasound starting around age 30–35 years [58]. Such patients should also be counseled on prophylactic hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO) after completion of childbearing, a recommendation supported by a large case-control study of women with Lynch that found 100% risk reduction in subsequent gynecologic malignancy [60]. Strong consideration should be given to concurrent TAH/BSO in LS patients requiring colectomy. Although LS patients are at risk for other malignancies besides colorectal and gynecologic cancers, the estimated lifetime risks for these other malignancies do not exceed 3% regardless of gene mutation [61]. Transitional cell malignancies within the urinary system occur more commonly relative to the average-risk population. Annual urinalysis effectively screens for urothelial cancers. Similarly, there is an elevated incidence of upper gastrointestinal epithelial malignancy; a baseline esophagogastroduodenoscopy (EGD) with patient-tailored surveillance should be done at age 30–35 years, and repeated every 2–3 years, especially in individuals with a family history of LS-related gastric cancers.

Surgical Treatment

Since knowledge of LS-related gene defects may influence recommendations for extent of surgery, it is preferable that biopsies of clinical cancers obtained during colonoscopy undergo routine testing for MMR gene products. If LS is either genetically confirmed or there is a high index of clinical suspicion, patients should be counseled on the surgical options for treating their colon cancer. Multiple studies favor total abdominal colectomy over segmental resection in patients with LS [62–65]. The most recent US Multisociety Task Force on CRC and ASCRS Clinical Practice Guidelines both recommend total abdominal colectomy with ileorectal anastomosis in LS patients [58, 59].

Extended resection reduces the risk for developing secondary colorectal malignancy. A large registry-based cohort study found that the risk of metachronous CRCs increases to over 60% at 30 years [64]. This risk was reduced in LS patients who underwent subtotal colectomy at the index diagnosis. Notably, the observed risk for developing a metachronous colon cancer in the segmental resection group approximated the de novo risk associated with LS, suggesting there was no risk reduction of subsequent malignancy when patients undergo segmental resection only [59]. Kalady et al. found that 47% of patients meeting Amsterdam clinical criteria for HNPCC developed advanced adenomas or CRC following index segmental colectomy at a median follow-up of 69 months, compared to only 19% of those treated with total colectomy [62]. Similar results were reported in a meta-analysis of almost 1000 LS patients; metachronous cancers developed more commonly following segmental vs. total colectomy (23.5 vs. 6.8%, respectively; OR 3.7) [63]. However, no difference in overall survival between the two groups was found. Others have confirmed the lack of demonstrable survival benefit following total colectomy [56].

Factors influencing the decision for less radical resection include tumor stage, age, fecal continence status, anticipated reliability with surveillance examinations, and patient preference. There is little benefit to prophylactic colectomy in patients with incurable stage IV disease. Compared to segmental resection, total abdominal colectomy leads to significantly greater stool frequency and adversely impacts social function [66]. LS patients should be counseled on the anticipated bowel function prior to surgery. Another reasonable option is subtotal colectomy and ileosigmoid anastomosis. Patients would be expected to enjoy nearly the same risk reduction as total abdominal colectomy and would still be able to undergo surveillance via flexible sigmoidoscopy while having improved bowel function.

Patients with LS and rectal cancer may be a group who are best served with segmental resection [59]. The alternative of total proctocolectomy with or without IPAA presents a pronounced functional difference from the patient perspective versus restorative proctectomy. However, the risk of developing a second colorectal malignancy following proctectomy varies between 15% and 27% within the first decade postoperatively, even with regular endoscopic surveillance [67, 68]. In addition to patient-specific features, factors such as the necessity of pelvic radiation and the prospects for sphincter salvage based on tumor location will impact this decision.

Given the significant risk for metachronous CRC, regular colonoscopy on an annual basis is recommended after colectomy [59]. Although no clear benefit has been demonstrated in terms of survival, such intensive surveillance may detect malignancy at an earlier stage [64].

Medical Treatment

Patients with stage III MMR-deficient CRCs are treated with oxaliplatin-based adjuvant chemotherapy (e.g., FOLFOX), similar to those with sporadic tumors [69, 70]. However, single-agent 5-FU-based chemotherapy may be less efficacious in patients with LS, and no survival benefit is seen in stage II MMR-deficient patients, even in the setting of other high-risk features [71]. Interestingly, although CRCs with mutated MMR genes present more commonly with poor differentiation and mucinous features, LS patients experience better stage-matched survival and fewer recurrences compared to sporadic cancers, particularly for cancers in the proximal colon [69, 70, 72, 73]. As mentioned above, MMR-deficient cancers express high levels of tumor-related neoantigens, prompting increased TIL presence [49]. An exciting recent development is clinical application of immune-modulating drugs for fighting solid tumors. Pembrolizumab and nivolumab are specific antibodies to the programmed cell death protein 1 (PD-1); collectively, these drugs are commonly termed immune checkpoint inhibitors [17]. Along with ipilimumab (an antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4)), these immunotherapies are FDA-approved for treating metastatic CRCs with high microsatellite instability. Evidence suggests that most MMR-deficient tumors respond to immunotherapy but most MMR proficient tumors do not [17]. A confirmatory phase III trial is underway, comparing overall survival from colon cancers with deficient mismatch repair treated with adjuvant FOLFOX vs. FOLFOX plus atezolizumab (a PD-L1 antibody) [45].

Long-term aspirin use seems to reduce the risk of subsequent CRC in LS patients. The CAPP2 randomized controlled trial investigated the utility of aspirin 600 mg/day in patients with LS [40]. Investigators found a 50% reduction in cancer incidence in patients randomized to the aspirin interventional arm over a period of 4 years. Notably, despite regular endoscopic surveillance, 7% of non-aspirin study participants developed CRC during the study. Routine aspirin use is recommended by the American Gastroenterological Association, while the American College of Gastroenterology makes it a conditional recommendation until further evidence is obtained [44, 74].

POLE/POLD1-Related Hereditary Cancer

A relatively newly described syndrome is polymerase proofreading-associated polyposis (PPAP). With an autosomal dominant inheritance and high penetrance, PPAP develops due to inactivating mutations in either *POLE* or *POLD1* [75, 76]. These proteins are members of the highly conserved DNA polymerase family of genes involved with both synthesizing and proofreading DNA. *POLD1* also participates in mismatch repair, and defective polymerase proofreading in combination with deficient MMR can contribute to the phenotype [77]. Patients with *POLD1* or *POLE* mutations exhibit limited adenomatous polyposis and are at increased risk for CRC, and women with *POLD1* mutations have elevated risk for endometrial and breast cancers [78]. No recommendations for screening exist, although frequent colonoscopy and colectomy as indicated based on phenotype seem reasonable [74].

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) accounts for approximately 1% of CRCs. The syndrome is clinically defined by the presence of over 100 synchronous colorectal adenomas. FAP affects men and women equally and has a prevalence between 2 and 3 cases per 100,000 worldwide [74]. Along with extracolonic manifestations as described below, FAP results in a near 100% risk for developing CRC by age 40 years [79]. While there is a strong familial association, de novo cases of FAP account for 25% of the disease, and these patients typically have invasive malignancy at presentation.

Genetic Mutations

FAP is inherited in an autosomal dominant manner with near 100% penetrance. The syndrome is caused by monoallelic mutation of the *APC* gene, a tumor suppressor located on chromosome 5q21. Adenoma formation occurs when the second gene copy is rendered nonfunctional through an acquired mutation or loss. The fact that 85% of sporadic CRCs (and 100% in FAP) harbor *APC* mutations reinforces its central role in progression to malignancy.

Over 800 mutations in *APC* have been described. Inactivating mutations most often occur towards the 5′ end of exon 15 in a portion termed the mutation cluster region. Limited genotype-phenotype correlations exist predicting the course of the disease. For instance, individuals with over 1000 polyps typically exhibit mutation in the mid-portion of the gene (exons 1250–1464). Specific mutations between exons 311 and 1444 predict congenital hypertrophy of the retinal pigment (CHRPE, see below), and mutations after 1444 correlate with desmoid development [80]. Such correlations remain imperfect; although more common with changes in specific coding regions, desmoid disease may occur with almost any described *APC* mutation [81]. No reliable predictors for upper gastrointestinal adenomas are known.

Extracolonic Manifestations

Several extracolonic conditions arise in patients with *APC* mutations. As prophylactic colectomy for FAP has become

widespread, these extracolonic manifestations now pose a greater mortality risk than CRC [82]. Duodenal adenomas develop in 90% of FAP patients, although the lifetime risk for duodenal cancer is only 5–10% [74, 83, 84]. Duodenal cancer usually presents around the fifth decade of life. Depending on location, polypectomy, segmental resection, or pancreaticoduodenectomy may be indicated. Up to 12% of FAP patients develop papillary thyroid cancer, with a female preponderance [85]. Affected patients are also at increased risk for bilio-pancreatic malignancy and hepatoblastoma. CHRPE is a benign finding consisting of black or brown spots on the retina. While no treatment is necessary, the presence of CHRPE may prompt genetic evaluation, since CHRPE is present in nearly 80% of FAP patients [86].

Desmoid tumors are histologically bland-appearing fibrous tumors that arise from connective tissue throughout the body. Approximately 15% of FAP patients develop desmoids.[87] Of these, roughly half will develop intra-abdominally, typically within 5 years of an inciting event such as surgical trauma. Risk factors for desmoid formation include a family history of desmoids, female sex, prior abdominal surgery, and specific mutations with the 3′ end of *APC* (specifically, codons 1399 and 1444) [87]. Notably, desmoids can occur with practically any *APC* mutation [81]. Desmoid behavior is unpredictable; they may grow, remain stable, or even spontaneously regress. Intra-abdominal desmoids may be staged based on symptoms, size, and involvement of other organs [88]. Advanced desmoids may cause mesenteric ischemia, ureteral or gastrointestinal obstruction, compression of the vena cava, and even death. One large single-center study reported a 5-year survival of only 53% in FAP patients with advanced desmoids who required TPN and narcotics [89]. Small or incidentally discovered desmoids may be resected surgically. However, asymptomatic desmoids should be observed to reduce the risk of further progression [88]. Patients with larger desmoids are often treated with NSAIDs such as sulindac and anti-estrogen agents (e.g., tamoxifen) [90]. Antisarcoma drugs (adriamycin/dacarbazine) may be used in extreme cases [89].

Screening Recommendations

FAP patients present with polyps at a mean age of 16 years, with hundreds of polyps developing by the second and third decade of life. Endoscopic screening should start at puberty. Flexible sigmoidoscopy is reasonable until polyps first develop, and then full colonoscopy is required [74]. The vast majority of polyps in FAP are tubular adenomas less than 5 mm in size. Additionally, histological findings unique to this syndrome are microadenomas or aberrant crypt foci, comprised of dysplastic epithelium in single mucosal crypts [91]. Colonoscopy should continue every 1–2 years until after puberty, at which point colectomy is recommended. A similar surveillance program should also be offered to first-degree relatives of FAP patients in whom genetic testing has not been performed or was inconclusive. Establishment of institutional or national FAP registries and screening of at-risk relatives has significantly improved survival [82, 92].

Upper endoscopy to evaluate for gastric and proximal small bowel adenomas should start at age 25–30 years, with frequency of follow-up exams based largely on the Spigelman stage of the visualized polyps. Consideration for annual thyroid ultrasound is on a case-by-case basis. Finally, in families with a history of hepatoblastoma, alpha-fetoprotein and liver ultrasound should be performed in children until age 7 years following genetic confirmation of *APC* mutation [74]. There are no consensus screening recommendations for desmoids.

Variants of FAP

Attenuated FAP

Patients with attenuated FAP (AFAP) typically present with fewer adenomatous polyps (12–100) at later age than FAP patients, with cancer developing between age 50 and 70 years. There may be a predilection for more proximal malignancy, with relative rectal sparing [93]. Mutations in AFAP occur at either the far proximal (5′) or distal ends of the *APC* gene, producing a truncated APC protein and resulting in an attenuated phenotype.[93] Screening with full colonoscopy should commence in the late teens to early 20s and continue every 1–2 years. Although CRC risk is attenuated, upper gastrointestinal polyp formation and risk are comparable to classic FAP [94]. Patients with AFAP can be managed with colonoscopic polypectomy and may not require colectomy. If colectomy is indicated, many patients with rectal sparing are adequately treated with total abdominal colectomy and ileorectal anastomosis, with ongoing surveillance of the rectum [74, 93].

Gardner Syndrome

Largely an antiquated moniker, Gardner syndrome is recognized as a variant of FAP caused by specific *APC* mutations. In addition to polyposis, patients with Gardner may develop osteomas of the jaw or skull, supernumerary teeth, and epidermoid cystic lesions.

Surgical Treatment

Colon screening with subsequent surgery decreases and almost eliminates mortality related to CRC in FAP [74, 95]. Prophylactic surgery timing is guided by polyp burden and size, polyp histology, and symptoms. While not unheard of, CRC before age 20 years is rare, and typically surgical resection can be postponed to early adulthood.

Generally, most FAP patients undergo total proctocolectomy with ileal pouch-anal anastomosis (IPAA). This operation removes the vast majority of polyp-bearing colonic mucosa and substantially reduces subsequent cancer risk.

However, IPAA reduces fecundity in females and has the potential to impair erectile and ejaculatory function in males [96, 97]. Quality of life following IPAA is reduced, and urinary and bowel dysfunction are common complaints [98]. The alternative of total colectomy with ileorectal anastomosis preserves the pelvic nerves and normal reproductive anatomy. This may be an acceptable option in FAP patients with fewer than 20 rectal polyps or in patients with AFAP. However, patients should be cautioned that eventual proctectomy is often required. Furthermore, registry-based data suggests that initial IPAA offers improved long-term survival to FAP patients, with the relative reduction in survival seen with ileorectal anastomosis largely due to the development of metachronous rectal cancer [99]. The rectum should be cleared of polyps endoscopically, and the histology of the polyps reviewed, prior to offering a patient a rectal-sparing operation for FAP. Others have explored using mutation analysis to guide surgery [100, 101]. Based on the site of *APC* mutation, patients having a "severe" genotype had a 61–74% risk of requiring subsequent proctectomy within 20 years of initial total colectomy. Total proctocolectomy with end ileostomy eliminates the risk of CRC.

Regardless of surgical approach, lifelong post-surgical surveillance is required. Annual proctoscopy is needed for patients with ileorectal anastomosis. Adenomas may also develop following IPAA, either in the retained anal transition zone or in the pouch itself [96, 102]. Considerable debate exists over the utility of mucosectomy during IPAA. A large meta-analysis comprised of more than 4100 patients found that nocturnal seepage occurred significantly more frequently in FAP patients who underwent mucosectomy [103]. Conversely, a trend towards more dysplasia was noted in the stapled cohort. Rectal adenocarcinomas have developed after both double-stapled IPAA and mucosectomy/hand-sewn IPAA but are rare, and no firm conclusions can be drawn regarding relative efficacy. As one would do prior to total abdominal colectomy, the transition zone and distal rectum should be cleared of polyps endoscopically, and the histology of the polyps reviewed, prior to offering a patient restorative proctocolectomy using a double-stapled technique for FAP.

MUTYH-Associated Polyposis

First described in 2002, MUTYH-associated polyposis (MAP) is a polyposis syndrome inherited in an autosomal recessive manner [104]. Patients typically present with an attenuated polyposis phenotype, such that the initial clinical definition included between 20 and 99 polyps to distinguish it from the more extensive polyposis seen in FAP. The majority of polyps are tubular adenomas, although tubulovillous and serrated adenomas may also occur [105]. Although most MAP patients will have significant polyposis, some malignancies occur in otherwise normal-appearing colon. Most MAP patients develop CRC in their 40s to 50s.

While significant polyposis is a defining feature, unlike FAP and AFAP, MAP patients do not have an identified *APC* mutation. The MUTYH protein is a base excision repair gene that repairs oxidative damage to DNA by excising oxidized guanosine that mis-pairs with adenosine. Dysfunctional MUTYH results in somatic G-to-T transversions within multiple genes, including *APC* and *KRAS*, leading to the development of colorectal neoplasia. The involvement of multiple genes likely explains the significant clinical heterogeneity in terms of age of onset, polyp type, and progression to invasion. Similar to the MMR-deficient malignancies seen with LS, MAP-related cancers occur more often proximally within the colon, and they tend to have higher rates of mucinous histology and TILs [106]. Likewise, overall survival tends to be better compared to sporadic cancers.

Polyps may be managed endoscopically, although often the disease burden precludes complete clearance. The diagnosis of invasive cancer should prompt total abdominal colectomy with ileorectal anastomosis and subsequent annual rectal surveillance. Patients with MAP-related rectal cancer should be considered for total proctocolectomy.

MAP should be suspected in any patient with CRC in the setting of significant polyposis but without an identified *APC* genetic mutation, or in young patients with a family history suggestive of autosomal recessive inheritance. Unlike other polyposis syndromes, offspring of affected patients have only 1–2% of having MAP since the estimated population incidence of a mutation in *MUTYH* is 1 in 45 [107]. However, siblings of the proband have a 25% likelihood of inheriting biallelic *MUTYH* mutations and should undergo genetic counseling and consider genetic testing, as mutation status may drive screening recommendations.

Patients with biallelic loss of *MUTYH* have a 50-fold risk of developing CRC relative to the general population, progressing to 80% incidence by age 70. Conversely, monoallelic mutation confers a threefold risk [108]. Colonoscopy every 1–2 years is recommend in patients with biallelic inactivating mutations, along with periodic EGD to evaluate for duodenal adenomas. Patients with MAP develop duodenal adenomas at a later age and less frequently than in FAP, although duodenal neoplasia still occurs in roughly one third of MAP patients [109].

Serrated Polyposis Syndrome

Serrated polyposis syndrome (SPS) is the most common polyposis syndrome currently known, found in as many as 1:111 individuals in screening cohorts [110, 111]. SPS increases the risk for CRC and predominantly occurs in patients of European lineage. The overall incidence is unknown but estimated at less than 1% of the population [112, 113]. Previously referred to as hyperplastic polyposis syndrome, the definition was broadened to include other serrated lesions such as sessile serrated polyps and serrated adenomas. SPS may have

considerable phenotypic overlap with MAP; testing for MUTYH mutation is reasonable in the setting of concurrent adenomas. BRAF mutations are also commonly observed. Recently, mutations in the ubiquitin ligase RNF43 have been identified in some families with SPS [114]. However, since the underlying genetic defects in SPS have not been fully elucidated, diagnosis relies exclusively on clinical criteria.

Diagnosis

With the increasing awareness of endoscopists of the malignant potential in serrated polyps, and the concomitant increase in detection and resection, the definition of SPS has evolved. The World Health Organization 2019 definition for SPS is the presence of one of the following conditions: (1) at least 5 serrated polyps proximal to the rectum, with 2 of these being greater than 10 mm in size, or (2) over 20 serrated polyps of any size distributed throughout the large bowel, with at least 5 being proximal to the rectum [110]. Notably, this is a cumulative lifetime polyp count.

Treatment

The lifetime risk for advanced neoplasia from SPS may be as high as 50%, although precise estimates are unknown [74, 112, 115]. Complete clearance of all polyps should be performed during colonoscopy, with a surveillance interval of 1–3 years based on polyp burden. Limited data suggest that intensive colonoscopic surveillance may reduce the risk for CRC developing in patient with SPS [116]. Patients who develop cancer should undergo segmental or total colectomy after informed discussion with the patient regarding risks and anticipated bowel function. Additionally, SPS is strongly associated with smoking [117]. The importance of smoking cessation as a modifiable risk factor should be reinforced in patients meeting clinical criteria for SPS.

Hamartomatous Polyposis Syndromes

While hamartomatous polyps themselves are non-neoplastic, the various hamartomatous polyposis syndromes predispose patients to developing colorectal adenocarcinoma. In addition to increased risk for malignancy, large polyp burden may necessitate surgical intervention for symptoms of gastrointestinal bleeding, obstruction secondary to intussusception, or abdominal pain [118]. Clinical criteria for assigning each syndrome based on phenotype and family history are largely being replaced with genetic evaluation with next-generation sequencing. The hamartomatous polyposis syndrome described below is all inherited in an autosomal dominant manner.

Juvenile Polyposis

Juvenile polyposis (JPS) is inherited most commonly through germline mutation of *SMAD4* or *BMPR1A*. Both these genes function as tumor suppressors within the TGF-ß pathway [119]. Specific mutations of *SMAD4* are also associated with hereditary hemorrhagic telangiectasias. Juvenile polyps may develop in the colon, stomach, small intestine, and duodenum. Polyps develop in the first decade of life; the average age at diagnosis is 18.5 years, when patients typically present with melena or hematochezia [74].

The lifetime risk of CRC in patients with JPS is approximately 40%, although estimates vary and the incidence may approach 68% by age 60 years [74, 120]. Cancer may develop at a young age, so recommendations for screening include initial colonoscopy at age 12 years, or earlier if presenting with symptoms [74]. All polyps should be cleared during each colonoscopy, and surveillance is based on polyp burden. Surveillance should also include regular EGD, as the lifetime incidence of gastric cancer approaches 30%.

Any patient with high-grade dysplasia, invasive malignancy, or polyp burden exceeding ability to manage endoscopically should undergo colectomy. Either total abdominal colectomy with ileorectal anastomosis or total proctocolectomy is acceptable. Patients offered the former option should be reliable and committed to regular flexible sigmoidoscopy of the rectum, as roughly half will require completion proctectomy due to excessive polyp formation [121].

Peutz-Jeghers Syndrome

Unlike JPS, hamartomas seen in Peutz-Jeghers syndrome (PJS) occur most frequently in the small bowel. Though smaller in number, PJS polyps tend to grow to larger size and more often cause symptoms through obstruction or abdominal pain. The majority of PJS patients develop mucocutaneous pigmentation, often seen at the vermillion border of the lips. The findings of perioral pigmentation and two or more hamartomatous polyps should prompt genetic evaluation for *STK11* mutations. This tumor suppressor is mutated in 94% of PJS families, although approximately 25% of PJS arises from de novo mutations [122, 123].

PJS leads to increased risk for both gastrointestinal and extraintestinal cancer. The estimated lifetime risks of developing malignancy are 39% for colorectal, 29% for gastric, 13% for small bowel, 21% for ovary, 10% for cervical or uterine, 9% for testicular, 15% for lung, and as high as 36% for pancreas [74]. The lifetime risk of breast cancer varies in PJS but may approach 50% in some cohorts. Screening for gastrointestinal involvement includes upper and lower endoscopy starting by age 8 years and then repeated every 3 years. Evaluation of the small bowel by either capsule endoscopy or CT enterography is also recommended.

Small bowel obstruction due to intermittent intussusception from a hamartoma develops in roughly 50% of PJS patients [124]. When operating for an obstructing lesion, the surgeon should thoroughly evaluate the remainder of the bowel for smaller polyps. This can be aided with on-table enteroscopy through the open ends of the resected segment.

Similar to other polyposis syndromes, progression to malignancy is best treated with total colectomy with ileorectal anastomosis. The role of STK11 as a tumor suppressor and evidence for unchecked neoplastic growth in its absence has led to efforts at chemoprevention. However, several studies with selective mTOR inhibitors (e.g., everolimus) have been plagued by poor patient accrual due to the rarity of PJS [125].

Cowden Syndrome

Also termed PTEN hamartoma tumor syndrome (PHTS), Cowden syndrome (CS) is caused by mutation of *PTEN*, a tumor suppressor gene involved in regulating intracellular signaling and apoptosis. Bannayan-Riley-Ruvalcaba syndrome is a variant that is also typically caused by *PTEN* mutation. Colonic polyps are found in 95% of CS patients, ranging from few to hundreds in number and distributed throughout the colon [74]. While hamartomatous polyps are the most common, multiple synchronous polyp types are often seen at colonoscopy, including adenomas, inflammatory polyps, ganglioneuromas, lipomas, and leiomyomas.

CS patients have a lifetime risk of CRC of 9–16%, with cancer often developing before the age of 50 years [126, 127]. Those identified with this disorder should start surveillance colonoscopy at age 15 years, followed by repeat exams every 2 years thereafter [74].

Conclusion

CRC is most commonly sporadic with a small percentage of cases being inherited. The genetic pathways involved and treatment of the tumors have substantial overlap, but the surveillance and need for preventive surgery differ substantially based on risk of tumor development.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7–30.
2. Stoffel EM, Koeppe E, Everett J, et al. Germline genetic features of young individuals with colorectal cancer. Gastroenterology. 2018;154:897–905 e891.
3. Siegel RL, Miller KD, Fedewa SA, et al. Colorectal cancer statistics, 2017. CA Cancer J Clin. 2017;67:177–93.
4. Brenner H, Hoffmeister M, Stegmaier C, Brenner G, Altenhofen L, Haug U. Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840,149 screening colonoscopies. Gut. 2007;56:1585–9.
5. Vieira AR, Abar L, Chan DSM, et al. Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. Ann Oncol. 2017;28:1788–802.
6. Feng Q, Liang S, Jia H, et al. Gut microbiome development along the colorectal adenoma-carcinoma sequence. Nat Commun. 2015;6:6528.
7. McTiernan A, Friedenreich CM, Katzmarzyk PT, et al. Physical activity in cancer prevention and survival: a systematic review. Med Sci Sports Exerc. 2019;51:1252–61.
8. Murphy N, Moreno V, Hughes DJ, et al. Lifestyle and dietary environmental factors in colorectal cancer susceptibility. Mol Asp Med. 2019;69:2–9.
9. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012;487: 330–337.
10. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61:759–67.
11. Giannakis M, Mu XJ, Shukla SA, et al. Genomic correlates of immune-cell infiltrates in colorectal carcinoma. Cell Rep. 2016;15:857–65.
12. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol. 2008;26:1626–34.
13. Tran B, Kopetz S, Tie J, et al. Impact of BRAF mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. Cancer. 2011;117:4623–32.
14. Kopetz S, Desai J, Chan E, et al. Phase II pilot study of vemurafenib in patients with metastatic BRAF-mutated colorectal cancer. J Clin Oncol. 2015;33:4032–8.
15. Vu T, Datta PK. Regulation of EMT in colorectal cancer: a culprit in metastasis. Cancers (Basel). 2017;9:171.
16. Sreekunmar R, Harris S, Moutasim K, DeMateos R, Patel A, Emo K, White S, Yagci T, Tulchinsky E, Thomas G, Primrose JN, Sayan AE, Mirnezami AH. Assessment of Nuclear ZEB2 is a biomarker for colorectal cancer outcome and TNM risk stratification. JAMA Network Open. 2018;1:e183115. https://doi.org/10.1001/jamanetworkopen.2018.3115.
17. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372:2509–20.
18. Hardiman KM, Sheppard BC. What to do when the pathology from last week's laparoscopic cholecystectomy is malignant and T1 or T2. J Gastrointest Surg. 2009;13:2037–9.
19. Ulintz PJ, Greenson JK, Wu R, Fearon ER, Hardiman KM. Lymph node metastases in colon cancer are polyclonal. Clin Cancer Res. 2018;24:2214–24.
20. Losi L, Baisse B, Bouzourene H, Benhattar J. Evolution of intratumoral genetic heterogeneity during colorectal cancer progression. Carcinogenesis. 2005;26:916–22.
21. Ptashkin RN, Pagan C, Yaeger R, et al. Chromosome 20q amplification defines a subtype of microsatellite stable, left-sided colon cancers with wild-type RAS/RAF and better overall survival. Mol Cancer Res. 2017;15:708–13.
22. Lengauer C, Kinzler KW, Vogelstein B. Genetic instability in colorectal cancers. Nature. 1997;386:623–7.
23. Weisenberger DJ, Siegmund KD, Campan M, et al. CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF mutation in colorectal cancer. Nat Genet. 2006;38:787–93.
24. Sakamoto N, Feng Y, Stolfi C, et al. BRAF(V600E) cooperates with CDX2 inactivation to promote serrated colorectal tumorigenesis. elife. 2017;6:e20331.
25. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. Nat Med. 2015;21:1350–6.
26. Lee MS, Menter DG, Kopetz S. Right versus left colon cancer biology: integrating the consensus molecular subtypes. J Natl Compr Cancer Netw. 2017;15:411–9.
27. Warschkow R, Sulz MC, Marti L, et al. Better survival in right-sided versus left-sided stage I - III colon cancer patients. BMC Cancer. 2016;16:554.
28. Weiss JM, Pfau PR, O'Connor ES, et al. Mortality by stage for right- versus left-sided colon cancer: analysis of surveillance, epidemiology, and end results--Medicare data. J Clin Oncol. 2011;29:4401–9.

29. Aljehani MA, Morgan JW, Guthrie LA, et al. Association of primary tumor site with mortality in patients receiving bevacizumab and cetuximab for metastatic colorectal cancer. JAMA Surg. 2018;153:60–7.
30. Mauri G, Sartore-Bianchi A, Russo AG, Marsoni S, Bardelli A, Siena S. Early-onset colorectal cancer in young individuals. Mol Oncol. 2019;13:109–31.
31. Bailey CE, Hu CY, You YN, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010. JAMA Surg. 2015;150:17–22.
32. Cavestro GM, Mannucci A, Zuppardo RA, Di Leo M, Stoffel E, Tonon G. Early onset sporadic colorectal cancer: worrisome trends and oncogenic features. Dig Liver Dis. 2018;50:521–32.
33. Peterse EFP, Meester RGS, Siegel RL, et al. The impact of the rising colorectal cancer incidence in young adults on the optimal age to start screening: microsimulation analysis I to inform the American Cancer Society colorectal cancer screening guideline. Cancer. 2018;124:2964–73.
34. NCCN clinical practice guidelines in oncology: colon cancer. Available from URL: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed 22 Nov 2019.
35. NCCN clinical practice guidelines in oncology: rectal cancer. Available from URL: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed 22 Nov 2019.
36. Pearlman R, Frankel WL, Swanson B, et al. Prevalence and spectrum of germline Cancer susceptibility gene mutations among patients with early-onset colorectal cancer. JAMA Oncol. 2017;3:464–71.
37. Lieu CH, Golemis EA, Serebriiskii IG, et al. Comprehensive genomic landscapes in early and later onset colorectal cancer. Clin Cancer Res. 2019;25:5852–8.
38. Valle L, Vilar E, Tavtigian SV, Stoffel EM. Genetic predisposition to colorectal cancer: syndromes, genes, classification of genetic variants and implications for precision medicine. J Pathol. 2019;247:574–88.
39. Moller P, Seppala T, Bernstein I, et al. Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut. 2017;66:464–72.
40. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet. 2011;378:2081–7.
41. Vasen HF, Abdirahman M, Brohet R, et al. One to 2-year surveillance intervals reduce risk of colorectal cancer in families with Lynch syndrome. Gastroenterology. 2010;138:2300–6.
42. Maby P, Tougeron D, Hamieh M, et al. Correlation between density of CD8+ T-cell infiltrate in microsatellite unstable colorectal cancers and frameshift mutations: a rationale for personalized immunotherapy. Cancer Res. 2015;75:3446–55.
43. Hampel H, Pearlman R, Beightol M, et al. Assessment of tumor sequencing as a replacement for Lynch syndrome screening and current molecular tests for patients with colorectal cancer. JAMA Oncol. 2018;4:806–13.
44. Rubenstein JH, Enns R, Heidelbaugh J, Barkun A, Clinical Guidelines C. American Gastroenterological Association Institute guideline on the diagnosis and management of Lynch syndrome. Gastroenterology. 2015;149:777–82; quiz e716–777.
45. Sinicrope FA. Lynch syndrome-associated colorectal cancer. N Engl J Med. 2018;379:764–73.
46. Lynch HT, Shaw MW, Magnuson CW, Larsen AL, Krush AJ. Hereditary factors in cancer. Study of two large Midwestern kindreds. Arch Intern Med. 1966;117:206–12.
47. Gupta S, Provenzale D, Llor X, et al. NCCN guidelines insights: genetic/familial high-risk assessment: colorectal, version 2.2019. J Natl Compr Cancer Netw. 2019;17:1032–41.
48. Koopman M, Kortman GA, Mekenkamp L, et al. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. Br J Cancer. 2009;100:266–73.
49. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357:409–13.
50. Khattab A, Monga DK. Turcot syndrome. Treasure Island: StatPearls; 2020.
51. John AM, Schwartz RA. Muir-Torre syndrome (MTS): an update and approach to diagnosis and management. J Am Acad Dermatol. 2016;74:558–66.
52. Lindor NM, Rabe K, Petersen GM, et al. Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. JAMA. 2005;293:1979–85.
53. Zetner DB, Bisgaard ML. Familial Colorectal Cancer Type X. Curr Genomics. 2017;18:341–59.
54. Newton K, Green K, Lalloo F, Evans DG, Hill J. Colonoscopy screening compliance and outcomes in patients with Lynch syndrome. Color Dis. 2015;17:38–46.
55. Jarvinen HJ, Renkonen-Sinisalo L, Aktan-Collan K, Peltomaki P, Aaltonen LA, Mecklin JP. Ten years after mutation testing for Lynch syndrome: cancer incidence and outcome in mutation-positive and mutation-negative family members. J Clin Oncol. 2009;27:4793–7.
56. Cirillo L, Urso ED, Parrinello G, et al. High risk of rectal cancer and of metachronous colorectal cancer in probands of families fulfilling the Amsterdam criteria. Ann Surg. 2013;257:900–4.
57. Jenkins MA, Dowty JG, Ait Ouakrim D, et al. Short-term risk of colorectal cancer in individuals with lynch syndrome: a meta-analysis. J Clin Oncol. 2015;33:326–31.
58. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US multi-society task force on colorectal cancer. Dis Colon Rectum. 2014;57:1025–48.
59. Herzig DO, Buie WD, Weiser MR, et al. Clinical practice guidelines for the surgical treatment of patients with Lynch syndrome. Dis Colon Rectum. 2017;60:137–43.
60. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med. 2006;354:261–9.
61. Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA. 2011;305:2304–10.
62. Kalady MF, McGannon E, Vogel JD, Manilich E, Fazio VW, Church JM. Risk of colorectal adenoma and carcinoma after colectomy for colorectal cancer in patients meeting Amsterdam criteria. Ann Surg. 2010;252:507–11; discussion 511–503.
63. Heneghan HM, Martin ST, Winter DC. Segmental vs extended colectomy in the management of hereditary nonpolyposis colorectal cancer: a systematic review and meta-analysis. Color Dis. 2015;17:382–9.
64. Parry S, Win AK, Parry B, et al. Metachronous colorectal cancer risk for mismatch repair gene mutation carriers: the advantage of more extensive colon surgery. Gut. 2011;60:950–7.
65. Natarajan N, Watson P, Silva-Lopez E, Lynch HT. Comparison of extended colectomy and limited resection in patients with Lynch syndrome. Dis Colon Rectum. 2010;53:77–82.
66. Haanstra JF, de Vos Tot Nederveen Cappel WH, Gopie JP, et al. Quality of life after surgery for colon cancer in patients with Lynch syndrome: partial versus subtotal colectomy. Dis Colon Rectum. 2012;55:653–9.
67. Kalady MF, Lipman J, McGannon E, Church JM. Risk of colonic neoplasia after proctectomy for rectal cancer in hereditary nonpolyposis colorectal cancer. Ann Surg. 2012;255:1121–5.

68. Win AK, Parry S, Parry B, et al. Risk of metachronous colon cancer following surgery for rectal cancer in mismatch repair gene mutation carriers. Ann Surg Oncol. 2013;20:1829–36.
69. Andre T, de Gramont A, Vernerey D, et al. Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC study. J Clin Oncol. 2015;33:4176–87.
70. Zaanan A, Shi Q, Taieb J, et al. Role of deficient DNA mismatch repair status in patients with stage III colon cancer treated with FOLFOX adjuvant chemotherapy: a pooled analysis from 2 randomized clinical trials. JAMA Oncol. 2018;4:379–83.
71. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol. 2010;28:3219–26.
72. Sinicrope FA, Shi Q, Allegra CJ, et al. Association of DNA mismatch repair and mutations in BRAF and KRAS with survival after recurrence in stage III colon cancers : a secondary analysis of 2 randomized clinical trials. JAMA Oncol. 2017;3:472–80.
73. Bruzzi M, Auclin E, Lo Dico R, et al. Influence of molecular status on recurrence site in patients treated for a stage III colon cancer: a post hoc analysis of the PETACC-8 trial. Ann Surg Oncol. 2019;26:3561–7.
74. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110:223–62; quiz 263.
75. Palles C, Cazier JB, Howarth KM, et al. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. Nat Genet. 2013;45:136–44.
76. Valle L, Hernandez-Illan E, Bellido F, et al. New insights into POLE and POLD1 germline mutations in familial colorectal cancer and polyposis. Hum Mol Genet. 2014;23:3506–12.
77. Valle L, de Voer RM, Goldberg Y, et al. Update on genetic predisposition to colorectal cancer and polyposis. Mol Asp Med. 2019;69:10–26.
78. Bellido F, Pineda M, Aiza G, et al. POLE and POLD1 mutations in 529 kindred with familial colorectal cancer and/or polyposis: review of reported cases and recommendations for genetic testing and surveillance. Genet Med. 2016;18:325–32.
79. Markowitz SD, Bertagnolli MM. Molecular origins of cancer: molecular basis of colorectal cancer. N Engl J Med. 2009;361:2449–60.
80. Nieuwenhuis MH, Vasen HF. Correlations between mutation site in APC and phenotype of familial adenomatous polyposis (FAP): a review of the literature. Crit Rev Oncol Hematol. 2007;61:153–61.
81. Church J, Xhaja X, LaGuardia L, O'Malley M, Burke C, Kalady M. Desmoids and genotype in familial adenomatous polyposis. Dis Colon Rectum. 2015;58:444–8.
82. Gibbons DC, Sinha A, Phillips RK, Clark SK. Colorectal cancer: no longer the issue in familial adenomatous polyposis? Familial Cancer. 2011;10:11–20.
83. Bulow S, Bjork J, Christensen IJ, et al. Duodenal adenomatosis in familial adenomatous polyposis. Gut. 2004;53:381–6.
84. Latchford AR, Neale KF, Spigelman AD, Phillips RK, Clark SK. Features of duodenal cancer in patients with familial adenomatous polyposis. Clin Gastroenterol Hepatol. 2009;7:659–63.
85. Herraiz M, Barbesino G, Faquin W, et al. Prevalence of thyroid cancer in familial adenomatous polyposis syndrome and the role of screening ultrasound examinations. Clin Gastroenterol Hepatol. 2007;5:367–73.
86. Nusliha A, Dalpatadu U, Amarasinghe B, Chandrasinghe PC, Deen KI. Congenital hypertrophy of retinal pigment epithelium (CHRPE) in patients with familial adenomatous polyposis (FAP); a polyposis registry experience. BMC Res Notes. 2014;7:734.
87. Sinha A, Tekkis PP, Gibbons DC, Phillips RK, Clark SK. Risk factors predicting desmoid occurrence in patients with familial adenomatous polyposis: a meta-analysis. Color Dis. 2011;13:1222–9.
88. Church J, Berk T, Boman BM, et al. Staging intra-abdominal desmoid tumors in familial adenomatous polyposis: a search for a uniform approach to a troubling disease. Dis Colon Rectum. 2005;48:1528–34.
89. Quintini C, Ward G, Shatnawei A, et al. Mortality of intra-abdominal desmoid tumors in patients with familial adenomatous polyposis: a single center review of 154 patients. Ann Surg. 2012;255:511–6.
90. Quast DR, Schneider R, Burdzik E, Hoppe S, Moslein G. Long-term outcome of sporadic and FAP-associated desmoid tumors treated with high-dose selective estrogen receptor modulators and sulindac: a single-center long-term observational study in 134 patients. Familial Cancer. 2016;15:31–40.
91. Matsumoto T, Iida M, Mizuno M, Shimizu M, Nakamura S, Fujishima M. In vivo observation of the ileal microadenoma in familial adenomatous polyposis. Am J Gastroenterol. 1999;94:3354–8.
92. Bulow S. Results of national registration of familial adenomatous polyposis. Gut. 2003;52:742–6.
93. Burt RW, Leppert MF, Slattery ML, et al. Genetic testing and phenotype in a large kindred with attenuated familial adenomatous polyposis. Gastroenterology. 2004;127:444–51.
94. Knudsen AL, Bisgaard ML, Bulow S. Attenuated familial adenomatous polyposis (AFAP). A review of the literature. Familial Cancer. 2003;2:43–55.
95. da Luz Moreira A, Church JM, Burke CA. The evolution of prophylactic colorectal surgery for familial adenomatous polyposis. Dis Colon Rectum. 2009;52:1481–6.
96. Kartheuser A, Stangherlin P, Brandt D, Remue C, Sempoux C. Restorative proctocolectomy and ileal pouch-anal anastomosis for familial adenomatous polyposis revisited. Familial Cancer. 2006;5:241–60; discussion 261–242.
97. Olsen KO, Juul S, Bulow S, et al. Female fecundity before and after operation for familial adenomatous polyposis. Br J Surg. 2003;90:227–31.
98. Gunther K, Braunrieder G, Bittorf BR, Hohenberger W, Matzel KE. Patients with familial adenomatous polyposis experience better bowel function and quality of life after ileorectal anastomosis than after ileoanal pouch. Color Dis. 2003;5:38–44.
99. Koskenvuo L, Mustonen H, Renkonen-Sinisalo L, Jarvinen HJ, Lepisto A. Comparison of proctocolectomy and ileal pouch-anal anastomosis to colectomy and ileorectal anastomosis in familial adenomatous polyposis. Familial Cancer. 2015;14:221–7.
100. Nieuwenhuis MH, Bulow S, Bjork J, et al. Genotype predicting phenotype in familial adenomatous polyposis: a practical application to the choice of surgery. Dis Colon Rectum. 2009;52:1259–63.
101. Nieuwenhuis MH, Mathus-Vliegen LM, Slors FJ, et al. Genotype-phenotype correlations as a guide in the management of familial adenomatous polyposis. Clin Gastroenterol Hepatol. 2007;5:374–8.
102. Church J. Ileoanal pouch neoplasia in familial adenomatous polyposis: an underestimated threat. Dis Colon Rectum. 2005;48:1708–13.
103. Lovegrove RE, Constantinides VA, Heriot AG, et al. A comparison of hand-sewn versus stapled ileal pouch anal anastomosis (IPAA) following proctocolectomy: a meta-analysis of 4183 patients. Ann Surg. 2006;244:18–26.
104. Al-Tassan N, Chmiel NH, Maynard J, et al. Inherited variants of MYH associated with somatic G:C-->T:A mutations in colorectal tumors. Nat Genet. 2002;30:227–32.
105. Guarinos C, Juarez M, Egoavil C, et al. Prevalence and characteristics of MUTYH-associated polyposis in patients with

multiple adenomatous and serrated polyps. Clin Cancer Res. 2014;20:1158–68.
106. Nielsen M, Morreau H, Vasen HF, Hes FJ. MUTYH-associated polyposis (MAP). Crit Rev Oncol Hematol. 2011;79:1–16.
107. Win AK, Jenkins MA, Dowty JG, et al. Prevalence and penetrance of major genes and polygenes for colorectal cancer. Cancer Epidemiol Biomark Prev. 2017;26:404–12.
108. Jenkins MA, Croitoru ME, Monga N, et al. Risk of colorectal cancer in monoallelic and biallelic carriers of MYH mutations: a population-based case-family study. Cancer Epidemiol Biomark Prev. 2006;15:312–4.
109. Walton SJ, Kallenberg FG, Clark SK, Dekker E, Latchford A. Frequency and features of duodenal adenomas in patients with MUTYH-associated polyposis. Clin Gastroenterol Hepatol. 2016;14:986–92.
110. Dekker E, Bleijenberg AGC, Balaguer F, et al. Update on the World Health Organization criteria for diagnosis of serrated polyposis syndrome. Gastroenterology. 2020;158(6):1520–3.
111. JEG IJ, Bevan R, Senore C, et al. Detection rate of serrated polyps and serrated polyposis syndrome in colorectal cancer screening cohorts: a European overview. Gut. 2017;66:1225–32.
112. Orlowska J. Hyperplastic polyposis syndrome and the risk of colorectal cancer. Gut. 2012;61:470–1; author reply 471–472.
113. Biswas S, Ellis AJ, Guy R, Savage H, Madronal K, East JE. High prevalence of hyperplastic polyposis syndrome (serrated polyposis) in the NHS bowel cancer screening programme. Gut. 2013;62:475.
114. Gala MK, Mizukami Y, Le LP, et al. Germline mutations in oncogene-induced senescence pathways are associated with multiple sessile serrated adenomas. Gastroenterology. 2014;146:520–9.
115. Bleijenberg AG, JE IJ, van Herwaarden YJ, et al. Personalised surveillance for serrated polyposis syndrome: results from a prospective 5-year international cohort study. Gut. 2020;69:112–21.
116. Parry S, Burt RW, Win AK, et al. Reducing the polyp burden in serrated polyposis by serial colonoscopy: the impact of nationally coordinated community surveillance. N Z Med J. 2017;130:57–67.
117. Jasperson KW, Kanth P, Kirchhoff AC, et al. Serrated polyposis: colonic phenotype, extracolonic features, and familial risk in a large cohort. Dis Colon Rectum. 2013;56:1211–6.
118. Gilad O, Rosner G, Fliss-Isakov N, et al. Clinical and histologic overlap and distinction among various hamartomatous polyposis syndromes. Clin Transl Gastroenterol. 2019;10:1–9.
119. Sayed MG, Ahmed AF, Ringold JR, et al. Germline SMAD4 or BMPR1A mutations and phenotype of juvenile polyposis. Ann Surg Oncol. 2002;9:901–6.
120. Brosens LA, van Hattem A, Hylind LM, et al. Risk of colorectal cancer in juvenile polyposis. Gut. 2007;56:965–7.
121. Oncel M, Church JM, Remzi FH, Fazio VW. Colonic surgery in patients with juvenile polyposis syndrome: a case series. Dis Colon Rectum. 2005;48:49–55; discussion 55–46.
122. Aretz S, Stienen D, Uhlhaas S, et al. High proportion of large genomic STK11 deletions in Peutz-Jeghers syndrome. Hum Mutat. 2005;26:513–9.
123. Schreibman IR, Baker M, Amos C, McGarrity TJ. The hamartomatous polyposis syndromes: a clinical and molecular review. Am J Gastroenterol. 2005;100:476–90.
124. Hearle N, Schumacher V, Menko FH, et al. STK11 status and intussusception risk in Peutz-Jeghers syndrome. J Med Genet. 2006;43:e41.
125. de Brabander J, Eskens F, Korsse SE, et al. Chemoprevention in patients with Peutz-Jeghers syndrome: lessons learned. Oncologist. 2018;23:399–e333.
126. Heald B, Mester J, Rybicki L, Orloff MS, Burke CA, Eng C. Frequent gastrointestinal polyps and colorectal adenocarcinomas in a prospective series of PTEN mutation carriers. Gastroenterology. 2010;139:1927–33.
127. Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res. 2012;18:400–7.

Management of Malignant Polyps

23

Dennis Yang and Mark H. Whiteford

Key Concepts

- Detailed polyp assessment is the first crucial step in determining the best therapeutic strategy.
- Endoscopic resection of low-risk T1 colorectal cancer is an effective treatment in select patients.
- En-bloc resection is crucial for adequate histopathologic assessment for curative intent.
- Transanal endoscopic surgery is another technique that permits full-thickness en-bloc resection for select malignant polyps or early cancers in the rectum.
- All polyps with predictors of deep submucosal invasion should be referred for surgery given the high risk for lymph node metastasis.

Overview

Colorectal cancer (CRC) remains a clinical problem as the third most common cancer worldwide and the second leading cause of cancer death [1]. Nearly all CRCs (>90%) are adenocarcinomas, and the majority (60–65%) arise sporadically as a consequence of somatic genetic and epigenetic mutations largely attributable to environmental risk factors [2]. A well-recognized characteristic of CRC carcinogenesis is that most cancers arise from benign precursor polyps. These polyps are growths or protuberances into the lumen above the adjacent colonic mucosa [3]. Benign polyps are lesions with dysplastic elements confined to the muscularis mucosa and have virtually negligible risk for lymph node metastasis. Conversely, malignant polyps are defined as lesions with dysplasia extending into the submucosa but not the muscularis propria and are classified as T1 lesions based on the current TMN classification [4, 5]. The key distinction between malignant polyps and their benign precursor lesions is the potential for lymph node metastasis, based on depth of submucosal invasion [6].

Colonoscopy has been shown to reduce CRC incidence and mortality by enabling the early detection and management of malignant polyps and its precursors [7–9]. Detailed lesion assessment is the first key step in directing the optimal endoscopic or surgical approach. In this chapter, we discuss the relative benefits and limitations of both endoscopic and surgical resection of malignant polyps, features associated with curative resection and assessment of lymph node metastasis, and surveillance strategies for patients with T1 colorectal cancers removed endoscopically.

Colorectal Cancer Precursor Lesions

Adenomatous polyps and serrated polyps represent the two main neoplastic subtypes that serve as direct precursors to most CRCs [3].

Adenomas

Adenomas are commonly regarded as the prototypical precursor of CRC, given that nearly 85–90% of sporadic CRCs derive from adenomas [10]. Histologically, adenomas are characterized by epithelial clusters of dysplastic glands and can be divided into tubular, tubulovillous, or villous types as per the World Health Organization (WHO) classification

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system [11]. By definition, a tubulovillous and villous adenoma have at least 25% and 75% of its volume with villous features, respectively [11]. Grading of dysplasia in adenomas is currently based on the revised Vienna classification of gastrointestinal epithelial neoplasia [12]. Adenomas with low-grade dysplasia (LGD) have neoplastic changes confined to the epithelial glands. In contrast, lesions with high-grade dysplasia (HGD) are characterized by a constellation of any of the following features: complex glandular crowding and irregularity, cribriform architecture, and severe cytological atypia [12, 13]. The principal distinction between an adenoma with HGD and a malignant polyp is that, in an adenoma with HCD, the dysplastic changes are confined to the epithelium without extending into the submucosa and thereby have no metastatic potential [14]. In general, lesions ≥1 cm, with predominantly villous features and/or HGD on histology are considered "advanced adenomas" with a higher risk of malignant transformation [15].

Serrated Polyps

Serrated polyps are an encompassing designation that includes hyperplastic polyps (HPs), sessile serrated lesions (SSLs), and traditional serrated adenomas (TSAs). HPs are the most common serrated polyp. They are usually less than 5 mm in size and are predominantly located in the rectosigmoid. Endoscopically, HPs are generally oval or round in shape and have a similar color to the surrounding normal colon mucosa. These lesions are often regarded as nonneoplastic. In contrast, both SSLs and TSAs are considered precursors lesions for CRC and may account for up to 25% of sporadic CRCs [10, 16]. Histologically, according to the WHO criteria, the presence of crypt distortion (e.g., horizontal crypts, dilated crypts, serrations extending to the crypt base) is the main feature that distinguishes SSLs from HPs [11]. SSLs are usually larger than HPs, are located predominantly in the right colon, and are characterized by an overlying mucous cap and poorly defined lateral margins on endoscopic evaluation. TSAs are a rare type of villous polyp that features prominent cytoplasmic eosinophilia, elongated nuclei, and ectopic crypts [11, 14]. On gross morphology, these lesions have an erythematous "pine cone" appearance and are mostly located in the distal colon [16, 17].

Colorectal Cancer Carcinogenic Pathways

Adenoma-Carcinoma Pathway

The adenoma-carcinoma sequence, in which the adenoma is the precursor to CRC, represents the "classic" or conventional pathway to CRC. In this stepwise model, gradual cumulative genetic and epigenetic mutations drive the transformation from normal colonic epithelium to adenoma and ultimately invasive cancer [18]. Early in this sequence, alterations in the adenomatous polyposis coli (APC) tumor suppressor gene result in overactivation of the Wnt/β-catenin signaling pathway, initiating dysregulated proliferation and adenoma development [19]. Subsequent "hits" in this classical pathway involve mutations to the KRAS oncogene and loss of function mutations of the TP53 tumor suppressor gene, which ultimately contributes to the progression from HGD to carcinoma [20]. This classical model of colorectal tumorigenesis forms the basis of the chromosomal instability (CIN) pathway [18–20].

Serrated Pathway

Similar to the classic adenoma-carcinoma sequence, the serrated pathway is also characterized by the accumulation of genetic and epigenetic alterations resulting in histological progression. It is widely accepted that the first step in this pathway involves the mutation in a gene that regulates the mitogen-activated protein kinase (MAPK) pathway, such as KRAS or BRAF [21]. Activating mutations of the oncogene BRAF induces both unregulated cellular proliferation through the MAPK pathway and methylation of CpG islands (CpG island methylator phenotype [CIMP]). Many tumor suppressor genes are silenced in the CIMP pathway, which subsequently promotes the progression of serrated polyps to CRC [22, 23].

Definition of Terms: Colorectal Cancer and the Malignant Polyp

CRC is defined as the invasion of neoplastic cells beyond the muscularis mucosa. Polyps with dysplastic elements (e.g., adenomas or serrated polyps) that are confined to the muscularis mucosa and without submucosal invasion do not meet the clinically accepted definition of CRC [5]. Historically, it was not unusual for pathologists to interchangeably use the terms *intramucosal adenocarcinoma*, *intraepithelial carcinoma*, *carcinoma* in situ, and HGD to label these lesions. This practice was rather confusing as the word "adenocarcinoma" can often be easily misinterpreted as being equivalent to CRC [24]. In contrast to any other organ in the gastrointestinal tract, the colonic mucosa is biologically unique in the sense that neoplastic invasion of the lamina propria (histologic area between the epithelium and muscularis mucosa) has negligible risk of lymphatic or distant metastasis [25]. Hence, these lesions, categorized as pT is on the TNM classification, should be considered "benign" and can be adequately treated with complete endoscopic resection without additional interventions [26].

The term *malignant polyp* is used to describe a colorectal lesion with dysplastic elements that appear benign macroscopically but has invaded through the muscularis mucosa and into the submucosa and are designated pT1 lesions according to the TMN classification [4, 5]. Malignant polyps account for approximately 12% of all polyps, and their incidence may be increasing due to the implementation of more effective screening programs [27]. The optimal management of malignant polyps is complex and requires a multidisciplinary approach. The critical initial step in the evaluation and management of malignant polyps revolves around careful lesion characterization, in an effort to recognize selected lesions that may be cured with endoscopic resection versus those that will require surgery.

Lesion Assessment

All colorectal polyps must be carefully examined during endoscopy, and features such as polyp size and location, macroscopic appearance, and pit/vascular pattern should be assessed and documented, as these features direct management decisions.

Polyp Morphology and Size

Lesions are initially characterized endoscopically by their macroscopic appearance (morphology) and size, which are two important features that may help differentiate benign precursor lesions and CRC.

The Paris classification is a consensus system used to describe the gross morphology of neoplastic lesions in the gastrointestinal tract [28]. This classification system, first introduced in 2002 by a multidisciplinary group of experts, has been widely validated and accepted as the standard nomenclature for colon polyps [29]. Based on the Paris classification (Fig. 23.1), lesions measuring 2.5 mm above the surrounding mucosa layer are broadly categorized as polypoid (type 0-I), whereas those measuring less than 2.5 mm are nonpolypoid (type 0-II). Polypoid type 0-I lesions can be pedunculated (0-Ip), subpedunculated (0-Isp), or sessile (0-Is). In general terms, pedunculated polyps are lesions that are attached to the underlying colonic mucosa by a stalk, while sessile polyps grow in a more flattened pattern across the mucosa thereby with less separation between the neoplastic epithelium from the underlying colonic mucosa. Nonpolypoid type 0-II can be further subdivided into those that are superficially elevated (0-IIa), flat (0-IIb), or depressed (0-IIc). Excavated lesions are designated as type 0-III. Lastly, polyps are considered mixed-type lesions if they have a combination of the above features (e.g., 0-IIa + IIc, 0-Is+IIa, 0-Is+IIc). It should be noted that the "0" is usually omitted in clinical practice—for example, an endoscopist is likely to label a polyp "type IIa" instead of "type 0-IIa."

The risk of invasion has been shown to be proportional to lesion size and the degree of polyp depression. In a prospective study of 1000 consecutive colonoscopies with 321 adenomas, polypoid lesions (Paris 0-I) ≤ 5 mm in size had essentially a 0% risk of harboring invasive cancer as compared to 90% in excavated lesions (Paris 0-III) ≥ 15 mm in size [30]. Similarly, in a prospective, multicenter observational study of 479 consecutive patients referred for endo-

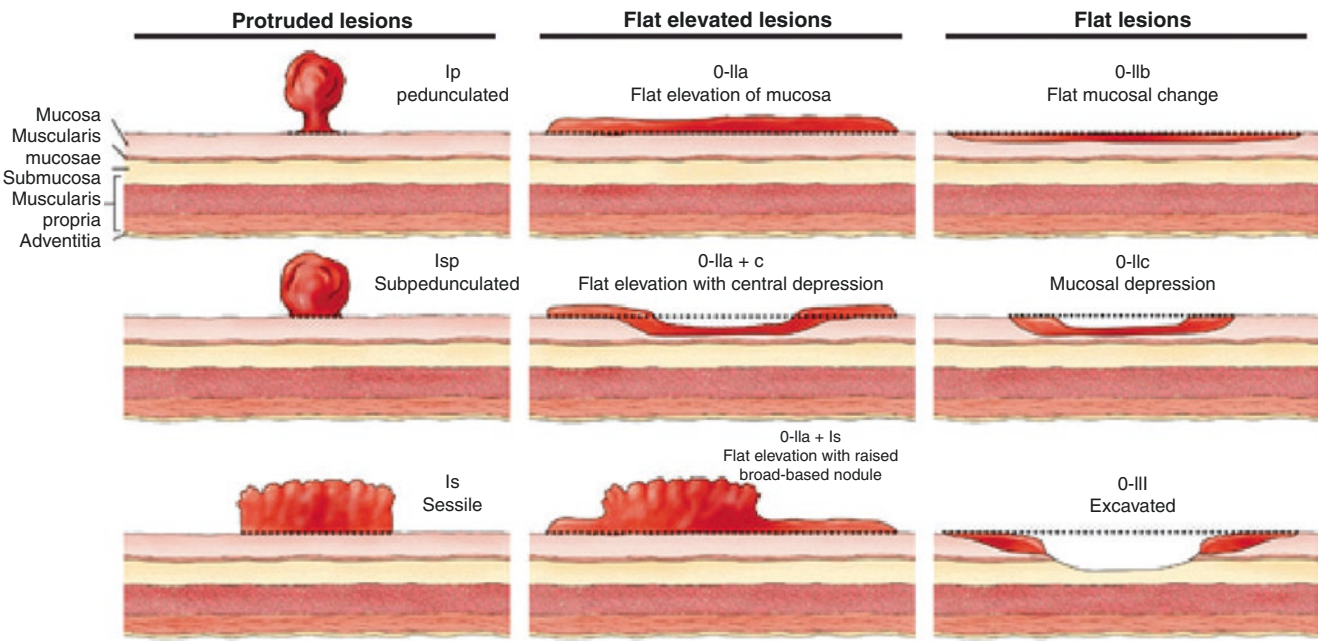


Fig. 23.1 Paris classification of polyps. (Reused with permission Holt and Bourke [95]. Copyright © 2012 Elsevier)

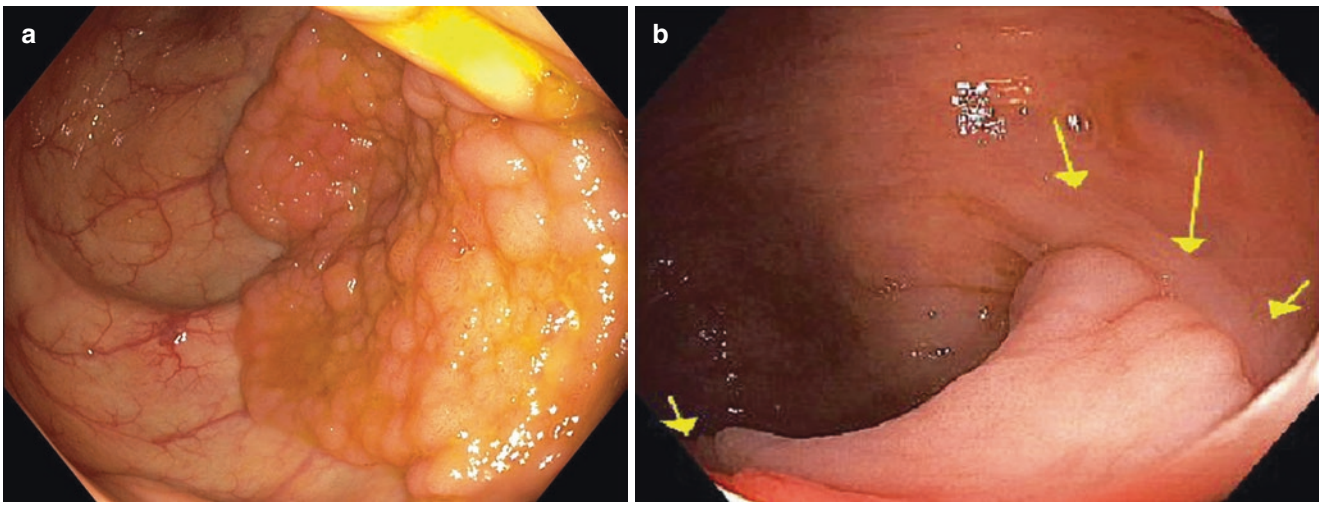


Fig. 23.2 Lateral spreading tumor with granular surface (LST-G) (**a**). Lateral spreading tumor non-granular type (LST-NG) highlighted by arrows (**b**)

scopic resection of sessile colon polyps ≥20 mm, Moss et al. identified lesions with depression (Paris 0-IIa + IIc) to be a risk factor for submucosal invasion [26]. Depressed lesions, particularly those with ulcerations or gross wall deformity should raise the suspicion of a deeply invasive cancer that may not be amenable for endoscopic resection.

Superficial nonpolypoid lesions measuring more than 10 mm in diameter that extend laterally rather than vertically are also referred as laterally spreading tumors (LSTs). The incidence of LST on routine colonoscopy is approximately 9% [31]. LSTs are broadly subclassified into the granular (LST-G) or non-granular type (LST-NG) (Fig. 23.2) [30]. LST-G is characterized by a nodular appearance that can be homogenous or mixed.

Similar to Paris classification, LST morphology is also prognostic for the risk of invasion. Homogenous LST-Gs have a low risk of local invasion (<2%) as compared to LST-Gs with mixed-size nodules (as high as 30% for those measuring more than 30 mm in size) [32]. Conversely, LST-NGs have a smooth surface and can be either flat or pseudo-depressed. The risk of submucosal invasion is even higher in LST-NGs with pseudo-depression, increasing from 12.5% for LST-NGs < 20 mm to 83% in those >30 mm in size [33]. In addition to polyp morphology and size, location is another important factor for risk of submucosal invasion. In a prospective study of 2277 LSTs in 2106 patients referred for endoscopic resection, Burgess et al. identified LST-NG or LST-G mixed-type lesions located in the rectosigmoid colon as having the highest risk for malignancy [34].

Polyp Surface Pit and Vascular Pattern

The shape of the opening of the crypts in the epithelium, or commonly referred to as pit pattern, has been shown to be associated with histologic prediction. Staining the surface of the colon with special dyes (e.g., indigo carmine) during conventional chromoendoscopy (CE) facilitates the evaluation of these pits. However, the main drawbacks include the cumbersome preparation and instillation of dyes, additional procedural time, and the lack of availability of some of these agents in many centers. Many newer generation endoscopes are equipped to enhance imaging by digitally manipulating and filtering the light source, e.g., narrow band imaging. This form of optical digital CE has the advantage of being more readily accessible and convenient to use, as opposed to conventional dye-based CE.

Kudo and colleagues first highlighted the feasibility of examining and classifying pit patterns to distinguish non-neoplastic from neoplastic polyps via magnifying endoscopy [35]. This scheme classifies pit patterns into seven types based on the pit appearance and structure (Fig. 23.3). Type I pits appear as round pits and are characteristic of normal colon mucosa. Type II includes stellate or papillary pits, which often correspond to hyperplasia. Type III-s pits appear as tubular or round pits smaller than in type I, whereas type III-L includes tubular or round pits larger than those in type I. Type IV pits have a dendritic or gyurs-like pattern. Type III to type IV pit patterns are often characteristic of adenomatous polyps, which can be resected endoscopically. Lastly, type Vi includes irregularly sized and arranged pit patterns, while type Vn describes lesions with an amorphous, nonstructured pit pattern. Both type Vi and Vn are indicative of either superficial or deep submucosal invasion, respectively, with only a select number of these cases amenable to endoscopic resection and the rest requiring surgery [36–38].

As noted previously, narrowband imaging (NBI) is a form of digital CE that facilitates detailed inspection of the capillary mucosal pattern by filtering white light into spe-

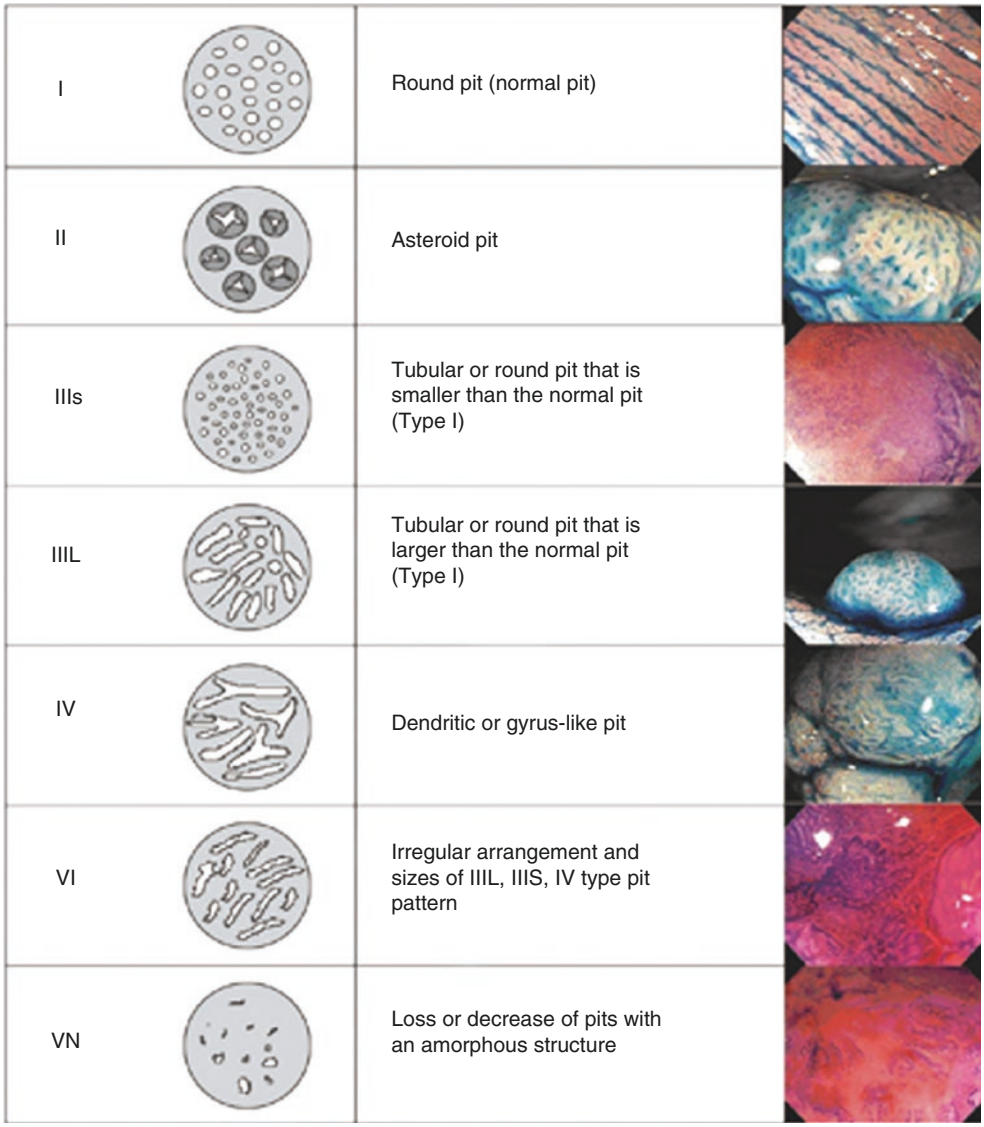
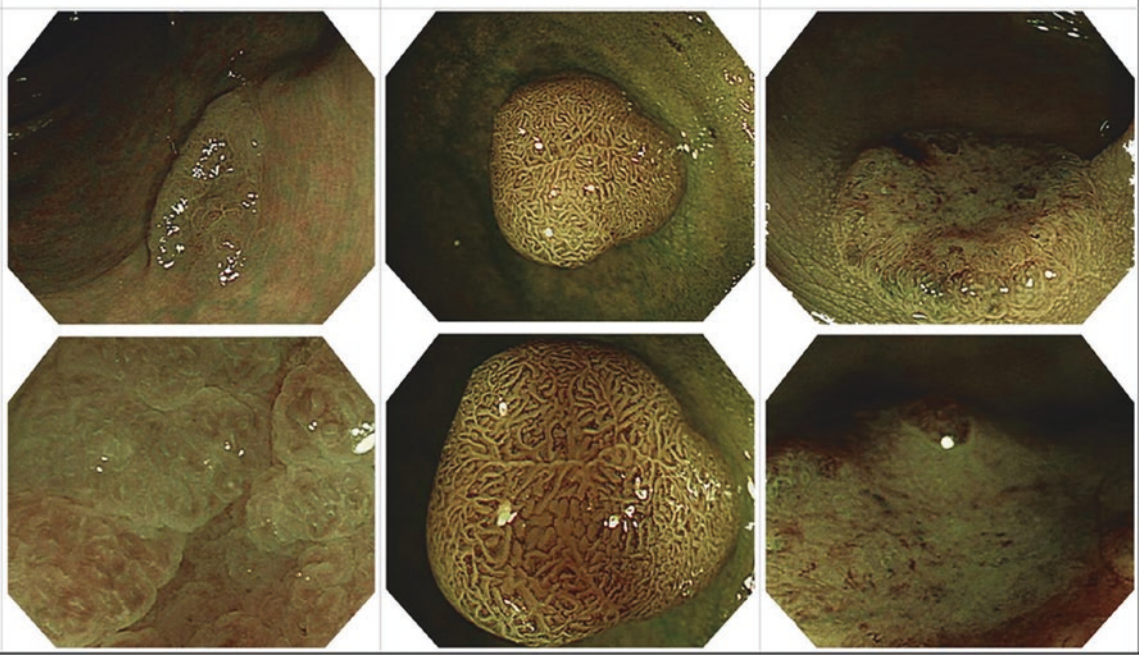


Fig. 23.3 Kudo pit pattern classification. (Reused with permission Tanaka et al. [96]. Copyright © 2006 Elsevier)

cific wavelengths that enhance the superficial microvasculature structures [39]. The Sano classification was the first published NBI magnifying endoscopic classification in 2006 [40] with several validation studies subsequently corroborating its usefulness in both qualitative and quantitative diagnosis of colorectal lesions [41–43]. In addition to Sano, there has been multiple other classification systems introduced in Japan over the years [44]. In an effort to develop a simpler classification system that could be adopted worldwide, particularly in non-Asian countries, the Colon Tumor NBI Interest Group (CTNIG) headed by both Eastern and Western expert endoscopists introduced the Narrow-Band Imaging International Colorectal Endoscopic (NICE) classification system in 2009 [45]. The NICE classification categorizes lesions into three types (1–3, and) based on color, vessels, and surface pattern (Fig. 23.4). Type I lesions, typically hyperplastic or serrated lesions, are characterized by having same or lighter color than the background, none or isolated lacy vessels, and dark or white spots of uniform size. Adenomatous polyps are classified as type II and feature browner color when compared to the background with brown vessels surrounding oval, tubular branched white structures. Lastly, type III lesions show a dark brown background, disrupted or missing vessel pattern, and amorphous or absent surface pattern, which most often corresponds to lesions with deep submucosal invasion [45]. The NICE classification system has been validated as an important tool for neoplasia classification and depth assessment [45, 46]. In a multicenter prospective study of 1634 consecutive patients with 2123 lesions >10 mm in size, the NICE classification identified those with deep invasion with 96.4% specificity [46].

NBI International colorectal endoscopic (NICE) Classification*

	Type 1	Type 2	Type 3
Color	Same or lighter than background	Browner relative to background (verify color arises from vessels)	Brown to dark brown relative to background; sometimes patchy whiter areas
Vessels	None, or isolated lcy vessels coursing across the lesion	Brown vessels surrounding white structures**	Has area(s) of disrupted or missing vessels
Surface Pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular or branched white structure surrounded by brown vessels**	Amorphous or absent surface pattern
Most likely pathology	**Hyperplastic**	**Adenoma*** **	**Deep submucosal invasive cancer**
Examples			

* Can be applied using colonscopes with or without optical (zoom) magnification
** These structures (regular or irregular) may represent the pits and the epithelium of the crypt opening.
*** Type 2 consists of vienna classification type 3, 4 and superficial 5 (all adenomas with either low or high grade dysplasia, or with superficial submucosal carcinoma). The presence of high grade dysplasia or superficia submucosal carcinoma may be suggested by an irregular vessel or surface pattern, and is often associated with atypical morphology (e.g., depressed area).

Fig. 23.4 NBI International Colorectal Endoscopic (NICE) classification. (Reused with permission Hayashi et al. Copyright © 2013 Elsevier)

Depth of Invasion

The depth of invasion is the most important feature when evaluating resectability and risk for lymph node metastasis. As previously alluded, polyps with dysplastic cells confined to the muscularis mucosa are benign lesions that can be cured endoscopically. Conversely, CRC is defined clinically by the invasion of neoplastic cells through the muscularis mucosa into the submucosa. The depth of submucosal invasion and other histological features often determine the risk of lymph node metastasis and thereby the optimal treatment strategy.

Haggitt Classification of Pedunculated Polyps

In 1985, Haggitt and colleagues introduced a classification system for protruded polyps based on the depth of invasion

[47]. According to this system, lesions are classified as levels 0–4 (Fig. 23.5). Level 0 corresponds to neoplastic cells limited to the mucosa without breaching the muscularis mucosa. It should be noted that the terms "carcinoma in situ" or "intramucosal carcinoma," which were used for level 0 lesions, should no longer be used as these lesions are by definition benign given the negligible risk for metastasis due to the absence of lymphatics in the mucosa layer. Levels 1–3 pertain specifically to pedunculated polyps. Level 1 corresponds to a pedunculated polyp in which cancer cells invade into the submucosa, but these changes are restricted to the head of the pedunculated polyp. Levels 2 and 3 indicate cancer cells invading into neck of the polyp (junction between the head and the stalk) and any region of the stalk, respectively. Lastly, level 4 indicates when cancer cells have invaded into the submucosa of the bowel wall below the stalk of the polyp.

Kudo and Kikuchi Classification of Sessile Polyps

Both Kudo et al. and Kikuchi et al. introduced the concept of classifying sessile polyps into three levels based on their degree of malignant submucosal invasion (SMI): Sm1, invasion into the upper third of the submucosa; Sm2, invasion into the middle third; and Sm3, invasion into the lower third (Fig. 23.6) [48, 49]. This classification system has direct clinical implications, as the risk of lymphatic spread is directly proportional with the depth of submucosal invasion, with the highest risk being in those lesions extending into the deepest third of the submucosa (Sm3) [50]. The main drawback of this system for routine clinical practice is the need of a significant portion of the submucosa within the resected specimen in order to define the deepest border of the submucosa. Most polypectomy specimens are limited to

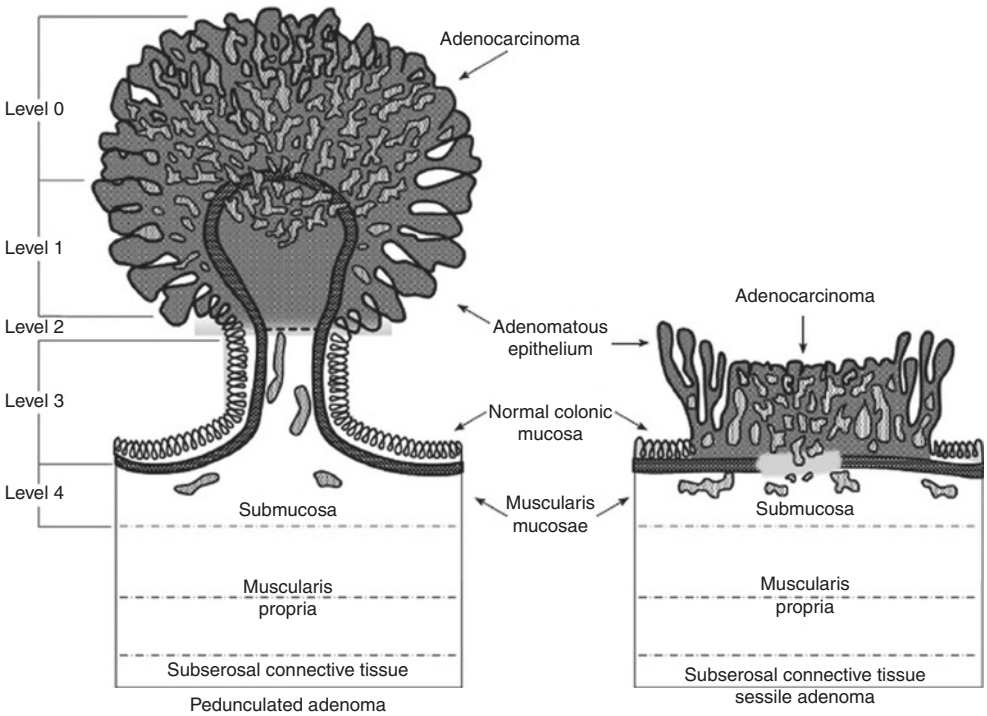


Fig. 23.5 Haggitt classification of pedunculated and sessile polyps. (Reused with permission Nivatvongs [97]. Copyright © 2002 Elsevier)

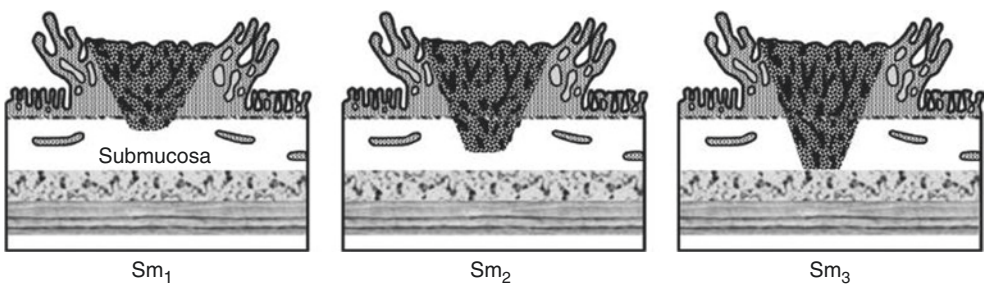


Fig. 23.6 Classification of submucosal invasion (SM) of malignant polyps. (Reused with permission Mohamed and Schofield [98]. Copyright © 2014 Elsevier)

the middle or deep submucosal layer and do not extend down to the muscularis propria, a landmark required to determine SM1, SM2, and SM3 invasion. As such, this classification system has been further modified as to assess risk of metastasis simply based on the depth of SMI from the muscularis mucosa [51].

Depth of Invasion and Risk of Lymph Node Metastases

Kitajima et al. standardized histopathological evaluation of SMI in CRC and determined that in pedunculated lesions, the rate of lymph node metastasis was 0% for Haggitt level 1 and in level 2 or 3 when SM depth was <3000 μm. For all non-pedunculated lesions, the risk of lymph node spread was 0% if SMI was <1000 μM, 3.9% if SMI was <2000 μM, and 17.1% if SMI was ≥2000 μM [52].

Histopathological Factors Influence the Risk of Lymph Node Metastasis in Early Colorectal Cancer

In addition to depth of invasion, several histopathological features have been associated with an increased risk of lymph node metastasis. In a study of 292 early invasive CRCs with surgical resection, Ueno et al. identified potential parameters associated with nodal involvement [52]. Unfavorable tumor grade (poorly differentiated adenocarcinoma and mucinous adenocarcinoma vs well- and moderately differentiated adenocarcinoma), lymphovascular invasion (evidence of cancer involvement of lymphatic and/or venous vessels), and tumor budding (single or cluster cancer cells) were all qualitative parameters associated with lymph node metastasis and unfavorable prognosis with endoscopic resection [52]. Indeed, in a subsequent systematic review and meta-analysis including 23 studies and 4510 patients, the main factors associated with lymph node spread included depth of SMI > 1000 μm (OR 3.87; 95% CI: 1.50–10.00, $P = 0.005$), unfavorable tumor grade (OR 5.60; 95% CI: 2.90–10.82, $P < 0.0001$), lymphovascular invasion (OR 4.81; 95% CI: 3.14–7.37, $P < 0.0001$), and tumor budding (OR 7.74; 95% CI: 4.47–13.39, $P < 0.001$) [53].

Endoscopic Resection of Malignant Polyps

The adequacy of endoscopic resection is dictated by the lesion's risk for lymph node metastasis, given that endoscopic resection does not remove or sample the lymph node drainage basin. Overall, endoscopic resection is the preferred treatment for benign precursor lesions (those without malignant invasion into the submucosa) given the negligible risk for lymph node metastasis and sparing the patient the significant cost, morbidity, and mortality associated with surgery [54, 55]. With advances in endoscopic resection techniques, select malignant polyps can also be adequately removed endoscopically, provided that SMI is <1000 μm and there are no unfavorable histopathological factors [53].

Endoscopic Mucosal Resection (EMR) Technique

In conventional terms, EMR in the GI tract refers to the technique of submucosal injection underneath the target lesion (lift) followed by snare resection. The purpose of the submucosal lift is to separate the target lesion from the underlying muscularis propria as to facilitate endoscopic resection. Submucosal injection also enhances polypectomy by making the tissue easier to resect with a snare; decreases bleeding and perforation risk by increasing the distance between mucosa and muscularis propria layers; and improves the chances of complete resection. Normal saline has been commonly used as the submucosal injection fluid given its safety and low cost. However, more recently, the use of viscous solutions in randomized trials has demonstrated a longer-lasting lift when compared to normal saline [56]. A contrast agent (indigo carmine or methylene blue) is usually added to the injection fluid. This blue-dyed injection fluid allows staining of the submucosa which permits differentiation of the layers of the colonic wall during endoscopic resection and early recognition of any deep injury to the nonstaining muscle wall layer. As liquid is injected into the bowel wall, the loose connective tissue of the submucosa can be separated, and the thin mucosal layer lifted up off of the muscularis propria. The "non-lifting sign," first described by Uno in 1994, refers to the phenomenon whereby a mucosal cancer has invaded into the submucosa and prevents the mucosal layer from being detached and elevated [56]. Non-lifting sign can also be observed when the submucosal layer has been scarred by previous submucosal tattoos, biopsy, or resection attempts.

It is critical to remember that the first endoscopic resection has the highest likelihood for successful complete polyp removal. The location of the injections for submucosal lift is performed strategically as to direct the target lesion toward the lumen and away from any folds. Deflection of the endoscope tip is performed during submucosal injection (known as dynamic injection) in order to help shape the submucosal mound favorably for EMR. Lesions should be removed in as few pieces as safely possible.

Following submucosal lifting, resection during EMR is performed with a snare. There are many sizes and shapes of snares, which usually range between 15 mm and 20 mm in

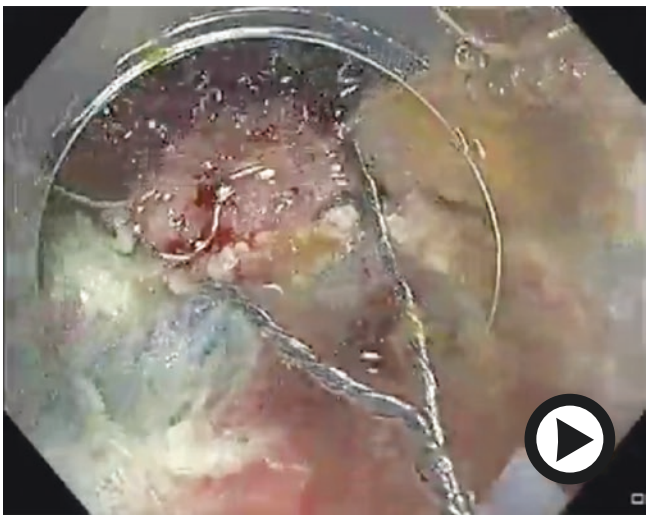


Fig. 23.7 Endoscopic mucosal resection (EMR) of a semi-circumferential lateral spreading tumor granular mixed-type (LST-G mixed) in the ascending colon. https://doi.org/10.1007/000-33d

diameter. Larger and stiffer snares are generally used to remove larger flat lesions. Given the size of the snares, en-bloc resection (one piece) can often be achieved for lesions measuring ≤20 mm, whereas piecemeal resection is required for larger lesions. Accurate snare placement should involve ensuring at least a 1 mm margin of healthy tissue at the perimeter of the polyp. During piecemeal EMR, successive pieces are removed in an orderly fashion, avoiding leaving "islands" of neoplastic tissue within the resection plane. As each section of the lesion is resected, the submucosal resection site should be washed and inspected for bleeding or muscle injury. Finally, prophylactic hemostasis and completeness of polyp removal can be achieved by ablating any visible submucosal vessels or islands of residual polyp with a coagulation forceps (Fig. 23.7).

Outcomes of EMR of Colorectal Polyps

EMR has been shown to be both effective and safe for the management of benign precursor colorectal polyps. In a prospective study of 1134 consecutive patients with mean lesion size of 36.4 mm, EMR was associated with complete resection in >90% of the cases [58]. Delayed bleeding is the most common adverse event, which has been historically reported in up to 7% of patients; albeit recent data suggest that prophylactic clip closure of the EMR resection site may reduce the risk in selected cases [59].

The main limitation of EMR in the management of colorectal polyps is the inability to resect lesions larger than 20 mm in en-bloc fashion. Piecemeal EMR increases the risk of recurrence, with varying rates ranging from 7% to 25% [58, 60]. The factors responsible for polyp recurrence after piecemeal EMR have not been completely elucidated, but incomplete resection at the lateral margins appears to be at the heart of the problem. While recurrence of benign polyps after piecemeal EMR can often be adequately treated endoscopically and new strategies have been introduced to reduce the risk of residual tissue [57, 58, 61], piecemeal EMR of a malignant polyp is considered non-curative. Piecemeal EMR significantly hinders histopathological evaluation, as the fragmented tissue specimens compromise specimen orientation and interpretability of the resection margins. Hence, as per the National Comprehensive Cancer Network practice guidelines, patients with endoscopically curable malignant polyps (limited SMI and favorable histopathological factors) who undergo piecemeal EMR inevitably still require surgery due to the high risk of understaging the lesion owing to the compromised pathological interpretation [62].

Endoscopic Submucosal Dissection Technique

Endoscopic submucosal dissection (ESD) was initially developed in Japan for the treatment of early gastric cancer [63]. The main advantage of ESD over conventional EMR is that it theoretically permits the en-bloc resection of any lesion, irrespective of size. Given its efficacy and safety among expert endoscopists in Japan, ESD has been expanded to include lesions in other parts of the GI tract, including the colon.

Delineation of the target lesion borders is often performed by placing cautery marks lateral to the margins of the polyp. Markings serve as a visual guide during dissection to ensure a negative pathological margin. Following this step, similar to EMR, submucosal injection is performed as to lift the polyp and to create a cushion between the lesion and the underlying muscularis propria. A viscous lifting solution is routinely used during ESD as the longer-lasting mucosal lift has been associated with increased procedural efficiency and safety [64, 65]. Upon completion of an adequate submucosal lift, a circumferential mucosal incision is traditionally performed to penetrate the muscularis mucosa and allow visual identification of the dye-stained submucosal space. After this initial incision, the exposed submucosal tissue is further dissected by repetitive injections and cutting with the ESD knife along the incision margins.

From a technical standpoint, ESD is a complex flexible endoscopic surgical procedure performed through an endoscope, hence, often described as "single-hand surgery with no help from assistants to provide traction." Maintaining adequate visualization of the dissection plane during ESD is often regarded the rate-limiting and most challenging aspect of the procedure. Providing adequate countertraction to expose the dissection field is key, and multiple techniques and novel platforms have been introduced, with promising

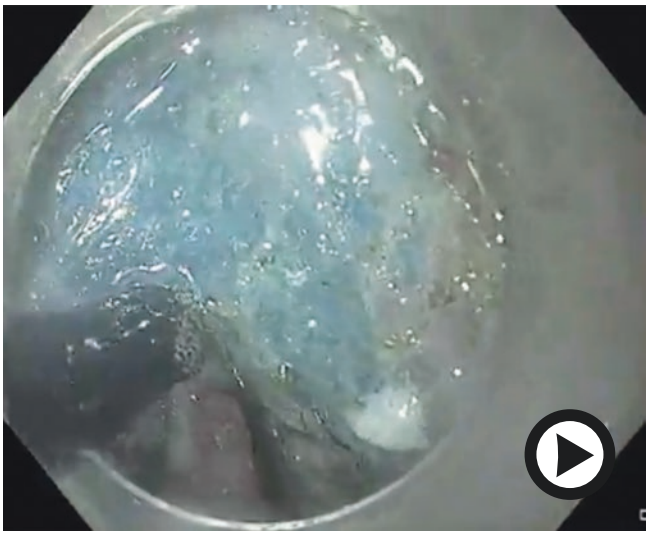


Fig. 23.8 Endoscopic submucosal dissection (ESD) of a large lateral spreading tumor granular type (LST-G) in the rectum using the "pocket-creation" technique. https://doi.org/10.1007/000-33c

results [67, 68]. In addition, one of the challenges during colorectal ESD is the rapid dissipation of the injected fluid from the mucosal incision line. As such, in 2016, the concept of the "pocket-creation" method was introduced (Fig. 23.8) [66]. Unlike conventional ESD in which a circumferential mucosal incision is performed around the polyp initially, with the pocket-creation technique only a small mucosal incision is initially performed. The endoscope is then inserted into this small opening and submucosal dissection/tunneling performed deep to the lesion, which results in less dissipation of the injectate. Following completion of the submucosal dissection, the initial mucosal incision is subsequently extended along the remaining margins of the lesion. In a retrospective study of 887 colorectal lesions treated with ESD, when compared to conventional ESD, the pocket-creation method was associated with higher en-bloc resection rate (100% vs 96%; $P < 0.001$), complete resection rate (91% vs 85%; $P = 0.03$), and shorter procedural time [69].

Outcomes of ESD for Colorectal Polyps

Early case series on colorectal ESD from Asia reported reasonable en-bloc resection rates of approximately 80% but were plagued by the frequency of serious adverse events, including perforation occurring in up to 10% in some studies [70]. However, with the development of dedicated ESD devices as well as improved proficiency in the technique, subsequent large studies from Asia have reported en-bloc and curative resection rates over 90–98%, with perforations occurring between 2.5% and 5% of the cases and <1% requiring surgical intervention [71, 72].

Although ESD has been rapidly embraced in Asia, the transition of ESD to the Western Hemisphere has been slower, particularly due to the technical complexity of the procedure, its steep learning curve, and the relative limited training opportunities in the West [73]. As such, initial studies have demonstrated lower complete resection and higher complication rates when compared to studies originating from Asia. In a systematic review and meta-analysis on clinical outcomes of ESD in 18,764 colorectal lesions, Fuccio and colleagues demonstrated that complete (R0) resection rate was significantly lower in Western vs Asian countries (71.3% vs 85.6%; $P < 0.001$) with a higher rate of both delayed bleeding (4.2% vs 2.4%; $P < 0.001$) and perforation (8.6% vs 4.5%; $P < 0.001$) [73, 74]. In a recent multicenter study from North America, rectal ESD ($n = 171$) was associated with an en-bloc and R0 resection rate of 82.5% and 74.9%, respectively and was curative in 81.8% of malignant polyps with favorable histologic features [75].

For benign and malignant polyps located within the rectum, transanal endoscopic surgery (TES) is a desirable option over flexible EMR and ESD. While ESD of large polyps is largely performed piecemeal and limited to the submucosal plane, TES can be performed in either the submucosal or full-thickness plane and is usually performed en-bloc with low rates of specimen fragmentation (<10%), positive margins (66–93%), and polyp recurrence (5–11%) [76–80]. TES is also feasible for endoscopically challenging polyps such as circumferential lesions and lesions which extend down into the anal canal. The limiting factor for TES is that the instruments are typically not flexible and it may be difficult to reach the proximal rectum [77].

Endoscopic Approach to Malignant Polyps

The first critical step in the management of malignant polyps is detailed lesion assessment as to potentially differentiate those amenable for endoscopic resection and those with features suggestive of advanced disease that will require surgery. As previously described, endoscopic features suggestive of deep SMI may include depressed lesions (Paris 0-IIc), those with surface ulceration/excavation (Paris 0-III) with abnormal/disrupted surface pit/vascular pattern (Kudo classification Type V/Vn and NICE type III). When a lesion with suspected deep SMI is identified, biopsies should be obtained from the portion of the lesion with such features and the patient referred for surgical resection. The site of the lesion should be inked with a tattoo for reference identification during surgery [81]. To improve polyp location at time of surgery, tattoo should be placed in multiple quadrants just distal to the polyp, photographed, and clearly documented in the colonoscopy report. The exception to the previous statement includes pedunculated polyps (Paris Ip) that may have endo-

scopic features of deep SMI limited to the head (Haggitt level 0–2). In these cases, en-bloc resection at the level of the stalk is associated with favorable prognosis [82].

All colorectal polyps without features of deep SMI, including malignant polyps with superficial SMI and favorable histological characteristics, are potential candidates for endoscopic resection. As mentioned previously, en-bloc endoscopic resection is mandatory for the removal of malignant polyps, as assessment of depth of SMI and resection margin status cannot be reliable obtained with a fragmented specimen. Malignant polyps that are 2 cm or smaller can often be removed en-bloc with EMR. For lesions >2 cm in size, ESD is usually required. Following endoscopic resection, the resected specimen should be pinned on a cork board or similar material as to maintain its in situ architecture. Placing the resected specimen in formalin without pinning can result in curling of the edges, which can make differentiation between the lateral and deep resection margins challenging and render the measurement of depth of SMI inaccurate [24, 83]. Endoscopic resection of a malignant polyp is considered curative if the following criteria are met on histopathological assessment: (1) all resection margins are negative, (2) SMI < 1000 μm, (3) well to moderately differentiated tumor grade, and (4) absence of lymphovascular invasion and/or tumor budding [84]. If endoscopic tattoo was not performed at the index colonoscopy, a repeat colonoscopy is necessary within 1–2 weeks and placement of a tattoo to facilitate endoscopic surveillance or intraoperative localization at the time of surgical resection.

Malignant polyps and early cancers located in the rectum are well suited for transanal endoscopic surgery (TES). As with benign polyps, TES can remove the lesion en-bloc. It is also possible to remove rectal lesions in full-thickness fashion where appropriate. This provides a "total biopsy" which permits optimal pathologic evaluation for SM level of invasion, tumor budding, and other high-risk features. Patients then can be better risk stratified and counseled regarding need for repeat endoscopic procedure, surveillance, or radical surgery [85, 86]. The downside of full-thickness resection is the additional morbidity, long-term functional derangements (especially for distal lesions), and the scarring that occurs outside of the rectal wall, which can make subsequent proctectomy more challenging.

Prior to attempting endoscopic resection of a potentially malignant polyp, it is advisable to obtain a carcinoembryonic antigen (CEA) level for surveillance if the lesion is proven to be malignant. Following the endoscopic resection of a malignant polyp, it is often advisable to obtain a baseline cross-sectional imaging (chest and abdominopelvic computed tomography) to exclude the possibility of metastatic disease. While there is no consensus on the timing, experts advise delaying endoscopic ultrasound or cross-sectional imaging at least 3–4 weeks after the endoscopic procedure as to allow the bowel wall to heal and any reactive inflammatory lymphadenopathy to subside [24]. This will avoid the problem of reactive lymphadenopathy being classified radiographically as metastatic spread, which could lead to overtreatment of the patient.

Predicting the Risk of Residual Mural Cancer or Lymph Node Metastasis Following Endoscopic Resection of Malignant Polyp

Assessing the risk of occult lymph node metastasis in T1 colorectal cancers is an imperfect science. There is no single histologic feature that can accurately predict this risk, yet clinicians need some estimate of risk to counsel patients regarding the decision to elect repeat endoscopic intervention, surveillance with watchful waiting, or radical surgical resection. In order to have an informed discussion, it is necessary to estimate both the risk of occult residual cancer and the risk of perioperative surgical morbidity and functional outcomes following surgery. As mentioned previously, prognostic indicators for increased risk of residual cancer include positive resection margin (less than 1 mm, or indeterminant), submucosal invasion less than 1 mm, lymphovascular invasion, tumor budding, and poorly differentiated histology. Multiple unfavorable features are also known to have an additive risk [85, 87].

It is not uncommon for pathology reports to omit many of these features as they have not been routinely included in guidelines for synoptic reports [88]. Ideally, the pathology slides should be reviewed at a multidisciplinary tumor board by dedicated gastrointestinal pathologists to identify and tally the number of high-risk features to better stratify the risk of recurrence. This can then be used to counsel the patient and guide management decisions.

The ACPGBI position statement for management of the malignant polyp provides a useful risk stratification tool (Table 23.1). High-risk histologic features are weighted and then added together to calculate a risk score and estimated risk of residual disease [4]. Over a 3-year period, the tool was utilized to guide the MDTs of a regional cancer network in the UK in the management of 173 patients after endoscopic resection of malignant colorectal polyps. Thirty-seven patients (21.4%) underwent primary surgical resection with a residual disease rate of 43%, while 136 patients managed with surveillance had a 4.4% recurrence [89].

Recurrence Following Endoscopic Resection

Given its higher en-bloc and curative resection rate when compared to EMR, ESD is often advocated as the preferred endoscopic approach for malignant polyps with superficial

Table 23.1 Criteria are based on histological description of endoscopically resected malignant polyp weighted for prognostic significance of each risk factor. Where more than one risk factor is present, the degree of risk is added together to give a total risk score

Histologic criteria		Degree of risk	
Resection margin <1 mm		4	
Resection margin 1–2 mm		1	
Pedunculated: Haggitt level 4		4	
Sessile: Kikuchi 2		2	
Sessile: Kikuchi 3		4	
Poor differentiation		3	
Mucinous tumor		1	
Tumor budding		1	
Lymphovascular invasion		2	
Total score	*Grade of risk*	*Estimated risk of residual cancer*	*Recommended course of action*
0	Very low	<3%	Routine follow-up
1	Low	<5%	Assess other factors, close follow-up
2	Medium	5–10%	Discuss risk/benefit of surgery vs follow-up
3	High	8–15%	Discuss risks, err toward surgery
≥4	Very high	> 20%	Recommend surgery unless patient unfit

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SMI (T1 CRC), particularly when larger than 2 cm in size [90]. Several studies have reported on the local recurrence and prognosis following ESD of malignant polyps. In a retrospective study evaluating clinical outcomes of ESD in 310 consecutive colorectal neoplasms, of which 53 were T1 CRCs, disease-free survival was 100%, and no distant metastasis was observed, whereas all local recurrences (2%) occurred in patients with piecemeal resection at a median follow-up of 3 years [91]. Similarly, Yoda and colleagues demonstrated that endoscopic resection of malignant polyps with favorable histological features is associated with excellent oncological outcomes, with 5-year disease-free survival and recurrence of 98% and 0.8%, respectively [92]. Based on these data, patients who undergo endoscopic resection of malignant polyps with favorable histologic criteria should be informed that the risk of residual or recurrent disease, particularly after en-bloc resection, is minimal, but not zero.

Surveillance After Endoscopic Resection

The post-polypectomy surveillance guidelines published in the USA and Europe have been mainly based on the aggregate data on the rate of metachronous advanced neoplasms and CRC death [93, 94]. In the case of endoscopic resection of malignant polyps, the risk of recurrence and/or metastatic disease has been mainly reported to occur within 3–5 years [91–93]. The European Society of Gastrointestinal Endoscopy (ESGE) recommends surveillance colonoscopy at 6 months following piecemeal endoscopic resection of all colorectal polyps larger than 10 mm; however, no definitive recommendation is given specifically for timing of surveillance post-resection of malignant polyps. Since local recurrence is rare following en-bloc resection, the Japan Gastroenterological Endoscopy Society (JGES) suggest that follow-up colonoscopy should be performed within 3 years after resection [84]. While experts suggest that tumor markers, such as carcinoembryonic antigen (CEA) and chest/abdominopelvic computed tomography, should be periodically done for surveillance, there is no consensus on the actual method or the timing of surveillance.

Conclusion

Endoscopic resection of low-risk T1 colorectal cancer is an effective treatment in select patients. Detailed lesion assessment is crucial in determining the best therapeutic strategy. Selected lesions with superficial SMI can be adequately managed with en-bloc endoscopic curative resection with either EMR or ESD. For malignant polyps or early cancers in the rectum, TES is another alternative, which can also provide full-thickness en-bloc resection where appropriate. All lesions with predictors of deep SMI should be referred to surgery given the high risk for lymph node metastasis.

References

1. International Agency for Research on Cancer. Globocan 2018: cancer fact sheets – colorectal cancer. IARC. http://gco.iarc.fr/today/data.factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf.
2. Fleming M, Ravula S, Tatischchev SF, Wang HL, et al. Colorectal carcinoma: pathologic aspects. J Gastrointest Oncol. 2013;3:153–73.
3. Conteduca V, Sansonno D, Russi S, et al. Precancerous colorectal lesions. Int J Oncol. 2013;43:973–84.
4. Williams JG, Pullan RD, Hill J, et al. Management of the malignant colorectal polyp: ACPGBI position statement. Colorectal Dis. 2013;15(Suppl 2):1–38.
5. National Comprehensive Cancer Network. Clinical practice guidelines in oncology; colon cancer (v3.2018). Available at https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
6. Rex DK, Hassan C, Bourke MJ. The colonoscopist's guide to the vocabulary of colorectal neoplasia: histology, morphology, and management. Gastrointest Endosc. 2017;86:253–63.
7. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med. 1993;329:1977–81.
8. Atkin W, Morson B, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl J Med. 1992;326:658–62.

9. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med. 2012;366:687–96.
10. Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. Nat Rev Gastroenterol Hepatol. 2019;16:713–32.
11. World Health Organization. Classification of tumours of the digestive tract. Lyon: IARC Press; 2019.
12. Dixon MF. Gastrointestinal epithelial neoplasia: Vienna revisited. Gut. 2002;51:130–1.
13. Salmo E, Haboubi N. Adenoma and malignant colorectal polyp: pathological considerations and clinical applications. EMJ Gastroenterol. 2018;7:92–102.
14. Fleming M, Ravula S, Tatishchev SF, et al. Colorectal carcinoma: pathologic aspects. J Gastrointest Oncol. 2012;3:153–73.
15. Heitman SJ, Ronskley PE, Hilsden RJ, et al. Prevalence of adenomas and colorectal cancer in average risk individuals: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2009;7:1272–8.
16. Crockett SD, Nagtegaal ID. Terminology, molecular features, epidemiology, and management of serrated colorectal neoplasia. Gastroenterology. 2019;157:949–66.
17. Saito S, Tajiri H, Ikegami M. Serrated polyps of the colon and rectum: endoscopic features including image enhanced endoscopy. World J Gastrointest Endosc. 2015;7:860–71.
18. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61:759–67.
19. Dow LE, O'Rourke KP, Simon J, et al. Apc restoration promotes cellular differentiation and reestablishes crypt homeostasis in colorectal cancer. Cell. 2015;161:1539–52.
20. Nakayama M, Oshima M. Mutant p53 in colon cancer. J Mol Cell Biol. 2019;11:267–76.
21. O'Brien MJ, Yang S, Clebanoff JL, et al. Hyperplastic (serrated) polyps of the colorectum: relationship of CpG island methylator phenotype and K-ras mutation to location and histologic subtype. Am J Surg Pathol. 2004;28:423–34.
22. Bond CE, Liu C, Kawamata F, et al. Oncogenic BRAF mutation induces DNA methylation changes in a murine model for human serrated colorectal neoplasia. Epigenetics. 2018;13:40–8.
23. Weisenberger DJ, Siegmund KD, Campman N, et al. CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF mutation in colorectal cancer. Nat Genet. 2006;38:787–93.
24. Rex DK, Shaukat A, Wallace MB. Optimal management of malignant polyps, from endoscopic assessment and resection to decisions about surgery. Clin Gastroenterol Hepatol. 2019;17:1428–37.
25. Compton CC. Key issues in reporting common cancer specimens: problems in pathologic staging of colon cancer. Arch Pathol Lab Med. 2006;130:318–24.
26. Moss A, Bourke MJ, Williams SJ, et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. Gastroenterology. 2011;140:1909–18.
27. Lopez A, Bouvier AM, Jooste V, et al. Outcomes following polypectomy for malignant colorectala polyps are similar to those following surgery in the general population. Gut. 2019;68:111–7.
28. The Paris endoscopic classification for superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc. 2003;58(6 suppl):S3–S43.
29. Endoscopic Classification Review Group. Update on the Paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy. 2005;37:570–8.
30. Okamoto T, Tanaka S, Haruma K, et al. Clinicopathologic evaluation on colorectal laterally spreading tumor (LST). Nihon Shokakibyo Gakkai Zasshi. 1996;93:83–9.
31. Soetikno RM, Kaltenbach T, Rouse RV, et al. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. JAMA. 2008;299:1027–35.
32. Rembacken BJ, Fujii T, Cairns A, et al. Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK. Lancet. 2000;355:1211–4.
33. Kudo S, Lambert R, Allen JL, et al. Nonpolypoid neoplastic lesions of the colorectal mucosa. Gastrointest Endosc. 2008;68(4 Suppl):S3–S47.
34. Burgess NG, Hourigan LF, Zanati SA, et al. Risk stratification for covert invasive cancer among patients referred for colonic endoscopic mucosal resection: a large multicenter cohort. Gastroenterology. 2017;153:732–42.
35. Kudo S, Hirota S, Nakajima T, et al. Colorectal tumours and pit pattern. J Clin Pathol. 1994;47:880–5.
36. Togashi K, Konishi F, Ishizuka T, et al. Efficacy of magnifying endoscopy in the differential diagnosis of neoplastic and non-neoplastic polyps of the large bowel. Dis Colon Rectum. 1999;42:1602–8.
37. Tung SY, Wu CS, Su MY. Magnifying colonoscopy in differentiating neoplastic from nonneoplastic colorectal lesions. Am J Gastroenterol. 2001;96:2628–32.
38. Konishi K, Kaneko K, Kurahashi T, et al. A comparison of magnifying and nonmagnifying colonoscopy for diagnosis of colorectal polyps: a prospective study. Gastrointest Endosc. 2003;57:48–53.
39. Draganov PV, Gotoda T, Yang D. Advanced techniques for endoscopic resection in the GI tract. 1st ed. Thorofare: Slack Incorporated; 2019. p. 26.
40. Sano Y, Horimatsu T, Fu KI, et al. Magnifying observation of microvascular architecture of colorectal lesions using a narrow band imaging system. Dig Endosc. 2006;18:S44–51.
41. Sano Y, Ikematsu H, Fu KI, et al. Meshed capillary vessels by use of narrow-band imaging for differential diagnosis of small colorectal polyps. Gastrointest Endosc. 2009;69:278–83.
42. Katagiri A, Fu KI, Sano Y, et al. Narrow band imaging with magnifying colonoscopy as a diagnostic tool for predicting the histology of early colorectal neoplasia. Aliment Pharmacol Ther. 2008;27:1269–74.
43. Ikematsu H, Matsuda T, Emura F, et al. Efficacy of capillary pattern type IIIA/IIIB by magnifying narrow band imaging for estimating depth of invasion of early colorectal neoplasms. BMC Gastroenterol. 2010;10:33.
44. Sano Y, Tanaka S, Kudo S, et al. Narrow-band imaging (NBI) magnifying endoscopic classification of colorectal tumors proposed by the Japan NBI Expert Team. Dig Endosc. 2016;28:526–33.
45. Hewett DG, Kaltenbach T, Sano Y, et al. Validation of a simple classification system for endoscopic diagnosis of small colorectal polyps using narrow-band imaging. Gastroenterology. 2012;143:599–607.
46. Puig I, Lopez-Ceron M, Arnau A, et al. Accuracy of the narrow-band imaging international colorectal endoscopic classification system in identification of deep invasion in colorectal polyps. Gastroenterology. 2019;156:75–87.
47. Haggitt RC, Glotzbach RE, Soffer EE, et al. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. Gastroenterology. 1985;89:328–36.
48. Kudo S. Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. Endoscopy. 1993;25:455–61.
49. Kikuchi R, Takano M, Takagi K, et al. Management of early invasive colorectal cancer. Risk of recurrence and clinical guidelines. Dis Colon Rectum. 1995;38:1286–95.
50. Nascimbeni R, Burgart LJ, Nivatvongs S, et al. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. Dis Colon Rectum. 2002;45:200–6.

51. Kitajima K, Fujimori T, Fujii S, et al. Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. J Gastroenterol. 2004;39:534–43.
52. Ueno H, Mochizuki H, Hashiguchi Y, et al. Risk factors for an adverse outcome in early invasive colorectal carcinoma. Gastroenterology. 2004;127:385–94.
53. Beaton C, Twine CP, Williams GL, et al. Systematic review and meta-analysis of histopathological factors influencing the risk of lymph node metastasis in early colorectal cancer. Colorectal Dis. 2013;15:788–97.
54. Jayanna M, Burgess NG, Sing R, et al. Cost-analysis of endoscopic mucosal resection vs surgery for large laterally spreading colorectal lesions. Clin Gastroenterol Hepatol. 2016;14:271–8.
55. Ahlenstiel G, Hourigan LF, Brown G, et al. Actual endoscopic versus predicted surgical mortality for treatment of advanced mucosal neoplasia of the colon. Gastrointest Endosc. 2014;80:668–76.
56. Uno Y, Munakata A. The non-lifting sign of invasive colon cancer. Gastrointest Endosc. 1994;40(4):485–9.
57. Repici A, Wallace M, Sharma P, et al. A novel submucosal injection solution for endoscopic resection of large colorectal lesions: a randomized, double-blind trial. Gastrointest Endosc. 2018;88:527–35.
58. Moss SJ, Williams LF, Hourigan LF, et al. Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. Gut. 2015;64:57–65.
59. Pohl H, Grimm IS, Moyet MT, et al. Clip closure prevents bleeding after endoscopic resection of large colon polyps in a randomized trial. Gastroenterology. 2019;157:977–84.
60. Khashab M, Eid E, Rusche M, et al. Incidence and predictors of "late" recurrences after endoscopic piecemeal resection of large sessile adenomas. Gastrointest Endosc. 2009;70:344–9.
61. Klein A, Tate DJ, Jayasekeran V, et al. Thermal ablation of mucosal defect margins reduces adenoma recurrence after colonic endoscopic mucosal resection. Gastroenterology. 2019;156:604–13.
62. Benson AB 3rd, Venook AP, Cederquist L, et al. Colon cancer, version 1.2017, NCCN clinical practice guideline in oncology. J Natl Compr Canc Netw. 2017;15:370–98.
63. Ono H, Kondo H, Gotoda T, et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut. 2001;48:225–9.
64. Fujishiro M, Yahagi N, Nakamura M, et al. Successful outcomes of a novel endoscopic treatment for GI tumors: endoscopic submucosal dissection with a mixture of high-molecular-weight hyaluronic acid, glycerin, and sugar. Gastrointest Endosc. 2006;63:243–9.
65. Mehta N, Strong AT, Franco M, et al. Optimal injection solution for endoscopic submucosal dissection: a randomized controlled trial of Western solutions in a porcine model. Dig Endosc. 2018;30:347–53.
66. Miura Y, Hayashi Y, Lefor AK, et al. The pocket-creation method of ESD for gastric neoplasms. Gastrointest Endosc. 2016;83:457–8.
67. Yang D, Draganov PV. Gaining traction: pulley-ing your weight during endoscopic submucosal dissection. Gastrointest Endosc. 2019;89:185–7.
68. Yang D, Jawaid S, Perbtani YB, et al. Endoscopic submucosal dissection of a large rectal lesion by use of a novel tissue retractor system. VideoGIE. 2019;4:37–9.
69. Takezawa T, Hayashi Y, Shinozaki S, et al. The pocket-creation method facilitates colonic endoscopic submucosal dissection (with video). Gastrointest Endosc. 2019;89:1045–53.
70. Taku K, Sano Y, Fu KI, et al. Iatrogenic perforation associated with therapeutic colonoscopy: a multicenter study in Japan. J Gastroenterol Hepatol. 2007;22:1409–14.
71. Lee EJ, Lee JB, Lee SH, et al. Endoscopic submucosal dissection for colorectal tumors – 1,000 colorectal ESD cases: one specialized institute's experiences. Surg Endosc. 2013;27:31–9.
72. Saito Y, Uraoka Y, Yamaguchi Y, et al. A prospective, multicenter study of 1111 colorectal endoscopic submucosal dissections (with video). Gastrointest Endosc. 2010;72:1217–25.
73. Kotzev AI, Yang D, Draganov PV. How to master endoscopic submucosal dissection in the USA. Dig Endosc. 2019;31:94–100.
74. Fuccio L, Hassan C, Ponchon T, et al. Clinical outcomes after endoscopic submucosal dissection for colorectal neoplasia: a systematic review and met-analysis. Gastrointest Endosc. 2017;86:74–86.
75. Yang D, Aihara H, Perbtani YB, et al. Safety and efficacy of endoscopic submucosal dissection for rectal neoplasia: a multicenter North American experience. Endosc Int Open. 2019;07:E1–9.
76. Moore JS, Cataldo PA, Osler T, et al. Transanal endoscopic microsurgery is more effective than traditional transanal excision for resection of rectal masses. Dis Colon Rectum. 2008;51:1026–31.
77. de Graaf EJR, Doornebosch PG, Tetteroo GWM, et al. Transanal endoscopic microsurgery is feasible for adenomas throughout the entire rectum: a prospective study. Dis Colon Rectum. 2009;52:1107–13.
78. Tsai BM, Finne CO, Nordenstam JF, et al. Transanal endoscopic microsurgery resection of rectal tumors: outcomes and recommendations. Dis Colon Rectum. 2010;53:16–23.
79. Barendse RM, Musters GD, de Graaf EJ, et al. Randomised controlled trial of transanal endoscopic microsurgery versus endoscopic mucosal resection for large rectal adenomas (TREND Study) Gut. 2018;67:837–46.
80. Lee L, Burke JP, deBeche-Adams T, et al. Transanal minimally invasive surgery for local excision of benign and malignant rectal neoplasia. Outcomes from 200 consecutive cases with midterm follow up. Ann Surg. 2018;267:910–6.
81. ASGE Technology Committee, Kethu SR, Banerjee S, Desilets D, et al. Endoscopic tattoing. Gastrointest Endosc. 2010;72:681–5.
82. Matsuda T, Fukuzawa M, Uraoka T, et al. Risk of lymph node metastasis in patients with pedunculated type early invasive colorectal cancer: a retrospective multicenter study. Cancer Sci. 2011;102:1693–7.
83. Yang D, Othman M, Draganov PV. Endoscopic mucosal resection vs endoscopic submucosal dissection for Barrett's esophagus and colorectal neoplasia. Clin Gastroenterol Hepatol. 2019;17:1019–28.
84. Tanaka S, Kashida H, Saito Y, et al. JGES guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. Dig Endosc. 2015;27:417–34.
85. Bach SP, Hill J, Monson JRT, Transanal Endoscopic Microsurgery (TEM) Collaboration, et al. A predictive model for local recurrence after transanal endoscopic microsurgery for rectal cancer. Br J Surg. 2009;96:280–90.
86. Allaix ME, Arezzo A, Caldart M, et al. Endoscopic microsurgery for rectal neoplasms: experience of 300 consecutive cases. Dis Colon Rectum. 2009;52:1831–6.
87. Chang HC, Huang SC, Chen JS, et al. Risk factors for lymph node metastasis in pT1 and pT2 rectal cancer: a single-institute experience in 943 patients and literature review. Ann Surg Oncol. 2012;19:2477–84.
88. Gimon TI, Dykstra MA, Chezar K, et al. Malignant colorectal polyp pathology: are we getting sufficient information to make decisions? Dis Colon Rectum. 2020;63:135–42.
89. Sharma V, Junejo MA, Mitchel PJ. Current management of malignant colorectal polyps across a regional United Kingdom cancer network. Dis Colon Rectum. 2020;63:39–45.

90. Cao Y, Liao C, Tan A, et al. Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. Endoscopy. 2009;41:751–7.
91. Niimi K, Fujishiro M, Kodashima S, et al. Long-term outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms. Endoscopy. 2010;42:723–9.
92. Yoda Y, Ikematsu H, Matsuda T, et al. A large-scale multicenter study of long-term outcomes after endoscopic resection for submucosal invasive colorectal cancer. Endoscopy. 2013;45:718–24.
93. Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on colorectal cancer. Gastroenterology. 2012;143:844–57.
94. Hassan C, Quintero E, Dumonceau JM, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy. 2013;45:842–51.
95. Holt BA, Bourke MJ. Wide field endoscopic resection for advanced colonic mucosal neoplasia: current status and future directions. Perspect Clin Gastroenterol Hepatol. 2012;10(9):969–79.
96. Tanaka S, et al. High-magnification colonoscopy (with videos). Gastrointest Endosc. 2006;64(4):604–13.
97. Nivatvongs S. Surgical management of malignant colorectal polyps. Surg Clin North Am. 2002;82:959–66.
98. Mohamed M, Schofield JB. The pathology of colorectal polyps and cancers (including biopsy). Surgery. 2014;32:165–71.

Colorectal Cancer: Preoperative Evaluation and Staging

24

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Key Concepts

- The method chosen to screen a patient for colorectal cancer (CRC) should be individualized based on patient comorbidities and life expectancy, access, cost, baseline risk, compliance, and tolerance for invasive procedures due to differing costs, sensitivities, and cadences of the various options.
- Defining the anatomic location where the sigmoid colon transitions to the rectum is increasingly determined by cross-sectional imaging due to its reproducibility and is less dependent on endoscopic localization alone, as body habitus and gender can influence the location of the peritoneal reflection.
- Proper tumor localization and staging is essential to establishing treatment recommendations; understanding the pitfalls of each staging modality is important to avoid under- or overtreatment.
- Magnetic resonance imaging (MRI) using a rectal cancer protocol is now standard of care for locally advanced rectal tumors. Endorectal ultrasound (ERUS) is being used less commonly as it is more operator dependent, less reproducible, and invasive for the patient; however, ERUS remains an important staging modality for early stage rectal tumors when determining eligibility for local excision.
- A combination of histologic and radiographic factors should be used to risk stratify CRC; higher-risk tumors should be considered for more aggressive neoadjuvant treatments; however, patient frailty or comorbidities may limit these treatment options and should be individualized.
- Preoperative optimization and preparation of the colorectal cancer patient is essential to maximizing postoperative and oncologic outcomes; a variety of tools, including guidelines and checklists, are available to assist the surgical team in this endeavor.

Diagnosis of Colorectal Cancer

A diagnostic workup for colorectal cancer may follow a positive result from one of the various screening tests available or follow investigation of symptoms, which may be acute or subacute. A positive noninvasive screening test or unexplained iron-deficiency anemia typically prompts colonoscopy, which then detects malignancy. Alternatively, a patient may present with abdominal pain or distension and seek emergent care. Cross-sectional imaging may then demonstrate an intraluminal lesion in the colon or rectum, resulting in further workup.

Screening and Diagnostic Modalities

The ideal screening test for any disease should be easily available, inexpensive, and noninvasive, with high sensitivity and specificity. Because CRC is often asymptomatic, screening tests are universally recommended for patients starting at either age 45 [1] or 50 [2] and ending between ages 75 and 86, based on the patient's life expectancy and health status (see Chap. 22). Once symptoms occur, the disease is typically in an advanced state with poorer survival rates.

There are a myriad of options for CRC screening; the choice for a specific patient should be individualized based on a constellation of factors, including personal and family history of CRC or polyps, family history of inherited CRC

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Table 24.1 Summary of the pros and cons of the most commonly used CRC screening modalities

	Pros	Cons
FOBT (fecal occult blood testing)	Inexpensive Noninvasive Reduces CRC mortality by 15–33% Convenient Widely available	Low specificity and sensitivity Requires annual testing Requires dietary/medication restrictions Inaccurate in setting of benign GI bleeding (peptic ulcers, hemorrhoids, diverticulosis) Requires daily testing for 3 days Cannot differentiate between polyp and cancer Positive test requires colonoscopy
FIT	Inexpensive Noninvasive No dietary/medication modification required Higher specificity than FOBT (less chance of false positive for UGIB) Comparable sensitivity to colonoscopy Recommended by USPSTF	Requires annual testing Cannot differentiate between polyp and cancer Positive test requires colonoscopy
DNA-FIT	Every 3 years Covered by Medicare 92% sensitive for all CRC (less sensitive for stage IV)	Expensive, insurance may not cover Minimal long-term data Positive test requires colonoscopy Higher false-positive rates Less sensitivity for adenomas
Colonoscopy	Can differentiate between polyps and cancer Preventative (removes adenomas before they progress to cancer) Diagnostic and therapeutic Highest specificity/sensitivity Longer time interval between tests (up to 10 years)	Requires bowel preparation Invasive with risk of serious complication Typically requires sedation Variable based on endoscopist skill May not be widely available Expensive

syndromes, personal history of inflammatory bowel disease (IBD), medical comorbidities, age/life expectancy, tolerance for risk, anxiety, access to healthcare resources, compliance with follow-up, and insurance coverage/cost.

It can be a confusing discussion for the physician to choose the appropriate screening modality for his or her patients. Understanding the benefits and drawbacks is essential for the patient and physician to make the correct choice. Table 24.1 may assist the healthcare team involved in this decision-making. We cover the available diagnostic and screening modalities for CRC below.

Fecal Sampling

The least invasive and most widely available screening test for asymptomatic, average-risk persons is fecal sampling for occult blood or tumor DNA. This method may be palatable for some patients as it avoids mechanical bowel preparation and is more practical in geographic areas with poor access to endoscopy. These tests do not replace endoscopy, and it should be noted that any positive test usually prompts colonoscopy. However, this initial triage test can conserve colonoscopy for a smaller population. The three fecal-based tests available are discussed below:

- *FOBT* (fecal occult blood test): a guaiac-based test detects presence of heme (nonprotein portion of hemoglobin) and detects blood for all sources (including animal). Patients are instructed to put a smear of their stool on a different stool card 3 days in a row and then mail the cards in. Testing is recommended on an annual basis. This is the oldest stool-based test available and is quite inexpensive. It requires dietary and medication modification for several days prior to the test, including avoiding red meat, raw produce, antacids, vitamin C, nonsteroidal anti-inflammatory agents, loperamide, and iron supplements. Menstruation is a relative contraindication. Relatively low specificity and pretest dietary and medication restrictions have made it less attractive than newer stool tests [3]
- *FIT* (fecal immunochemical test): a.k.a. "safety-chemical" method detects antibodies to the human protein globin portion of hemoglobin found in red blood cells. This results in less cross-reactivity to nonhuman blood and improved specificity over FOBT [3]. It also requires only a single card and thus better compliance. However, it is still a test that is recommended to be performed annually.
- *Multitarget stool DNA-FIT* (Cologuard®) test: combines the FIT test with an additional test that detects genetic mutations found in cancer cells ((KRAS, NDRG4, BMP3, β-actin). It has a 13% false-positive and 8% false-negative rate. It is recommended to be performed every 3 years. It was approved for use in 2014. However, it is relatively expensive ($649 out-of-pocket) compared to other stool assays and may not be covered by insurance. Further, it

cannot differentiate between advanced polyps and adenocarcinoma [4, 5]

Flexible Sigmoidoscopy

Flexible sigmoidoscopy can examine the distal portion of the colon and can be performed in an office setting with minimal preparation and without sedation. Flexible sigmoidoscopy is typically more easily tolerated than rigid proctoscopy and can extend beyond 25 cm. It has been suggested as a screening tool in younger adults since there is a higher incidence of left-sided cancers in this population and was used historically in conjunction with barium enema. It is, however, insufficient in older individuals due to a shift of polyps and cancers to the more proximal colon. As such, it has been combined with FIT or FOBT which theoretically enhances detection.

Computed Tomography (CT) Colonography

CT colonography (CTC or "virtual colonoscopy") is another option available for screening. The technique involves obtaining multiple thin-slice CT images after carbon dioxide insufflation of the colon via a rectal tube, typically in two positions (supine and lateral). The images are reconstructed to give both two and three dimensional views of the colon mucosa. The advantage of CTC is that it avoids the need for sedation and may be preferable for patients with comorbidities who cannot undergo optical colonoscopy or who have a tortuous colon. It does, however, require a full cathartic bowel preparation prior to the procedure, and any suspicious findings usually prompt subsequent optical colonoscopy. Patients are exposed to radiation and may have a risk of contrast nephropathy. It has comparable sensitivity to colonoscopy for polyps greater than 1 cm but is less effective for detecting smaller lesions as they are difficult to differentiate from stool [4]. Since it involves the instillation of air or carbon dioxide into the rectum, it may be associated with abdominal cramping and may rarely result in perforation. It may also identify incidental abdominal findings that may require subsequent additional investigation. Lastly, this test is typically not covered by Medicare. It can be difficult to obtain insurance approval, despite receiving an "A" grade from the US Preventive Services Task Force.

CTC is the procedure of choice in the setting of incomplete colonoscopy due to technical limitations, or an obstructing lesion, and provides better imaging resolution than more traditional fluoroscopic tests (i.e., contrast enema). However, in the setting of a known malignancy, the costs and risks of CTC should be considered in light of how treatment decisions would be altered by CTC findings. If a patient has been diagnosed with CRC and has an endoscopically obstructing tumor of the proximal colon that does not allow for completion colonoscopy, it is unlikely that a CTC will provide any findings that would drastically change management, as the colon proximal to the tumor will likely be resected. For patients with endoscopically obstructing tumors of the distal colon, CTC may be helpful to rule out synchronous tumors preoperatively. However, it is also reasonable to forgo CTC, as these patients will receive staging via CT scan which, although not as sensitive as CT colonography, should at least be able to detect any synchronous large lesions. Furthermore, even if CTC does detect a small proximal lesion, it cannot be biopsied in the setting of a distal untraversable lesion. Therefore, in these settings, the patient's clinical situation needs to be carefully considered regarding the benefit of any further assessment for synchronous lesions. If the patient is to undergo any neoadjuvant treatment, this will hopefully allow completion colonoscopy after tumor shrinkage and prior to surgical resection.

Colonoscopy

Colonoscopy is the most sensitive and specific test for colorectal cancer and polyps, being both diagnostic (i.e., detects polyps and cancers), therapeutic (can remove polyps), and preventive (can prevent polyp progression to cancer). It can also detect other abnormalities, such as inflammatory bowel disease or diverticulosis. However, it is the most invasive option, requiring full bowel preparation, which is associated with nausea, vomiting, abdominal pain, and dehydration, and is generally distasteful. It also carries periprocedural risks, including colonic perforation (0.1%), gastrointestinal bleeding (especially after biopsy or polypectomy), missing a lesion (false negative), or incomplete procedure (either knowingly or unknowingly, which occurs about 5–10% of the time) [5]. Also, the quality of the procedure varies based on the performing physician's technical expertise, which can lead to false negatives. Lastly, most rural areas have lower volume providers and less access to endoscopy overall, often resulting in unacceptably long travel times for patients.

If during colonoscopy a neoplasm is encountered, the endoscopist should then consider the potential benefits of biopsy and tumor localization. For patients with obvious adenomatous neoplasms of the intraperitoneal colon which will clearly require colectomy, it could be argued that biopsy results will be unlikely to change subsequent management and may incur unnecessary cost to the patient, can exacerbate bleeding, carries a risk of perforation, and can have false-negative results that only serve to confuse the patient. However, biopsy may be helpful in detecting Lynch syndrome preoperatively (which may alter treatment decisions)

and help guide chemotherapeutic choices if the patient is found to have incurable distant metastatic disease on preoperative staging and is to be treated nonoperatively. Moreover, insurance companies may refuse to cover the cost of staging tests without a histologic cancer diagnosis. If the etiology of the lesion is in question, i.e., possible lymphoma or ischemic ulcer, then biopsy is warranted. If the tumor is small and unlikely to be appreciated from the serosal side intraoperatively, the distal extent of the tumor should be marked with tattoo to assist with intraoperative localization (see Chaps. 23 and 25).

If a rectal tumor is encountered, biopsy should be performed routinely, and molecular testing including immunohistochemistry for mismatch repair proteins (IHC for MMR) should be performed. Rectal cancer patients are often treated with neoadjuvant radiotherapy and chemotherapy, which may alter the tumor so that molecular analysis is not possible postoperatively. In addition, some medical and radiation oncologists will be reluctant to initiate neoadjuvant therapy in a patient without histologic confirmation of adenocarcinoma. The distal extent of the tumor should be marked with tattoo to ensure complete resection following neoadjuvant therapy.

Delineating Colon Versus Rectum

Where the colon ends and the rectum begins is hotly debated. The various potential modalities used to make this distinction include intraoperative visualization, endoscopy, and cross-sectional imaging. A reproducible definition is important for numerous reasons, including eligibility for clinical trials, localization for serial surveillance of rectal cancer, determining treatment plans (i.e., upfront surgery versus neoadjuvant chemoradiation), and for prognostic estimates. The clinical implications are also critical, since rectal tumors demonstrate clinical features that differ from colon tumors, such as risk of peritoneal disease, lymphatic drainage, threatened radial and/or distal margins, consideration of sphincter preservation, and need for protecting ileostomy.

According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, the rectum is defined as beginning at a virtual line drawn from the sacral promontory and symphysis pubis on magnetic resonance imaging (MRI) of the pelvis, ending at the upper border of the anorectal ring [6, 7]. The rectum is arbitrarily divided into three parts, based on measurement on rigid proctoscopy: low (0–6 cm from the anal verge); mid (7–11 cm), and high (12–15 cm) (Fig. 24.1) [8].

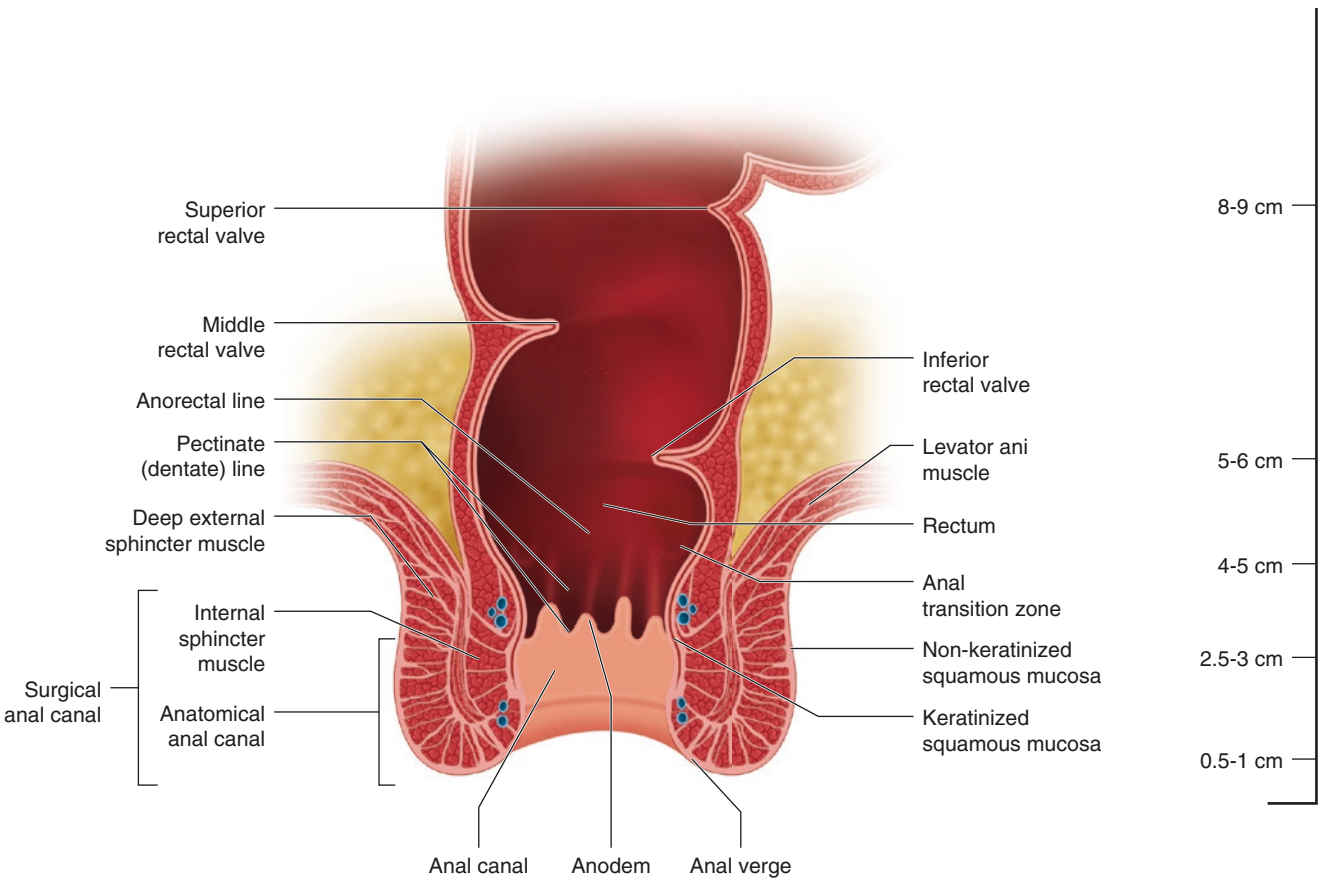

Fig. 24.1 Delineation of the low, mid, and upper rectum with relevant landmarks

Table 24.2 Commonly used criteria for delineating colon from rectum

Intraoperative/ Surgical Criteria	Cross-sectional imaging (CT/MRI)	Endoscopic
- where the teniae splay - where the epiploica terminate at the peritoneal reflection (varies by gender) the sacral promontory	- a delineating line between the sacral promontory and the pubic symphysis - the sigmoid "takeoff" from the rectum (i.e., end of the mesorectum), seen as an acute angulation	- distance from the anal verge on rigid proctoscopy (typically 12 or 15 cm) - beyond the third rectal valve

Initial National Cancer Institute consensus guidelines [7] used 12 cm via rigid proctoscopy in the left lateral decubitus position as the commonly accepted cutoff for the rectosigmoid junction. However, an international Delphi consensus concluded that the "sigmoid takeoff" should be utilized, as seen on cross-sectional imaging, marking a shift from a single clinician's physical evaluation to a radiographic one [9]. One of the drivers behind this transition is the growing use of MRI in staging newly diagnosed rectal cancers, buoyed by the growth of programs such as the National Accreditation Program for Rectal Cancer (NAPRC) [10], newer staging guidelines, and criteria for clinical trial eligibility, all of which favor, or even require, MRI for initial staging. The purported benefit of using MRI versus endoscopic evaluation for staging is that imaging is more reproducible and thus more easily interpreted and comparable over time in multidisciplinary discussions such as tumor boards. However, there is still clear variation in all these definitions and a wide variety of clinical implications for each modality, which will be discussed later on in the chapter. In Table 24.2, we compile the most commonly used criteria for delineating the colon from the rectum.

Adding to this complexity is a newer algorithm for treating locally advanced colon cancer with upfront chemotherapy, as seen in the recently published FOxTROT trial [11]. This is also an option for bulky upper rectal cancers and is in line with NCCN guidelines [7]. Although in daily practice it can be challenging to definitiviely differentiate a colon from a rectal location of the tumor, every attempt should be made to do so as the clinical behavior and treatment recommendations differ.

Staging and Workup of Colon and Rectal Cancer

Once the diagnosis of colorectal cancer has been established, the extent of locoregional and distant spread should be determined. Many of the staging examinations are similar for colon and rectal cancers. However, the locoregional staging of rectal cancer does involve additional evaluation. Appropriate staging is especially important for rectal cancer as it drives treatment decisions in order to minimize under- or overtreating the tumor, both of which have future implications with respect to prognosis and quality of life (see Table 24.3).

TNM Staging

Both colon and rectal cancers are staged according to the American Joint Committee on Cancer (AJCC) TNM staging system, eighth edition [12], which is based on the depth of invasion of the tumor (T stage), the extent of lymph node involvement (N stage), and the presence of distant metastases (M stage) (see Table 24.4). For rectal cancer, staging requires consideration of both the initial clinical stage upon which treatment decisions are made and the final pathologic stage which may be the most important prognosticator (Table 24.5) [13]. The prefix "c" for clinical is added to denote an *estimate* of stage based typically upon radiographic imaging, and "p" is added to denote histologic staging postoperatively, while the prefix "yp" is used to denote histologic staging following neoadjuvant treatment [12].

History

Initial workup should include a complete tumor-specific history, such as duration of symptoms, abdominal or pelvic pain, rectal bleeding and its characterization whether mixed in with stool, bright red or maroon in color, tenesmus, incontinence, change in bowel habits (new onset constipation, diarrhea, frequent thin stools), and weight loss. Patients may also present with fatigue, shortness of breath, and reduced endurance during exertion due to iron-deficiency anemia. Urinary problems, baseline fecal continence, and sexual function should also be ascertained with regard to rectal cancers. In addition, family history should be elicited to rule out the possibility of a hereditary or familial syndrome which

Table 24.3 Diagnostic workup of primary rectal cancer

Parameter	Method of choice
Location (distance from anal verge)	Digital rectal exam (DRE) Rigid sigmoidoscopy
Visualization of colon	Colonoscopy Virtual colonography
Morphological verification	Biopsy
cT stage	
-Early	ERUS, MRI
-Intermediate/advanced	MRI, preferred over ERUS
-Sphincter infiltration	MRI, DRE, ERUS
cN stage	MRI preferred, CT, ERUS
M stage	CT chest and abdomen, PET/CT if extensive EMVI for other sites

Table 24.4 American Joint Committee on Cancer (AJCC) TNM Staging Classification for Colorectal Cancer 8th ed, 2017

T-PRIMARY TUMOR	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades subserosa or into non-peritonealized pericolic or perirectal tissue
T4	Tumor directly invades other organs or structure and/or perforates visceral peritoneum
T4a	Tumor perforates visceral peritoneum
T4b	Tumor directly invades other organs or structures
N -REGIONAL NODES	
Nx	Regional nodes cannot be assessed
N0	No regional lymph nodes identified
N1	Metastasis in one to three lymph nodes (tumor in lymph nodes measuring ≥0.2 mm) or any number of tumor deposits are present, and all identifiable lymph nodes are negative
N1a	Metastasis in one regional node
N1b	Metastasis in two to three regional lymph nodes
N1c	No regional lymph nodes are positive, but there are tumor deposits, i.e., satellites in the subserosa or in non-peritonealized pericolic or perirectal soft tissue without lymph node metastasis
N2	Metastasis in four or more regional lymph nodes
N2a	Metastasis in four to six regional lymph nodes
N2b	Metastasis in seven or more regional lymph nodes
M -DISTANT METASTASIS	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ-liver, lung, ovary, non-regional lymph nodes without peritoneal metastasis
M1b	Metastasis in more than one organ
M1c	Metastasis to the peritoneum with or without other organ involvement
T categories Although these categories have not changed, and T4 was divided into T4a and T4b in the previous edition, further clarification that tumors with perforation in which tumor cells are continuous with the serosal surface through inflammation are considered to be T4a. In the lower rectum, in the absence of peritoneal covering, tumors that invade or directly adhere to adjacent organs or structures are considered T4b.	
N categories There is a discussion regarding isolated tumor cells in lymph nodes and micrometastases. Isolated cells consist of up to 20 cells within subcapsular or marginal sinus of a lymph node should be designated N0 (or NOi+), but their presence does not change the state to stage III. Micrometastases are clusters of 20 or more cells or metastases measuring >0.2 mm and <2 mm in diameter. Lymph nodes with micrometastases are considered positive and designated N1. Outcomes in tumors with nodal micrometastases ranging from 0.2 to 2 mm are similar to those with metastases >2 mm; thus the designation of N1mi is unnecessary. The interpretation of discrete tumor nodules found within the lymph drainage area of the primary rectal carcinoma is clarified. Nodules that contain no identifiable lymph tissue or vascular/neural structures should be considered tumor deposits and designated N1c. Tumor deposits within a vessel wall should be considered lymphovascular invasion with the site-specific designations of L+ for lymphatic or small vein invasion and V+ for deposits in endothelial cell-lined spaces with associated red blood cells or smooth muscle cells. If tumor nodules are found around neural structures, they are classified as perineural invasion. N1c changes the disease to stage III even in the absence of nodal metastases. The number of deposits has no influence on the designation and is not added to the number of positive nodes.	
M categories M1c which denotes peritoneal metastases has been added	

Key changes to AJCC staging of colorectal cancer [12]

would prompt genetic counseling and testing. Comorbidities must be ascertained in order to establish suitability for surgical procedures or chemotherapy. The patient may warrant a cardiology or pulmonary assessment, nutritional consult, and, if appropriate, a geriatric evaluation including frailty screening [14] prior to recommendation of treatment. Past surgical history should also be queried since this may affect choice of future surgical approach.

Physical Examination

On physical examination, the abdomen should be assessed for previous scars, as well as palpable masses, hepatomegaly, or abdominal distention, especially in the presence of suspected obstruction. If the patient has a thin body habitus and a large intra-abdominal luminal mass, it may be possible to palpate the mass on abdominal exam. In the presence of a high-grade obstruction, the patient may present with abdom-

Table 24.5 American Joint Committee on Cancer (AJCC)

Stage 0	T1s	N0	M0
Stage 1	T1,T2	N0	M0
Stage II	T3, T4	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	Any T	N1,N2	M0
Stage IIIA	T1, T2	N1	M0
	T1	N2a	M0
Stage IIIB	T1, T2	N2b	M0
	T2, T3	N2a	M0
	T3, T4a	N1	M0
	T4a	N2a	M0
	T4b	N1, N2	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

TNM Staging System for Colorectal Cancer 8th ed., 2017

inal distention and pain. For distal rectal tumors, perhaps the most important diagnostic test is a thorough digital rectal exam (DRE). If the lesion is palpable, the surgeon should determine and document: percentage of luminal circumference involved; quadrant(s) involved; distance between the distal margin of the tumor and the superior aspect of the anorectal ring; tactile characteristics (firm versus soft, mobile versus tethered versus fixed, etc.), and involvement of other structures (anal sphincter muscles, posterior vaginal wall, levator muscles, prostate). In addition, DRE allows the evaluation of sphincter bulk and tone, which is important should restorative proctectomy be considered. DRE is limited in that it can only be used to assess distal tumors that are within range of the examining finger and may be also limited by patient body habitus.

Proctoscopy

Proctoscopy should be performed by the operating surgeon to determine the exact location of any tumor reported to be in the rectosigmoid by the endoscopist at index colonoscopy, prior to initiation of treatment. This examination is critical, as determination of tumor location at index colonoscopy is often inaccurate [15]. This is especially true for tumors described as being in the "sigmoid" or "rectosigmoid" which are subsequently found to be in the mid or distal rectum [15]. For rectal cancers, it is important to clearly delineate tumor location relative to anatomic landmarks in order to determine if sphincter-sparing surgery would be an option and to mark the distal extent of the tumor with tattoo (see above). It is also useful as a surveillance tool to assess tumor response to neoadjuvant therapy. Proctoscopy can be performed in clinic without sedation, with only an enema preparation in most patients. Rigid proctoscopy requires less equipment, but one cannot see beyond 25 cm, and it can be challenging to see lateral lesions. Furthermore, it can be quite uncomfortable for some patients and technically difficult in patients with a larger body habitus. Video flexible proctosigmoidoscopy is better tolerated by the patient and allows for photo documentation of tumor morphology and location; however, it is still subject to the vagaries of exact delineation of distance as previously mentioned .

Colonoscopy

Colonoscopy is required to fully evaluate the colon after the diagnosis of a colorectal malignancy or unresectable polyp has been made to exclude synchronous cancers which may occur in 3–5% of patients with primary rectal cancer as well as synchronous polyps which occur in as many as 30% [16]. In general, sufficient biopsies of the tumor should be obtained to confirm both the diagnosis of cancer, as well as to obtain tissue for immunohistochemistry to ascertain biomarkers which may guide chemotherapeutic options and prognosis.

Occasionally, there are conditions that may preclude a complete examination of the colon preoperatively, such as the presence of an obstructing lesion or perforation. In some cases, a water-soluble contrast enema could be considered in patients who present with acutely obstructing tumors of the left colon or rectum, in order to rule out distal synchronous large lesions and help prep the distal colon should intraoperative colonoscopy be required. CT with rectal contrast is generally preferred over water-soluble enema due to three-dimensional perspective, but typically the patient has already received a CT in the emergency room, so the risks of a repeated scan must be weighed against the benefits. Evaluation of the proximal colon may occasionally be obtained via CT colonography in cases of partial obstruction or deferred until the postoperative period or after reversal of a diverting ileostomy. If a patient presents with a completely obstructing colon or rectal cancer and either diverting loop colostomy or Hartmann's resection are performed, completion colonoscopy can be performed prior to resection or Hartmann reversal via both limbs of the stoma or via the colostomy and rectal stump to ensure that a synchronous tumor or polyp will not be ignored at the time of reanastomosis. Another feasible option in the face of an obstructing lesion is the placement of an endoscopic stent, which allows the opportunity for biopsy and can serve as a bridge to surgery following resolution of the obstruction, as well as facilitate pre-treatment colonoscopy (See Chap. 25).

Tumor Localization

Endoscopic tattooing is recommended for all colonic lesions for surgical localization. Endoscopic measurements either via landmarks or centimeters from the anal verge are notoriously inaccurate. With the exception of the cecum, which has distinct, reproducible anatomic landmarks (ileocecal valve,

appendiceal orifice), the standard recommendation is submucosal tattooing with India ink distal to the tumor in at least two quadrants.

However, because referring endoscopists may differ in their routine practice, it is imperative that the surgeon communicate with the endoscopist regarding if and how a tumor was marked with tattoo. This is especially important in the setting of a malignant polyp that has been completely removed endoscopically and is later found to have invasive carcinoma, typically to the endoscopist's surprise. In this situation, the endoscopist should repeat the colonoscopy as soon as possible in order to detect the polypectomy scar and tattoo just distal to that site. This can be quite challenging in the setting of multiple polypectomies and may require multiple tattoos, which poses treatment dilemmas for the operative surgeon [17, 18]. It is always favored to have the index endoscopist perform the repeat colonoscopy for tattooing as that individual will have the greatest chance of accurately localizing the polypectomy site in question. These cases are often best managed by a multidisciplinary discussion with the surgeon and the endoscopist. Fortunately, even when the polypectomy site may not be visible to the naked eye on endoscopy, once the surgical resection specimen has been fixed, it can often be detected pathologically, confirming resection of the appropriate segment.

As noted above, rectal tumors must be accurately localized prior to initiation of neoadjuvant treatment since assessment of distal resection margins after treatment is often difficult due to downstaging of the tumor. A few caveats should be mentioned. Tattooing with India ink for rectal cancer has been found by some investigators to be inaccurate with error rates ranging from 2% to 21% [19]. It should be remembered that submucosal tattoos that are placed preoperatively are often difficult to visualize from the abdomen because of the thick mesorectum. Some authors have suggested that submucosal rectal wall tattoos be placed in the operating room at the time of resection to accurately mark the distal resection margin [20], although this may not be possible in the setting of complete clinical response, which is why placement of tattoo at the time of diagnosis is favored. Unlike for intraperitoneal colon cancers, tattoo of extraperitoneal rectal cancers will primarily be visible during intraoperative endoscopy, and a flexible colonoscope/sigmoidoscope or rigid proctoscope should be available for localization during resection. Several case reports have also raised the issue of potential tumor implantation by improper endoscopic tattooing directly through the tumor, which obviously should be avoided [21]. In addition, tattooing may induce altered appearance of the rectal wall on MR or reactive lymphadenopathy, with possible resultant overstaging on MRI [22]. Thus, if a rectal tumor was not tattooed at diagnosis, it is optimal to obtain staging MRI and CT prior to marking the tumor endoscopically with ink. If tattoo is placed transmurally, it can render resection more difficult because the dye can obscure normal anatomic planes [23]. As such, preoperative clipping has been suggested as a feasible alternative; however, clips carry the risk of falling off [19].

Blood Work

Blood work including complete blood count, basic chemistry, and carcinoembryonic antigen (CEA) should be obtained. CEA is used as a prognosticator whereby levels <5 ng/ml have been found to have better prognoses stage for stage as opposed to CEA ≥5 ng/ml [24]. Moreover, normalization of previously elevated CEA levels in patients who were treated with neoadjuvant treatment has been associated with complete pathologic response [25]. CEA levels that fail to normalize post-resection should raise the suspicion of metastatic or residual disease. CEA should be routinely measured during surveillance of patients posttreatment since elevation of previously normal levels may signal the development of recurrent or metastatic disease. Routine testing for transaminases, bilirubin, and/or alkaline phosphatase, unless indicated for other reasons, is not necessary preoperatively as they have been found to be neither sensitive nor specific for the diagnosis of liver metastases and are no longer routinely recommended by NCCN for staging or surveillance [6], although their use is still advocated by the European Society of Medical Oncology [26].

Imaging

Computed Tomography (CT) Scan

Initial staging includes CT scan of chest, abdomen, and pelvis in order to detect the presence of synchronous metastatic disease which may be present in 30% of patients at presentation. CT scan of the chest is used to determine the presence of lung metastases and to set a baseline for any preexisting suspected benign lesions [7]. Its overall accuracy in detecting lung metastases is 84% with a sensitivity and specificity of 73% and 74%, respectively [27]. CT will also detect indeterminate pulmonary lesions in 4–42% of patients; however, upon further evaluation, only 1% are eventually confirmed as metastases [28]. Abdominal CT will indicate the presence of liver metastases, which may occur in 20–34% of patients [7]. CT is the most common imaging modality used to stage metastatic disease with an estimated sensitivity of 85%, positive predictive value of 96%, and false-positive rate of 4% [29]. For liver lesions measuring <10 mm, MRI outperforms CT because of enhanced soft tissue resolution [30]. CT may also demonstrate tumor-related complications such as perforation, obstruction, and invasion of adjacent organs and should be done with both oral and IV contrast whenever possible. If a patient has an iodine allergy, they can be prepped with steroids and diphenhydramine. In the case of renal insuffi-

ciency, an alternative is to obtain a non-contrast CT of the chest with a gadolinium-enhanced MRI of the abdomen and pelvis. Another alternative is positron emission tomography (PET) with 2-[18F] fluoro-2-deoxy-D-glucose (FDG) with fused CT imaging (PET-CT), as discussed below [13].

In general, CT cannot accurately predict metastatic spread to mesocolic or mesorectal lymph nodes. With regard to rectal tumors, CT cannot routinely determine depth of invasion or mesorectal fascial involvement, primarily because CT is unable to distinguish between tumor extension and peritumoral fibrosis. In addition, assessment of tumor involvement of adjacent organs or the pelvic sidewall is often inaccurate. The primary value of CT is its ability to detect distant metastases.

PET-CT

PET-CT is not generally recommended for initial staging of colorectal cancers but may be used to assess equivocal findings on CT scan, to rule out extrahepatic disease with established hepatic metastases when radical surgery is being planned, to confirm features associated with a high risk of metastases such as EMVI (extramural vascular invasion) on MRI or high CEA levels, and in patients with a contraindication to intravenous contrast as previously mentioned [7]. FDG (fludeoxyglucose) accumulates in malignant tumors as well as in inflammatory tissue and adenomas, thus is less sensitive with a potential for false positives [13, 31], such as in necrosis following radiation therapy. False negatives have also been reported in mucinous tumors [13], because of the relatively low cell/tumor volume ratio or any lesion <10 mm.

Rectal Cancer-Specific Staging Modalities

Appropriate staging is essential for rectal cancer, since many current treatment algorithms are driven by estimates of tumor stage. Accurate staging is paramount when considering neoadjuvant therapy, chance of future sphincter preservation, and eligibility for clinical trials, including the choice of definitive chemoradiotherapy ("watch and wait") for complete clinical responders (see Chap. 28). Following clinical staging, patients should be discussed at a multidisciplinary tumor board consisting of surgeons, medical oncologists, radiation oncologists, pathologists, and radiologists so that the most efficacious recommendations can be made for each individual patient.

Endorectal Ultrasound

Endorectal ultrasound (ERUS) and MRI are the main modalities used for local staging of a rectal cancer. ERUS involves the insertion of a water-filled balloon into the patient's rectum allowing a full circumferential view of the lumen. The five layers of the rectal wall are defined. These include (1) the area between the balloon and the mucosa, (2) mucosa and muscularis mucosa, (3) submucosa, (4) muscularis propria, and (5) the area between the muscularis propria and perirectal fat. Thus, theoretically, this modality is highly useful in determining T stage since it is able to depict invasion of the rectal wall layers (Fig. 24.2). It is technically challenging due to the necessity of constantly having to adjust the angle of the probe in relation to the rectal wall due to the presence of clot or stool that may prevent its apposition to the rectal mucosa. In addition, bulky tumors may constrict the lumen and not allow for adequate balloon distention. As such, there is a reported variation in the accuracy of ERUS in predicting

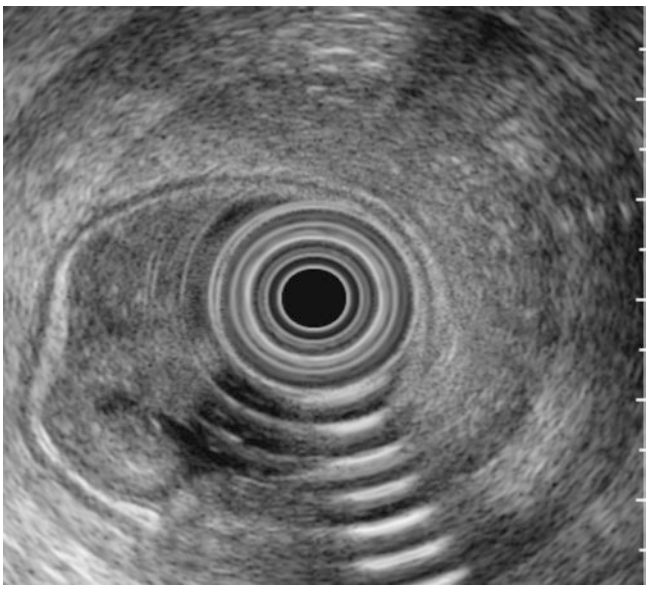

Fig. 24.2 Endorectal ultrasound of T1 tumor. (Courtesy of Lehel Somogyi, MD)

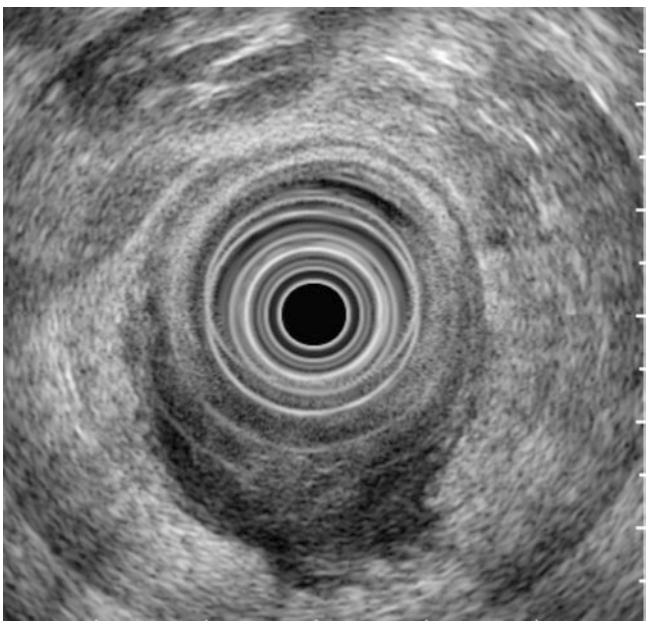

Fig. 24.3 Endorectal ultrasound of T3 tumor. (Courtesy of Lehel Somogyi, MD)

T stage ranging between 63% and 96% [32]. Although an earlier published meta-analysis of 42 studies of 5000 patients who underwent ERUS for rectal cancer staging found a pooled sensitivity of 81–96% and specificity of 91–98% for T stage [33], more recent data have shown a decline in T stage accuracy ranging from 55% to 82% (Fig. 24.3) [30].

Limitations of ERUS are that it is operator dependent; has difficulty differentiating between peritumoral inflammation versus desmoplastic reaction, especially after biopsy; and thus has difficulty in differentiating between a T2 tumor that invades the muscularis propria from an early T3 with microscopic infiltration of the perirectal fat, and some patients may require a cathartic bowel preparation if enemas cannot clear the rectum of stool [32]. Its advantage is that it may be able to differentiate T1 from T2 tumors. ERUS has an accuracy of 73% for T1 lesions with a sensitivity of 71% and specificity of 100% [34]. ERUS may also be able to stratify T1 tumors. Sessile T1 lesions have been subdivided on the basis of the depth of submucosal invasion into sm1 (slight submucosal invasion), sm2 (intermediate between sm1 and sm3), and sm3 (invasion into lamina propria) [35]. Since its main use is in the differentiation between T1 and T2 tumors, ERUS should be performed if local excision is being contemplated, where local excision is considered appropriate for low risk T1 cancers, but not favored for T2 cancers (see Chap. 27). However, it may be difficult to during ERUS to visualize the mesorectal fascia except at the level of the vagina or seminal vesicles, and thus it is suboptimal for determination of the predicted circumferential resection margin (CRM) when performing standard mesorectal excision, which may be the most important component of staging for locally advanced tumors [36]. As current multimodality treatment of rectal cancer mandates precise evaluation of the mesorectal fascia, the major limitation of ERUS is its inability to accurately define it.

In assessment of nodal status, ERUS has been found to have an accuracy of 75% (Fig. 24.4). The main limitation in assessing lymph nodes is the lack of criteria available to discriminate between malignant and inflammatory nodes. The 5 mm size criterion used to define a malignant node has a poor predictive value when compared to histology [37].

Rectal Cancer-Specific Pelvic MRI

High-resolution MRI is the recommended imaging modality for accurate locoregional staging of rectal cancer. The standard rectal cancer MRI protocol includes thin-slice, high spatial resolution T2-weighted images in order to encompass the rectal tumor and the surrounding perirectal tissues and mesorectum [30] obtaining images in three planes of view: oblique axial perpendicular to the tumor; sagittal determined by the longitudinal axis; and oblique coronal plane parallel to the anal canal (Fig. 24.5a, b). The routine use of an endorectal coil or endorectal contrast is not advised as its use may stretch the rectum thus hindering accurate interpretation of mural invasion. Although the addition of intravenous gadolinium contrast does not uniformly improve diagnostic accuracy, several studies have demonstrated that the addition of gadolinium resulted in the alteration of 24% of treatments due to downstaging of T stage which obviated the need for neoadjuvant treatment [38]. In addition, it may improve detection of extramural vascular invasion (EMVI) [23]. MRI provides information on tumor size, location, relation to the sphincters and peritoneal reflection, evidence of EMVI, and, most importantly, on the predicted circumferential resection margin (CRM). The CRM is the lateral or radial resection margin and is defined as the closest distance of the tumor to

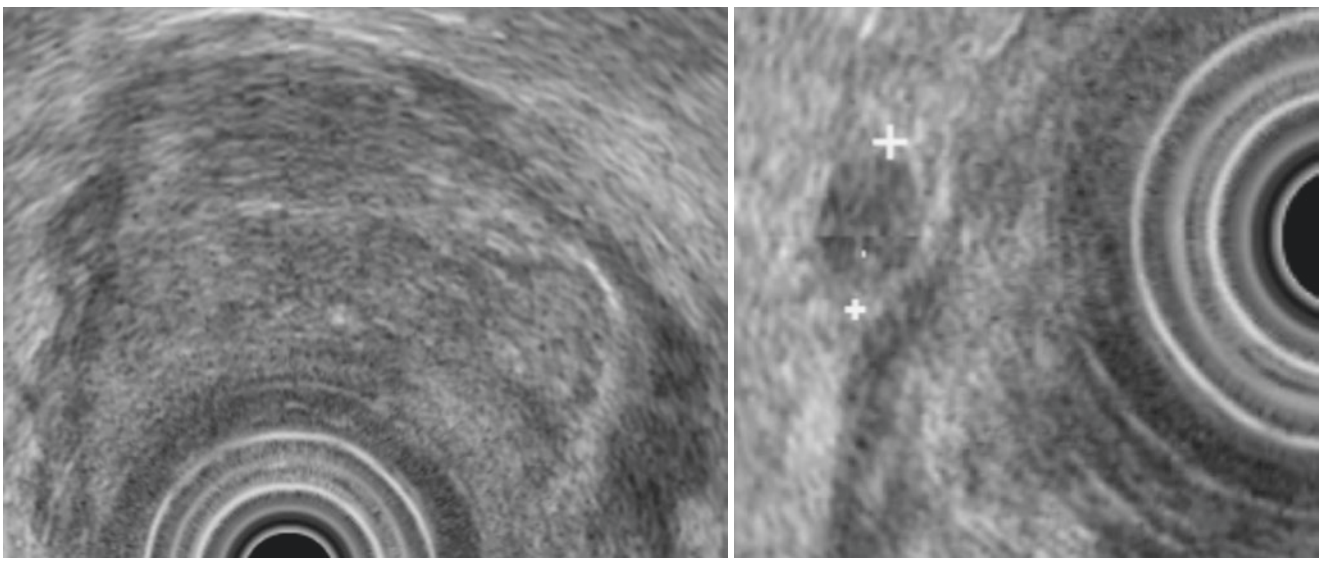

Fig. 24.4 Endorectal ultrasound of T3N1 tumor. (Courtesy of Lehel Somogyi, MD)

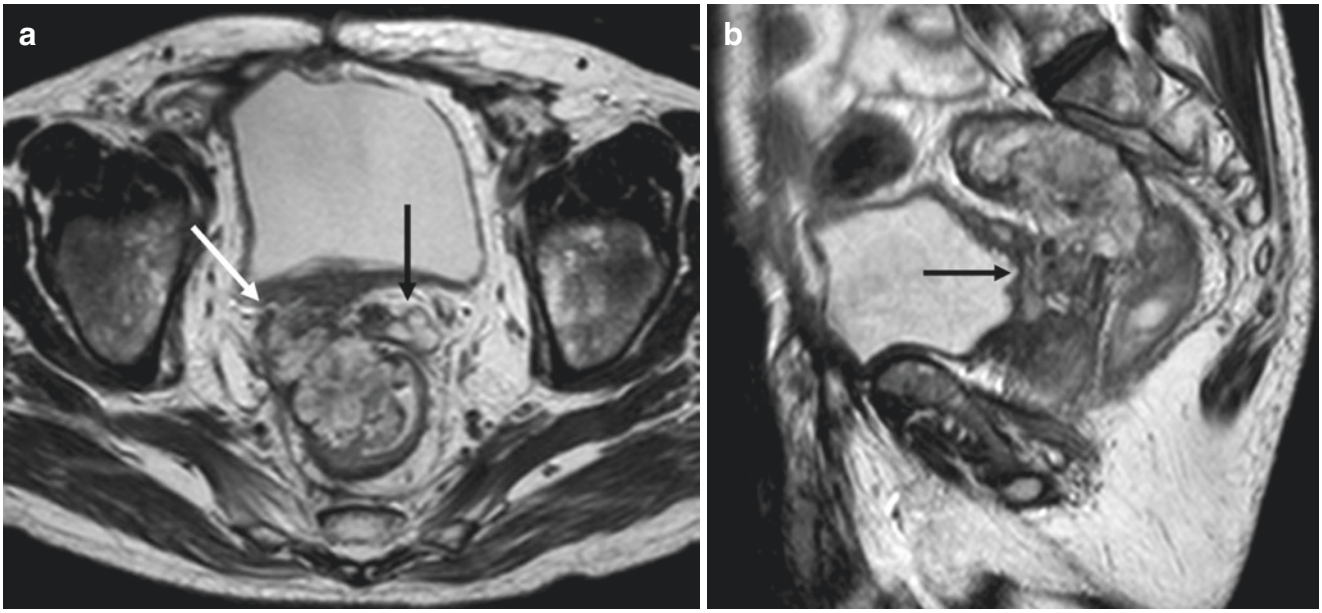

Fig. 24.5 MRI of a T4 tumor. (**a**). Axial and (**b**). sagittal T2 images show a bright, therefore mucinous, rectal cancer with direct invasion of the right seminal vesicle (white arrow); black arrow shows the normal left seminal vesicle which is fluid filled. (Courtesy of Vincent Pelsser, MD)

the mesorectal fascia. The CRM is considered to be positive when the tumor extends within 1 mm or less of the mesorectal fascia (Fig. 24.6a–e). With neoadjuvant treatment, tumor retraction from the CRM is regarded as an good prognostic feature (Fig. 24.7a–c) [36]. Local recurrence rates are higher with positive CRM. MRI is superior to ERUS for assessing the CRM because of its ability to identify the mesorectal fascia. MRI was found to have sensitivity for CRM involvement of 77%, while specificity was 94% [39]. CRM assessment by high-resolution MRI was the only preoperative variable that significantly predicted local recurrence, disease-free, and overall survival in one study [40]. A negative CRM is associated with a 67% 5 year survival versus 47% with a positive CRM.

The accuracy of T stage has been found to improve with increasing T stage (Fig. 24.8a, b). However, as is the case with ERUS, there is variability in the ability to discriminate between a T2 and an early T3 lesion, often misinterpreted so as to overstage the tumor [30]. Characterization of T3 and T4 lesions has overall accuracy of nearly 100% (Fig. 24.9). High-quality MRI also allows for subclassification of T3 lesions (Fig. 24.10). Although not mentioned in the AJCC staging eighth edition or any TNM version, the European Society for Medical Oncology (ESMO) subclassifies T3 lesions based on depth of invasion from the muscularis propria to the outer edge of the tumor into T3a (<1 mm), T3b (1–5 mm), T3c (6–15 mm), and T3d (>15 mm) [26]. This subclassification has major potential clinical applications since there are differences in recurrence and survival rates within the T3 category [41]. Moreover, this subclassification has the ability to better risk stratify tumors, into need for neoadjuvant treatment (for more advanced T3 lesion) versus upfront resection with proctectomy alone (for early T3 lesions), a practice that is more common in Europe than in North America. The Canadian Quicksilver Trial, a prospective nonrandomized trial looking at the safety and feasibility of using MRI criteria to identify patients with good prognostic rectal cancer features, found that MRI criteria were able to select patients who could undergo primary rectal cancer surgery instead of initial chemoradiotherapy and achieve a low rate of CRM positivity of 4.9% compared to 10% in historical controls [42].

MRI is used primarily used to evaluate the relationship of the tumor to the mesorectal fascia or other structures in close proximity (i.e., any threatened radial margin), as well as to the peritoneal reflection, as this will predict oncologic prognosis [40]. Small T3 tumors of the upper rectum that are confined to the rectum and mesorectum alone may be amenable to upfront resection, whereas in the converse situation (a bulky upper rectal tumor that abuts the mesorectal fascia), neoadjuvant radiotherapy is more likely to have a clinical impact (Fig. 24.11a–c). These nuances should guide neoadjuvant treatment decisions more than an arbitrary anatomic delineation.

Low rectal cancers (defined as extending from the anal verge to 6 cm) are classified by MRI as extending to or below the origin of the levators on the pelvic sidewall. An estimated one-third of rectal cancers are low [43]; these tumors are associated with relatively poor outcomes despite radical operative procedures. This has prompted the creation of a MRI-based staging system based on the relationship of the

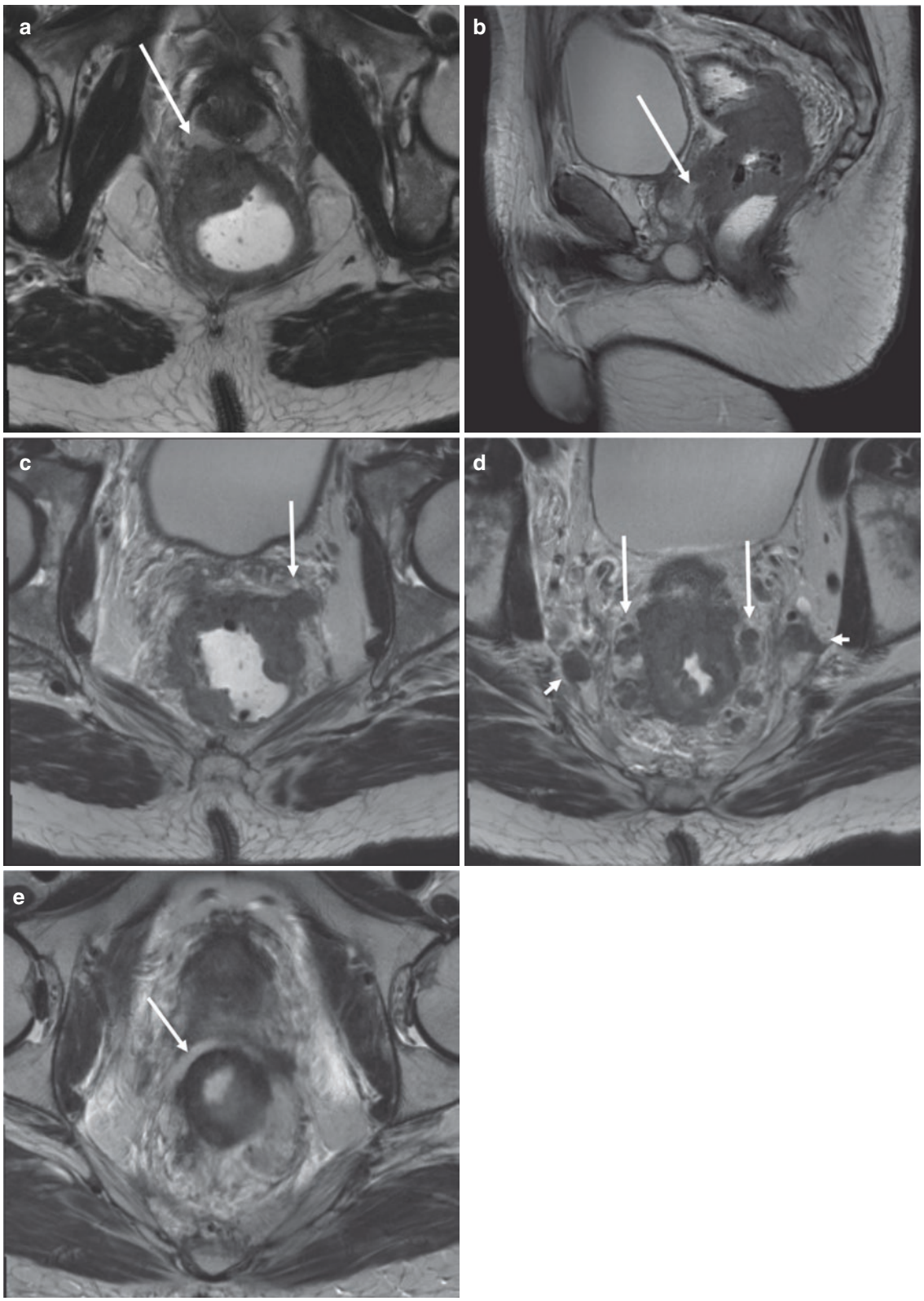

Fig. 24.6 MRI of a T4 tumor with CRM involvement and subsequent treatment regression. (**a**) Axial and (**b**) sagittal T2 images show an anterior T4 rectal cancer with direct invasion of the peripheral zone of the prostate (white arrow). The primary tumor has intermediate signal on the T2 sequence. (**c**) Axial T2 image shows extramural extension of the rectal cancer with transgression the mesorectal fascia (CRM +) (white arrow). (**d**) Axial T2 image shows multiple irregular mesorectal lymph nodes of abnormal signal (N2 – more than three nodes) (long white arrows) and pelvic sidewall adenopathy (short white arrows). (**e**) Axial T2 image after treatment shows good response of the tumor to therapy with profound T2 dark signal of the tumor from fibrosis (tumor regression grade 2) (white arrow). Note the significantly darker signal of the contracted tumor site after treatment as opposed to the intermediate signal prior to therapy as seen on image (**a**). (Courtesy of Vincent Pelsser, MD)

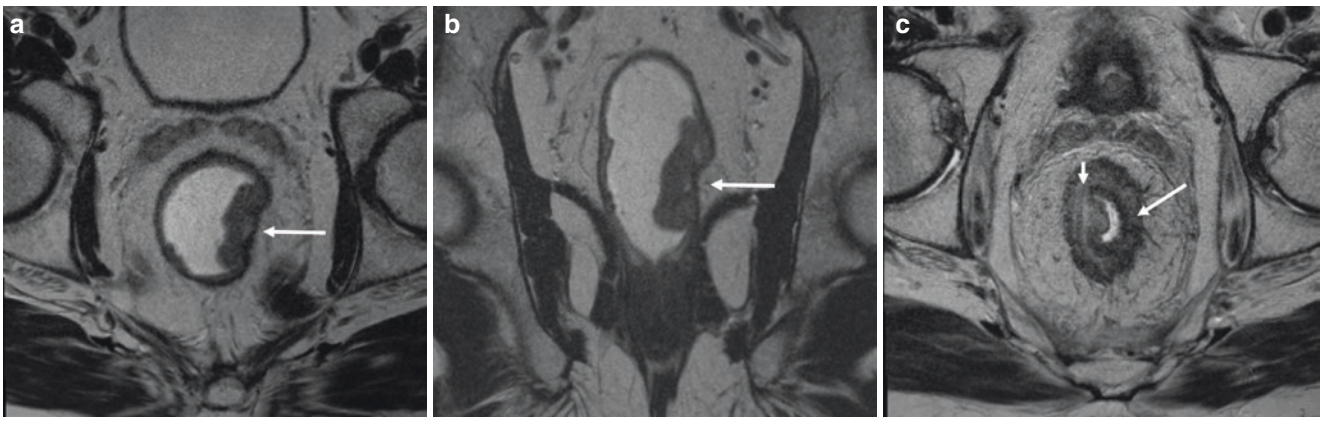

Fig. 24.7 MRI of T1/2 tumor with posttreatment regression. (**a**) Axial and (**b**) coronal T2 images show a rectal tumor not extending beyond the outer muscular layer (T1-T2 tumor) (white arrow). (**c**) Axial T2 image after treatment shows good response of the tumor to therapy with profound T2 dark signal of the tumor from fibrosis (tumor regression grade 2) (long white arrow); submucosal T2 bright signal is present circumferentially from radiotherapy edema (short white arrow). (Courtesy of Vincent Pelsser, MD)

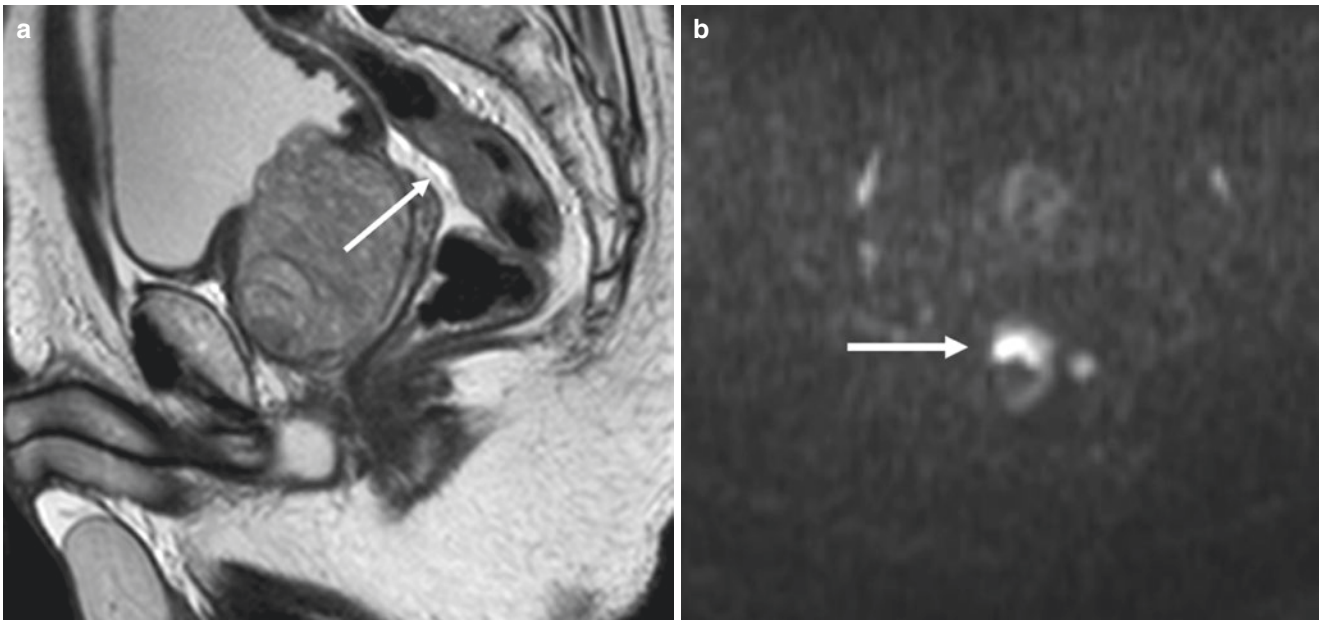

Fig. 24.8 MRI of T1/2 tumor with with diffusion-weighted imaging. (**a**) Sagittal T2 image shows a muscle contained (T1-T2 tumor) focal rectal cancer (white arrow). (**b**) with positive bright signal on axial diffusion imaging (white arrow). (Courtesy of Vincent Pelsser, MD)

tumor to the intersphincteric space and levators. More superficial tumors (T1 and 2) that have not invaded the intersphincteric plane are more likely to be resected with clear CRM and thus require a less radical procedure as compared to T3 and T4 tumors that have invaded the intersphincteric space or levators. These tumors have an 18-fold increased incidence of CRM involvement and often require extralevator abdominal perineal resection (ELAPE) or exenteration to achieve clear margins.

The soft tissue contrast seen on MRI makes it an ideal modality to identify mesorectal nodes (Fig. 24.12). Morphological appearance of nodes has been found to be a better discriminant of nodal involvement than size due to capsule disruption from tumor infiltration, resulting in necrosis within the node [30]. Using the criteria of irregular border and mixed signal intensity, MRI-detected lymph node has been reported to have a sensitivity of 85% and specificity of 97%. A meta-analysis of 21 studies on the use of MRI for rectal cancer, however, reported a sensitivity of 77% and specificity of 71% for MRI-predicted lymph node involvement [39].

Rectal cancers assessed by MRI have been grouped into: [30]

- The *"Good"*: T1-T3a/b, N0, No EMVI, CRM clear; predicted local recurrence risk <10%
- The *"Bad"*: T3c/d-T4 or N1/2, CRM clear, predicted local recurrence risk 10–20%
- The *"Ugly"*: threatened (<1 mm) or involved CRM, EMVI present, low rectal cancer with involved intersphincteric plane or levators; local recurrence risk >20%

MRI enables assessment of the pelvic side wall lymph nodes (PSWLN), which is reported to be one of the reasons for local recurrence, despite optimal surgery in the plane of the mesorectum [according the principles of "total mesorectal excision" (TME)] especially in distal third cancers, which spread along the internal iliac artery and then to the lateral pelvic side wall [44]. Distal rectal cancers have been reported to be associated with a 15% incidence of PSWLN compared to 8% incidence in higher tumors [45].

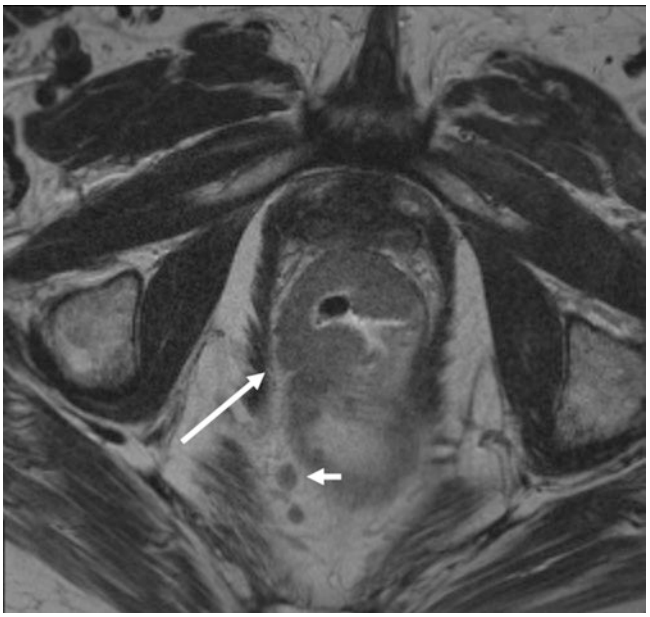

Fig. 24.9 MRI of T3bN1 tumor. Axial T2 image shows a low rectal cancer with focal extension beyond the outer muscular layer (T3b) (long white arrow); positive mesorectal adenopathy (N1: three or fewer nodes) is present posteriorly (short white arrow). (Courtesy of Vincent Pelsser, MD)

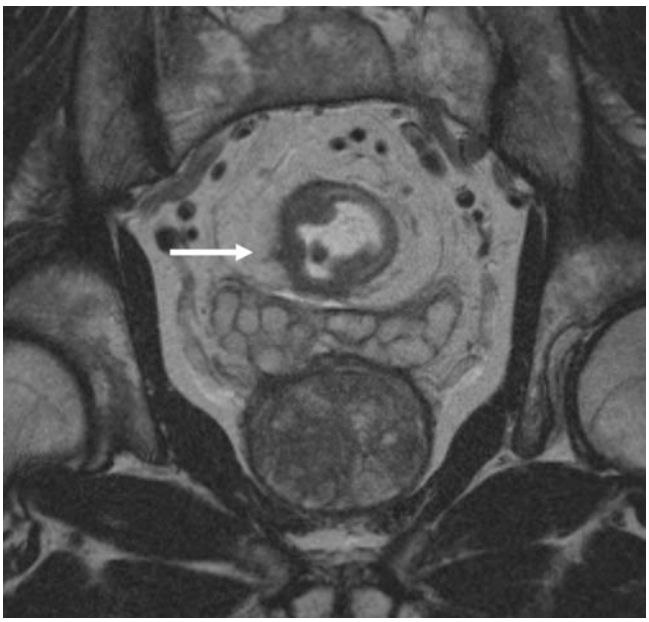

Fig. 24.10 MRI of T3b tumor. Axial T2 image shows a rectal cancer with focal extension beyond the outer muscular layer (T3b) (white arrow). (Courtesy of Vincent Pelsser, MD)

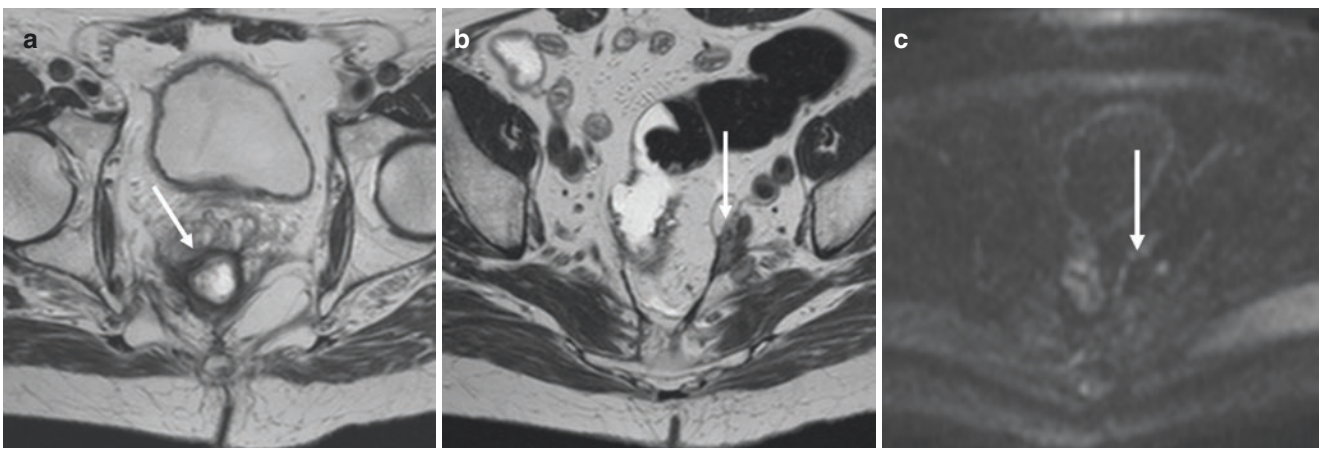

Fig. 24.11 MRI of T3b tumor with posttreatment regression. (**a**) Axial T2 image shows a rectal cancer with focal extension beyond the outer muscular layer (T3b) (white arrow). (**b**) Axial T2 image after treatment of a tumor shows T2 dark signal at the original tumor site from fibrosis (tumor regression grade 2) (white arrow). (**c**) The same patient had a left-sided T2 intermediate small mass (**b**) along the pelvis sidewall (white arrow); diffusion imaging (**c**) was negative showing dark signal (white arrow) indicating absence of tumor in this location, which was subsequently confirmed by PET scan (images not shown) and stability over time. (Courtesy of Vincent Pelsser, MD)

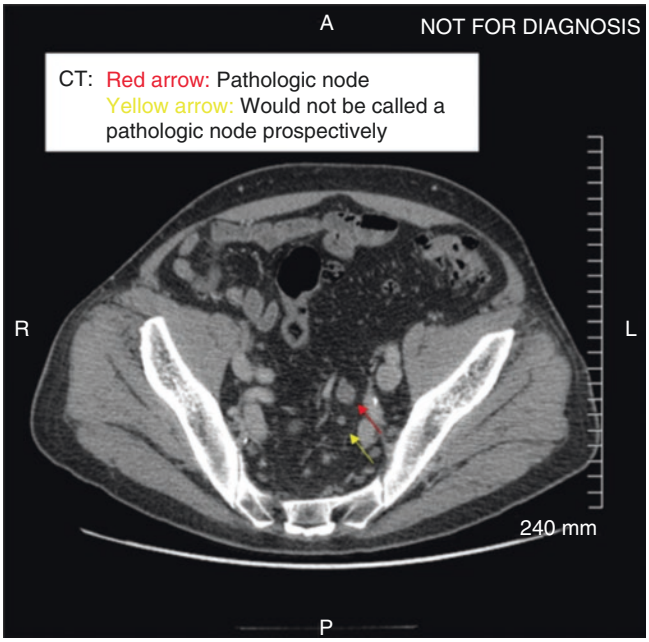

Fig. 24.12 Diffusion-weighted MRI showing a positive and negative mesorectal lymph node

Table 24.6 Performance of MRI at restaging (yMRI)

	Sensitivity	Specificity
yT	50.4%	91.2%
yN	76.5%	59.8%
yMRF	76.3%	85.9%

Table 24.7 Tumor regression grade (TRG) scale

mrTRG1	Complete response. No evidence of treated tumor
mTRG2	Good response. Dense fibrosis without obvious residual tumor
mTRG3	Moderate response:>50% fibrosis or mucin along with intermediate intensity tumor
mTRG4	Slight response: small areas of fibrosis/mucin with mostly tumor
mTRG5	No response: no change in appearance or bulk from original tumor

The value of restaging MRI following neoadjuvant therapy is controversial. For evaluation of the effects of neoadjuvant treatment on the tumor, MRI with diffusion-weighted and T2-weighted sequences has been suggested as an imaging modality to reliably predict regression response with increased sensitivity of 84% compared to 50% with T2 -weighted sequences alone for evaluation of T stage. In terms of nodal response, T2-weighted MRI is better to denote complete disappearance of nodes [46]. However, the performance of MRI for restaging is lower than for the primary staging (see Table 24.6).

Response of the tumor on MRI after neoadjuvant therapy can be graded by comparing pre- and posttreatment MRIs using the MR tumor regression grade (mrTRG) scale (Table 24.7), in which the relative amounts of viable tumor, fibrosis, necrosis, and inflammation are compared and classified. Some studies have demonstrated that MRI can predict complete pathologic response with high accuracy; however, results have not been uniformly reproduced (see Chap. 28).

Preoperative Evaluation

Prior to considering restorative proctectomy, baseline fecal, urinary, and sexual function should be documented and the risk of postoperative dysfunction discussed. As the vast majority of patients undergoing proctectomy for rectal cancer will undergo creation of temporary or permanent intestinal stoma, the patient should be seen by an enterostomal therapist for preoperative marking of an appropriate stoma site and education. For any patient of child-bearing age, the opportunities for sperm-banking or egg donation should be discussed prior to any radiation treatment or operation (if no neoadjuvant radiotherapy). If interested, they should be expeditiously referred to reproductive endocrinologist and infertility (REI) specialist. Patients with extensive comorbidities should be appropriately risk-stratified and optimized perioperatively. Two online resources available via the American College of Surgeons include the ACS NSQIP risk calculator and the "Strong for Surgery" checklist [47, 48].

Optimizing and standardizing preoperative care given to rectal cancer patients have been found to be associated with better-quality pathologic specimens and decreased 30-day morbidity [49]. A best practice preoperative checklist was developed by the American Society of Colon and Rectal Surgeons which outlines the measures necessary to optimize patient care and improve outcomes in patients with rectal cancer (Table 24.8) [50]. Garfinkle et al. looked at compli-

Table 24.8 ASCRS preoperative evaluation checklist

Formal pathology review was performed that confirmed invasive carcinoma
In the unobstructed patient, a complete colonic evaluation was performed
The tumor location within the rectum (distance from anal verge, tumor length, anterior, posterior, left, right), as well as relationship to levators and anorectal ring was documented
An assessment of family history, preoperative stool continence and sexual function were documented
Clinical staging of the primary tumor (MRI +/− ERUS) was performed
Clinical staging for distant metastases (chest, abdomen, pelvis) was performed
Preoperative or perioperative CEA level was measured
Consideration of neoadjuvant treatment for > T2 or node positive disease has been documented
Among those who received neoadjuvant treatment, the tumor was restaged, and location was reconfirmed just prior to operation
A multidisciplinary discussion of care, preferably during a formal tumor board conference, was documented
If a stoma is considered, the site was preoperatively marked

ance with the preoperative checklist and found that compliance with the checklist was associated with improved histologic and 30-day postoperative outcomes [50, 51]. In an effort to standardize and improve the quality of rectal cancer care, the American College of Surgeons Commission on Cancer has developed the National Accreditation Program for Rectal Cancer (NAPRC) which evaluated process and procedure measures for patients who underwent proctectomy. The process measures included clinical staging completion, treatment starting fewer than 60 days from diagnosis, CEA level drawn before treatment, tumor regression, and grading and margin assessment. The performance measures included negative proximal, distal, and circumferential margins and > or equal to 12 lymph nodes harvested during resection [52].

Prognostic Factors Associated with Overall and Disease-Free Survival

A combination of pathologic, clinical, and tumor-specific characteristics allows for a better prediction of oncologic outcome. A recent study of rectal cancer patients after surgical resection with curative intent found that patient age, tumor regression grade, pathologic stage, extranodal tumor deposits, and positive margins had the greatest impact on overall and disease-free survival [53]. The presence of tumor deposits was the strongest independent predictor of poorer outcome. Patients who achieved complete pathologic response after neoadjuvant treatment enjoyed significant improvement in overall and disease-free survival. A more complete discussion of the various prognostic factors follows below.

Pathologic Features: Pre-Resection

Although it is clear that a well-performed surgical resection (i.e., negative circumferential margins, complete mesorectal or mesocolic excision) is the most important prognostic indicator for nonmetastatic colorectal cancers, tumor biologic behavior also influences the risk of recurrence and distant metastasis and can influence choice and duration of adjuvant chemotherapy.

Poor pathologic features include lymphovascular invasion, perineural invasion, tumor budding, lymph node positivity and ratio, microsatellite stability, poorly differentiated tumors, and adverse histologic type. These features can be very influential when determining the risk of local recurrence and/or lymphatic spread and are especially helpful for stratifying risk when considering oncologic resection of locally excised malignant polyps [54].

Lymphovascular Invasion (LVI)

LVI is a marker for possible lymph node involvement and is identified when tumor cells are found around lymphatic channels, suggesting the tumor is in transit to regional lymph nodes. When this feature is present in resected stage I or II colorectal cancers, adjuvant chemotherapy should be considered. Additionally, when found in malignant polyp specimens, this would strengthen the recommendation for radical resection.

Perineural Invasion (PNI)

PNI refers to cancer involving the space surrounding a nerve. While PNI has been associated with poor prognosis and a high risk of recurrence, a recent single center study found that prognosis was better in patients with PNI negative cancers. PNI was found to be a significant risk factor for recurrence [55]. PNI has been found to be an independent prognosticator over LVI and lymph node involvement in patients treated with neoadjuvant treatment. It is hypothesized that tumor in the perineural space around the rectum may be more radioresistant than tumor in lymphovascular spaces [56].

Tumor Budding

Tumor budding is a pathologic feature that is being increasingly used to stratify the risk of lymphatic spread and is especially clinically relevant for malignant polyps. (See Chap. 23.) Defined as the presence of tumor cells or clusters within the stroma of the tumor (intratumoral budding) or at the tumor edge (peritumoral budding), it is thought to represent epithelial-mesenchymal transition and is associated with worse prognosis. Tumor cell density indicates the relative proportion of tumor cells to other constituents of the tumor area. A lower tumor cell density has been found to be associated with poorer prognosis and is a strong predictor of lymph node metastasis, lymphovascular invasion, local recurrence, and poor disease-free survival. High tumor budding has been found to be associated with an infiltrative growth pattern and lymphovascular invasion [57]. Clinically, it is similar to LVI/PNI, suggesting that a more aggressive treatment approach should be employed for these tumors [58, 59].

Mismatch Repair (MMR) Deficient or Microsatellite Instability-High (MSI) Status

It is now routine for all colorectal cancers to be evaluated for genotypic evidence of Lynch syndrome, performing immunohistochemistry on biopsy specimens if possible, or resected specimen at minimum, looking for absent expression of MMR proteins and/or evaluation for MSI-high status (see Chap. 22). Any MMR-deficient (with normal BRAF) or MSI-high tumor should prompt consideration of genetic counseling and/or germline mutational analysis to assess for Lynch syndrome. This may have immediate surgical implications (i.e., determining the extent of resection), as well as neoadjuvant or adju-

vant treatment considerations (i.e., MSI-high tumors are less responsive to 5U-based therapy). In addition, it will help risk stratify at-risk relatives. The recent approval of immunotherapy (PD1 inhibitors) for metastatic, unresectable, or borderline resectable MSI-high tumors can have major treatment implications for patients. Overall, MSI-high tumors carry a better prognosis than MSI-low tumors, likely because they are considered to be less aggressive overall, potentially due to an improved host immune response to the tumor. This is despite the fact that these tumors are often poorly differentiated and that 5-fluorouracil (5-FU)-based chemotherapy is less effective. (See Chap. 30.) However, it is likely that the lack of efficacy of 5-FU is due to the fact that these tumors have such a better prognosis at baseline that chemotherapy is less able to show a significant effect [60].

Tumor Grade

Tumor grade is a stage-independent prognostic factor, with undifferentiated or poorly differentiated tumors being associated with poorer prognosis than moderately or well-differentiated tumors. This is considered to be a marker for more aggressive tumors.

Histologic Type

Histologic types that are associated with worse prognoses include mucinous, signet ring (>50% of the tumor contains intracytoplasmic mucin), and adenosquamous. This is thought to be due to the relative chemoresistance of these predominantly acellular tumors.

Pathologic Factors: Post-Resection

Lymph Node Positivity and Ratio

Guidelines have acknowledged that the minimum acceptable number of lymph nodes for accurate staging is 12. An association between lymph node harvest (LNH) and survival has been demonstrated, and it has been suggested that patients in stage II disease with a lower LNH have a worse prognosis [61]. The number of retrieved lymph nodes often falls short of the recommended 12. Factors that may be responsible include patient age, body mass index, tumor location, neoadjuvant therapy, surgical technique, and the pathologists' assessment. LNH is often intrinsically less with age (possibly due to a weaker immune response to the tumor) and tumor location in the rectum. Furthermore, the number of lymph nodes retrieved following neoadjuvant treatment is often less than what is retrieved after surgery alone, likely due to the effect of radiation on the lymphatic system [62]. Retrieval of fewer nodes may, in fact, be a marker of higher tumor response and better prognosis following neoadjuvant treatment [63]. LNH is enhanced in MSI-H tumors due to the immune response linked to the lymphocytic infiltrate.

The importance of lymph node ratio (LNR), the ratio of metastatic nodes to the total number of nodes harvested, has been highlighted as a prognostic tool with a lower LNR associated with a better prognosis. Increasing LNR has been found to be an independent predictor of decreased overall and disease-free survival [64]. In fact, the IDEA trial demonstrated that for patients with adequate LNH and low lymph node positivity (1 or 2), a reduced duration of 3 versus 6 months of FOLFOX chemotherapy had equivalent oncologic outcomes with less morbidity [65].

Extranodal Tumor Deposits

Extranodal tumor deposits are irregular discrete tumor deposits found in the pericolonic or perirectal fat or in adjacent mesentery away from the leading edge of the tumor within the lymphatic drainage area of the primary tumor, but not associated with a lymph node. Most are thought to be due to LVI or PNI but are not counted as lymph nodes replaced by tumor. The presence of extranodal tumor deposits is associated with relatively poor survival. Tumors with comparable T stage and without satellite nodules have been found to have higher 5-year survival rates compared to the same T stage with nodules (2% vs 37% $p < 0.0001$) [66]. Moreover, the presence of tumor deposits has been associated with decreased survival following neoadjuvant therapy [67].

Mesorectal Grade

The quality of mesorectal excision has been shown to be an independent factor of local and overall recurrence. Perforation of the rectum during surgery is also associated with poor prognosis and should be recorded as pT4 [68, 69]. It has also been suggested that mesorectal grade correlates inversely with size of the tumor, i.e., perforation during surgery or incomplete excision may occur more often during excision of large, bulky, locally advanced tumors with extensive fibrosis.

Tumor Regression Score

As neoadjuvant therapy has become the standard of care for many rectal cancers, the size of viable tumor remaining is a measure of the effectiveness of therapy, with the absence of

Table 24.9 Tumor regression score

Tumor regression score	Description
0	Complete response
1	Near-complete response
2	Partial response
3	Poor or no response

viable tumor and minimal residual disease being associated with better outcome [70]. Complete pathologic response following treatment is associated with a favorable prognosis [25]. A tumor regression score is used to assess the response of the tumor and not the nodes (Table 24.9) [70].

Clinical or Imaging-Based Factors

Age

Younger age (<45) at presentation has been associated with poor prognosis overall, possibly due to the presence of adverse prognostic features and advanced tumor stage at diagnosis. However, after controlling for disease stage, patient, and treatment factors, prognosis may be more favorable in younger patients since these patients can be treated more aggressively [71]. Also, advanced age is often associated with frailty which may limit the ability to tolerate chemotherapy or chemoradiotherapy.

Older patients also have worse baseline bowel dysfunction and continence. Therefore, older patients with rectal cancer are often not good candidates for restorative proctectomy with low colorectal or coloanal anastomosis, nor do older patients tolerate temporary diverting ileostomy well due to the reduced drive to drink fluids with age and increased risk of dehydration. Therefore, frail patients with rectal cancer but without a threatened CRM should be considered for upfront nonrestorative proctectomy, Hartmann resection, or abdominoperineal resection, depending on location of the tumor relative to the pelvic floor. If there is concern for a threatened radial margin, another option is neoadjuvant short-course radiotherapy (4–5 Gy for 5 days, for a total of 20–25 Gy) followed by resection. Neoadjuvant short-course radiotherapy is better tolerated than long-course chemoradiotherapy and has shown equivalent oncologic outcomes [72].

Extramural Vascular Invasion (EMVI)

EMVI is a strong predictor of poor prognosis which, as previously mentioned, can be predicted on prestaging MRI. EMVI is defined as the presence of tumor cells in the microvasculature beyond the muscularis propria and is more prevalent in locally advanced T3/T4 lesions, although it may be present with early stage tumors as well [30]. Histologically confirmed EMVI has been associated with a higher risk of local recurrence and poorer survival regardless of nodal status or depth of mural invasion. The incidence of EMVI ranges from 9% to 61% [73]. Brown has described MRI-directed EMVI grading system which is able to predict histologic EMVI with a high specificity ranging between 88% and 96% but with low sensitivity of 29–62% due to the inability to accurately visualize small caliber vessels. MRI evaluation of EMVI has been suggested by some authors to be more accurate than histologic assessment [74]. MRI-detected EMVI predicts both risk of recurrence, as well as synchronous metastases [34, 75]. MRI-detected EMVI was also associated with a fourfold risk of developing metachronous metastases within 1 year of diagnosis [76]. Thus the presence of EMVI on MRI may signify tumor embolization into the systemic circulation. Therefore, even for T1 or T2 tumors, patients with MRI-detected EMVI should be considered for chemotherapy to improve distant control [73].

Circumferential Radial Margin (CRM) Status

In addition to locally advanced tumors (T3/T4), other factors predictive of CRM involvement include tumor <4 cm from the anal verge, anterior quadrant invasion, and EMVI [77]. The presence of all four features predicts a risk of incomplete resection as high as 60%. These patients may benefit from total neoadjuvant therapy with radiotherapy and multidrug systemic chemotherapy prior to resection.

The NCCN recommends neoadjuvant treatment for all clinical stage II (cT3/T4; N0) and clinical stage III (any cT; N1/2) rectal cancers [78], but this includes a heterogeneous group of patients, some of whom may be overtreated. As a result, the UK and ESMO have shifted their treatment decision-making from being based purely on TNM to one that is guided by MRI findings. This allows personalized rectal cancer management based on selective MRI criteria in order to minimize the risks of over- and undertreatment, based on the risk of local recurrence [30].

An involved CRM increases the risk of local recurrence and mortality with both colon and rectal tumors. Although more commonly associated with a discussion on rectal cancer, the radial margin of the colon is formed by its mesenteric attachment point along with the cut edge of nonserosalized or retroperitoneal segments at the time of colon resection. Radial margin positivity is associated with multivisceral resection and conversion from laparoscopic to open resection and is a stage-independent outcome predictor strongly associated with recurrence and shorter survival [79]. Even with complete mesocolic excision, a radial margin <1 mm was found to be an independent predictor of survival and recurrence [80]. Russell et al. used a cancer-predictive mode [81] that included older age, male sex, African-American race, as well as advanced AJCC stage especially T stage, signet ring his-

tology, and poor/undifferentiated grade were associated with a positive circumferential margin.

If involved CRM is suspected preoperatively, careful surgical planning for extended resection and possible consideration for neoadjuvant multidrug chemotherapy are warranted. With respect to rectal cancer, tumor involvement of the CRM is the most critical factor in predicting local recurrence. For locally advanced rectal cancers, neoadjuvant therapy may result in downstaging, but if the CRM is still positive, the risk of local recurrence is increased. CRM is both an indicator of quality surgery and the success of neoadjuvant therapy. The AJCC manual also suggests that the surgeon mark the specimen on the non-peritonealized margins of resection with ink, especially in the area with the deepest involvement of tumor, to allow the pathologist to evaluate the radial margin and thus the completeness of resection [12]. This should be done routinely for all cases where colon or rectal neoplasia (cancer or polyp possibly containing cancer) is resected.

Tumor Location

It has been suggested that primary tumor location is a prognostic feature in colorectal cancer. With respect to colon cancer, tumors located distal to the splenic flexure compared to right-sided tumors have been associated with better prognosis independent of stage [82, 83]. However, it has also been suggested that tumor location may be a proxy for tumor biology in that proximal tumors, being commonly associated with β-RAF or KRAS mutations, are associated with poorer prognosis. However, the relationship between tumor sidedness and prognosis is not straightforward and may be dependent on stage and histologic characteristics especially in stage III disease [84].

With respect to rectal cancer, low tumors are associated with a relatively poorer prognosis, partially due to the rigid, narrow configuration of the pelvis and the technical challenges this poses intraoperatively. The consequence is a lower rate of complete mesorectal excision and higher rate of radial and distant margin positivity, as tumor location moves more distally.

Conclusion

Once a diagnosis of colorectal cancer has been made, it is essential that proper localization and staging be done to assure that the patient will be assigned to the correct treatment protocol as determined by multidisciplinary tumor boards. Doing so will enable the patient to receive optimal management in order to effect the goals of long-term disease-free and overall survival.

References

1. American Cancer Society guideline for colorectal cancer screening. American Cancer Society; 2018.
2. USPSTF A and B recommendations. U.S. Preventive Services Task Force; 2020.
3. Dancourt V, Lejeune C, Lepage C, Gailliard MC, Meny B, Faivre J. Immunochemical faecal occult blood tests are superior to guaiac-based tests for the detection of colorectal neoplasms. Eur J Cancer [Internet]. 2008;44(15):2254–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0959804908005273.
4. Wolf AMD, Fontham ETH, Church TR, Flowers CR, Guerra CE, LaMonte SJ, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin [Internet]. 2018;68(4):250–81. Available from: http://doi.wiley.com/10.3322/caac.21457.
5. Hayman AV, Guihan M, Fisher MJ, Murphy D, Anaya BC, Parachuri R, et al. Colonoscopy is high yield in spinal cord injury. J Spinal Cord Med [Internet]. 2013;36(5):436–42. Available from: http://www.tandfonline.com/doi/full/10.1179/2045772313Y.0000000091.
6. Rectal cancer Version 1.2020. NCCN Clin Pract Guidel Oncol; 2020.
7. Benson AB, Venook AP, Al-Hawary MM, Cederquist L, Chen Y-J, Ciombor KK, et al. Rectal cancer, version 2.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw [Internet]. 2018;16(7):874–901. Available from: https://jnccn.org/doi/10.6004/jnccn.2018.0061.
8. Salerno G, Sinnatamby C, Branagan G, Daniels IR, Heald RJ, Moran BJ. Defining the rectum: surgically, radiologically and anatomically. Colorectal Dis. 2006;8(s3):5–9.
9. D'Souza N, de Neree Tot Babberich MPM, D'Hoore A, Tiret E, Xynos E, Beets-Tan RGH, et al. Definition of the rectum. Ann Surg [Internet]. 2019;270(6):955–9. Available from: http://insights.ovid.com/crossref?an=00000658-201912000-00005m
10. Kenig J, Richter P. Definition of the rectum and level of the peritoneal reflection – still a matter of debate? Videosurg Other Miniinvasive Tech [Internet]. 2013;3:183–6. Available from: http://www.termedia.pl/doi/10.5114/wiitm.2011.34205.
11. Seymour MT, Morton D. FOxTROT: an international randomised controlled trial in 1052 patients (pts) evaluating neoadjuvant chemotherapy (NAC) for colon cancer. J Clin Oncol [Internet]. 2019;37(15_suppl):3504. Available from: http://ascopubs.org/doi/10.1200/JCO.2019.37.15_suppl.3504.
12. Amin MB, Edge SB, editors. AJCC cancer staging manual. In: Epidemiologia e prevenzione. 8th ed. New York: Springer; 2002.
13. Papamichael D, Audisio RA, Glimelius B, de Gramont A, Glynne-Jones R, Haller D, et al. Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013. Ann Oncol [Internet]. 2015;26(3):463–76. Available from: https://doi.org/10.1093/annonc/mdu253.
14. Papamichael D, Audisio RA, Glimelius B, de Gramont A, Glynne-Jones R, Haller D, et al. Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013. Ann Oncol [Internet]. 2015;26(3):463–76. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0923753419314115.
15. Piscatelli N, Hyman N, Osler T. Localizing colorectal cancer by colonoscopy. Arch Surg. 2005;140(10):932–5.
16. Pappou E, Weiser MR. Principles of rectal cancer management: preoperative staging, neoadjuvant treatment, basic principles of TME, and adjuvant treatment. In: The SAGES manual of colorectal surgery [Internet]. Cham: Springer International Publishing; 2020. p. 331–51. Available from: http://link.springer.com/10.1007/978-3-030-24812-3_22.

17. Reynolds IS, Majeed MH, Soric I, Whelan M, Deasy J, McNamara DA. Endoscopic tattooing to aid tumour localisation in colon cancer: the need for standardisation. Irish J Med Sci (1971) [Internet]. 2017;186(1):75–80. Available from: http://link.springer.com/10.1007/s11845-016-1502-y.
18. Kethu SR, Banerjee S, Desilets D, Diehl DL, Farraye FA, Kaul V, et al. Endoscopic tattooing. Gastrointest Endosc. 2010;72(4):681–5.
19. Hyun JH, Han KS, Kim BC, Hong CW, Oh JH, Park SC, et al. Preoperative endoscopic clipping for rectal tumor localization in laparoscopic anterior resection. Minim Invasive Ther Allied Technol [Internet]. 2019;28(6):326–31. Available from: https://doi.org/10.1080/13645706.2018.1547765.
20. Kirchoff DD, Hang JH, Cekic V, Baxter K, Kumar P, Shehebar J, et al. Endoscopic tattooing to mark distal margin for low anterior rectal and select sigmoid resections. Surg Innov. 2014;21(4):376–80.
21. Sun B. Endoscopic tattooing: a risk for tumor implantation. Int J Colorectal Dis. 2020;35:571–4.
22. Gasljevic G, Boc N, Brecelj E, But Hadzic J, Klancic M, Mlakar J. Overstaged rectal cancer by MRI due to fibrosis induced by tattoo marker. Case Rep Gastroenterol. 2018;12(3):602–7.
23. Liu L, Yang L, Jin E, Wang Z, Yang Z. Effect of gadolinium contrast-enhanced T1-weighted magnetic resonance imaging for detecting extramural venous invasion in rectal cancer. Abdom Radiol. 2016;41(9):1736–43.
24. Duffy MJ, Van Dalen A, Haglund C, Hansson L, Klapdor R, Lamerz R, et al. Clinical utility of biochemical markers in colorectal cancer: European Group on Tumour Markers (EGTM) guidelines. Eur J Cancer. 2003;39(6):718–27.
25. Kleiman A, Al-Khamis A, Farsi A, Kezouh A, Vuong T, Gordon PH, et al. Normalization of CEA levels post-neoadjuvant therapy is a strong predictor of pathologic complete response in rectal cancer. J Gastrointest Surg. 2015;19(6):1106–12.
26. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, et al. Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol [Internet]. 2017;28:iv22–40. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0923753419421522.
27. Choi DJ, Kwak JM, Kim J, Woo SU, Kim SH. Preoperative chest computerized tomography in patients with locally advanced mid or lower rectal cancer: its role in staging and impact on treatment strategy. J Surg Oncol [Internet]. 2010;102(6):588–92. Available from: http://doi.wiley.com/10.1002/jso.21651.
28. Nordholm-Carstensen A, Jorgensen LN, Wille-Jørgensen PA, Hansen H, Harling H. Indeterminate pulmonary nodules in colorectal-cancer: do radiologists agree? Ann Surg Oncol. 2015;22(2):543–9.
29. Valls C, Andía E, Sánchez A, Gumà A, Figueras J, Torras J, et al. Hepatic metastases from colorectal cancer: preoperative detection and assessment of resectability with helical CT. Radiology [Internet]. 2001;218(1):55–60. Available from: http://pubs.rsna.org/doi/10.1148/radiology.218.1.r01dc1155.
30. Dattani M, Brown G. Rectal carcinoma: imaging for staging. In: Fundamentals of anorectal surgery [Internet]. Cham: Springer International Publishing; 2019. p. 359–89. Available from: http://link.springer.com/10.1007/978-3-319-65966-4_21.
31. Berger KL, Nicholson SA, Dehdashti F, Siegel BA. FDG PET evaluation of mucinous neoplasms: correlation of FDG uptake with histopathologic features. Am J Roentgenol. 2000;174(4):1005–8.
32. Skandarajah AR, Tjandra JJ. Preoperative loco-regional imaging in rectal cancer. ANZ J Surg. 2006;76(6):497–504.
33. Puli SR, Bechtold ML, Reddy JBK, Choudhary A, Antillon MR, Brugge WR. How good is endoscopic ultrasound in differentiating various t stages of rectal cancer? Meta-analysis and systematic review. Ann Surg Oncol. 2009;16(2):254–65.
34. Sohn B, Lim J-S, Kim H, Myoung S, Choi J, Kim NK, et al. MRI-detected extramural vascular invasion is an independent prognostic factor for synchronous metastasis in patients with rectal cancer. Eur Radiol. 2015;25(5):1347–55.
35. Kikuchi R, Takano M, Takagi K, Fujimoto N, Nozaki R, Fujiyoshi T, et al. Management of early invasive colorectal cancer. Dis Colon Rectum [Internet]. 1995;38(12):1286–95. Available from: http://journals.lww.com/00003453-199538120-00009.
36. Silviera M, Hoffman RL. Rectal cancer staging. Semin Colon Rectal Surg [Internet]. 2019;30(2):53–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S104314891930020X.
37. Kim JC, Kim HC, Yu CS, Han KR, Kim JR, Lee KH, et al. Efficacy of 3-dimensional endorectal ultrasonography compared with conventional ultrasonography and computed tomography in preoperative rectal cancer staging. Am J Surg. 2006;192(1):89–97.
38. Corines MJ, Nougaret S, Weiser MR, Khan M, Gollub MJ. Gadolinium-based contrast agent during pelvic MRI. Dis Colon Rectum [Internet]. 2018;61(2):193–201. Available from: http://journals.lww.com/00003453-201802000-00011.
39. Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor JC, Schmocker S, et al. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. Ann Surg Oncol [Internet]. 2012;19(7):2212–23. Available from: http://link.springer.com/10.1245/s10434-011-2210-5.
40. Taylor FGM, Quirke P, Heald RJ, Moran BJ, Blomqvist L, Swift IR, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. J Clin Oncol. 2014;32(1):34–43.
41. Nicholls RJ, Zinicola R, Haboubi N. Extramural spread of rectal cancer and the AJCC Cancer staging manual 8th edition, 2017. Ann Oncol [Internet]. 2019;30(8):1394–5. Available from: https://doi.org/10.1093/annonc/mdz147.
42. Kennedy ED, Simunovic M, Jhaveri K, Kirsch R, Brierley J, Drolet S, et al. Safety and feasibility of using magnetic resonance imaging criteria to identify patients with "good prognosis" rectal cancer eligible for primary surgery: the phase 2 nonrandomized QuickSilver clinical trial. JAMA Oncol. 2019;5(7):961–6.
43. Shihab OC, Moran BJ, Heald RJ, Quirke P, Brown G. MRI staging of low rectal cancer. Eur Radiol [Internet]. 2009;19(3):643–50. Available from: http://link.springer.com/10.1007/s00330-008-1184-6.
44. Bell SW, Sasaki J, Sinclair G, Chapuis PH, Bokey EL. Understanding the anatomy of lymphatic drainage and the use of blue-dye mapping to determine the extent of lymphadenectomy in rectal cancer surgery: unresolved issues. Colorectal Dis. 2009;11(5):443–9.
45. Sugihara K, Kobayashi H, Kato T, Mori T, Mochizuki H, Kameoka S, et al. Indication and benefit of pelvic sidewall dissection for rectal cancer. Dis Colon Rectum [Internet]. 2006;49(11):1663–72. Available from: http://journals.lww.com/00003453-200649110-00001.
46. Arya S, Sen S, Engineer R, Saklani A, Pandey T. Imaging and management of rectal cancer. Semin Ultrasound CT MRI [Internet]. 2020 [cited 2020 Feb 18]. Available from: https://www.sciencedirect.com/science/article/abs/pii/S088721712030007X.
47. Surgical risk calculator [Internet]. American College of Surgeons, ACS NSQIP. [cited 2020 Apr 2]. Available from: https://riskcalculator.facs.org/RiskCalculator/.
48. Strong for surgery [Internet]. American College of Surgeons. [cited 2020 Feb 4]. Available from: https://www.facs.org/quality-programs/strong-for-surgery.
49. Hill SS, Chung SK, Meyer DC, Crawford AS, Sturrock PR, Harnsberger CR, et al. Impact of preoperative care for rectal adenocarcinoma on pathologic specimen quality and postoperative morbidity: a NSQIP analysis. J Am Coll Surg [Internet]. 2020;230(1):17–25. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1072751519321039.

50. Glasgow SC, Morris AM, Baxter NN, Fleshman JW, Alavi KS, Luchtefeld MA, et al. Development of the American Society of Colon and Rectal Surgeons' rectal cancer surgery checklist. Dis Colon Rectum [Internet]. 2016;59(7):601–6. Available from: http://journals.lww.com/00003453-201607000-00003.
51. Garfinkle R, Vasilevsky CA, Ghitulescu G, Morin N, Faria J, Boutros M. Compliance with preoperative elements of the American Society of Colon and Rectal Surgeons rectal cancer surgery checklist improves pathologic and postoperative outcomes. Dis Colon Rectum. 2020;63(1):30–8.
52. Brady JT, Xu Z, Scarberry KB, Saad A, Fleming FJ, Remzi FH, et al. Evaluating the current status of rectal cancer care in the US: where we stand at the start of the commission on cancer's national accreditation program for rectal cancer. J Am Coll Surg [Internet]. 2018;226(5):881–90. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1072751518301534.
53. Jarrar A, Edalatpour A, Sebikali-Potts A, Vitello D, Valente M, Liska D, et al. An up-to-date predictive model for rectal cancer survivorship reflecting tumor biology and clinical factors. Am J Surg [Internet]. 2020;219(3):515–20. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002961019310256.
54. Aarons CB, Shanmugan S, Bleier JI. Management of malignant colon polyps: current status and controversies. World J Gastroenterol [Internet]. 2014;20(43):16178. Available from: http://www.wjgnet.com/1007-9327/full/v20/i43/16178.htm.
55. Kinugasa T, Mizobe T, Shiraiwa S, Akagi Y, Shirouzu K. Perineural invasion is a prognostic factor and treatment indicator in patients with rectal cancer undergoing curative surgery: 2000–2011 data from a single-center study. Anticancer Res. 2017;37(7):3961–8.
56. Kim CH, Yeom SS, Lee SY, Kim HR, Kim YJ, Lee KH, et al. Prognostic impact of perineural invasion in rectal cancer after neoadjuvant chemoradiotherapy. World J Surg [Internet]. 2019;43(1):260–72. Available from: https://doi.org/10.1007/s00268-018-4774-8.
57. Wang LM, Kevans D, Mulcahy H, O'Sullivan J, Fennelly D, Hyland J, et al. Tumor budding is a strong and reproducible prognostic marker in T3N0 colorectal cancer. Am J Surg Pathol. 2009;33(1):134–41.
58. Mitrovic B, Schaeffer DF, Riddell RH, Kirsch R. Tumor budding in colorectal carcinoma: time to take notice. Mod Pathol [Internet]. 2012;25(10):1315–25. Available from: http://www.nature.com/articles/modpathol201294.
59. Koelzer VH, Zlobec I, Lugli A. Tumor budding in colorectal cancer—ready for diagnostic practice? Hum Pathol [Internet]. 2016;47(1):4–19. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0046817715003123.
60. Des Guetz G, Lecaille C, Mariani P, Bennamoun M, Uzzan B, Nicolas P, et al. Prognostic impact of microsatellite instability in colorectal cancer patients treated with adjuvant FOLFOX. Anticancer Res. 2010;30(10):4297–301.
61. Mcdonald JH, Dunn KW. Statistical tests for measures of colocalization in biological microscopy. J Microsc [Internet]. 2013;252(3):295–302. Available from: http://doi.wiley.com/10.1111/jmi.12093.
62. Han J, Noh GT, Yeo SA, Cheong C, Cho MS, Hur H, et al. The number of retrieved lymph nodes needed for accurate staging differs based on the presence of preoperative chemoradiation for rectal cancer. Medicine (United States). 2016;95(38):e4891.
63. Kim HJ, Jo JS, Lee SY, Kim CH, Kim YJ, Kim HR. Low lymph node retrieval after preoperative chemoradiation for rectal cancer is associated with improved prognosis in patients with a good tumor response. Ann Surg Oncol. 2015;22(6):2075–81.
64. Leonard D, Remue C, Abbes Orabi N, van Maanen A, Danse E, Dragean A, et al. Lymph node ratio and surgical quality are strong prognostic factors of rectal cancer: results from a single referral centre. Colorectal Dis. 2016;18(6):O175–84.
65. Grothey A, Sobrero AF, Shields AF, Yoshino T, Paul J, Taieb J, et al. Duration of adjuvant chemotherapy for stage III colon cancer. N Engl J Med [Internet]. 2018;378(13):1177–88. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1713709.
66. Ueno H, Mochizuki H, Hashiguchi Y, Ishiguro M, Miyoshi M, Kajiwara Y, et al. Extramural cancer deposits without nodal structure in colorectal cancer: optimal categorization for prognostic staging. Am J Clin Pathol. 2007;127(2):287–94.
67. Gopal P, Lu P, Ayers GD, Herline AJ, Washington MK. Tumor deposits in rectal adenocarcinoma after neoadjuvant chemoradiation are associated with poor prognosis. Mod Pathol. 2014;27(9):1281–7.
68. Valentini V, Schmoll H-J, van de Velde CJH, editors. Multidisciplinary management of rectal cancer. Cham: Springer International Publishing; 2018.
69. Young CA, West NP. Is TNM staging the most relevant prognostic clinical factor to consider for treatment decisions before and after surgery? In: Multidisciplinary management of rectal cancer [Internet]. Cham: Springer International Publishing; 2018. p. 45–50. Available from: http://link.springer.com/10.1007/978-3-319-43217-5_6.
70. Kakar S. Pathologic staging of colorectal adenocarcinoma: changes and updates in the American Joint Committee on Cancer (AJCC) 8th edition and College of American Pathologists' cancer protocol. AJSP Rev Rep. 2018;23(3):138.
71. McKay A, Donaleshen J, Helewa RM, Park J, Wirtzfeld D, Hochman D, et al. Does young age influence the prognosis of colorectal cancer: a population-based analysis. World J Surg Oncol [Internet]. 2014;12(1):370. Available from: http://wjso.biomedcentral.com/articles/10.1186/1477-7819-12-370.
72. Roy A, Mahasittiwat P, Weiner AA, Hunt SR, Mutch MG, Birnbaum EH, et al. Preoperative short-course radiation therapy for rectal cancer provides excellent disease control and toxicity: results from a single US institution. Pract Radiat Oncol [Internet]. 2017;7(1):e51–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S187985001630162X.
73. Chand M. Systematic review of prognostic importance of extramural venous invasion in rectal cancer. World J Gastroenterol [Internet]. 2016;22(4):1721. Available from: http://www.wjgnet.com/1007-9327/full/v22/i4/1721.htm.
74. Messenger DE, Driman DK, Kirsch R. Developments in the assessment of venous invasion in colorectal cancer: implications for future practice and patient outcome. Hum Pathol [Internet]. 2012;43(7):965–73. Available from: https://doi.org/10.1016/j.humpath.2011.11.015.
75. Smith NJ, Barbachano Y, Norman AR, Swift RI, Abulafi AM, Brown G. Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. Br J Surg. 2008;95(2):229–36.
76. Bugg WG, Andreou AK, Biswas D, Toms AP, Williams SM. The prognostic significance of MRI-detected extramural venous invasion in rectal carcinoma. Clin Radiol [Internet]. 2014;69(6):619–23. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0009926014000361.
77. Battersby NJ, How P, Moran B, Stelzner S, West NP, Branagan G, et al. Prospective validation of a low rectal cancer magnetic resonance imaging staging system and development of a local recurrence risk stratification model: the mercury II study. Ann Surg. 2016;263(4):751–60.
78. Nielsen LBJ, Wille-Jørgensen P. National and international guidelines for rectal cancer. Colorectal Dis. 2014;16(11):854–65.
79. Amri R, Bordeianou LG, Sylla P, Berger DL. Association of radial margin positivity with colon cancer. JAMA Surg [Internet]. 2015;150(9):890. Available from: http://archsurg.jamanetwork.com/article.aspx?doi=10.1001/jamasurg.2015.1525.
80. Lee JM, Chung T, Kim KM, Simon NSM, Han YD, Cho MS, et al. Significance of radial margin in patients undergoing complete mesocolic excision for colon cancer. Dis Colon Rectum [Internet]. 2020;63(4):488–96. Available from: http://journals.lww.com/10.1097/DCR.0000000000001569.

81. Russell MC, You YN, Hu C-Y, Cormier JN, Feig BW, Skibber JM, et al. A novel risk-adjusted nomogram for rectal cancer surgery outcomes. JAMA Surg [Internet]. 2013;148(8):769. Available from: http://archsurg.jamanetwork.com/article.aspx?doi=10.1001/jamasurg.2013.2136.
82. Zhang Y, Ma J, Zhang S, Deng G, Wu X, He J, et al. A prognostic analysis of 895 cases of stage III colon cancer in different colon subsites. Int J Colorectal Dis [Internet]. 2015;30(9):1173–83. Available from: http://link.springer.com/10.1007/s00384-015-2273-z.
83. Holch JW, Ricard I, Stintzing S, Modest DP, Heinemann V. The relevance of primary tumour location in patients with metastatic colorectal cancer: a meta-analysis of first-line clinical trials. Eur J Cancer [Internet]. 2017;70:87–98. Available from: https://linkinghub.elsevier.com/retrieve/pii/S095980491632490X.
84. Li Y, Feng Y, Dai W, Li Q, Cai S, Peng J. Prognostic effect of tumor sidedness in colorectal cancer: a SEER-based analysis. Clin Colorectal Cancer [Internet]. 2019;18(1):e104–16. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1533002818304560.

Colon Cancer Surgical Treatment: Principles of Colectomy

25

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Key Concepts

- Surgical resection of the primary tumor remains the cornerstone of treatment for stage I–III colon cancer and plays a role in treating surgically resectable stage IV disease.
- Extent of colectomy is based on the anatomic location of the tumor.
- Goals of resection are to achieve negative circumferential margins and to remove the mesentery at greatest risk for lymphatic spread.
- Examination of lymph nodes allows for accurate cancer staging, which is imperative for selection of patients for adjuvant therapy.

Introduction

Colorectal cancer is among the most common cancers in the United States, with an estimated 145,600 new cases and 51,020 associated deaths in 2019 (1). The 5-year survival rate is 64.4%, based on data from 2009 to 2015. The most accurate predictor of outcomes, based on the globally recognized TNM system for classification of malignant tumors, is pathologic stage. Preoperative clinical staging with imaging can determine the extent of local disease and detect distant metastases, which may affect the treatment plan and sequence of treatments. Surgical resection of the primary tumor remains the cornerstone of treatment for stage I–III colon cancer and plays a role in treating surgically resectable stage IV disease. A clear understanding of anatomy, as well as the appropriate extent of resection, guides the surgical approach and has an important bearing on oncologic outcomes.

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Preoperative Tumor Localization

When planning a colectomy, it is essential to determine the precise location of the tumor. Typically, the diagnosis of neoplasia is made after identification and biopsy of the tumor on colonoscopy, with note of the location of the tumor made on the report. However, mislocalization of the tumor, based on preoperative colonoscopy alone, occurs in 11–21% of cases and can result in a different surgical procedure than originally planned in 11% of cases (2–5). This number may be even higher when cecal and rectal tumors are excluded, due to the lack of definitive landmarks in the distal ascending, transverse and left colon, and variations in patient anatomy. It should also be noted that localization based on "centimeters from the anal verge" should never be relied upon, as this is often a highly inaccurate measurement when performed during the course of flexible colonoscopy. This is especially important for tumors in the rectosigmoid, where misclassification of tumor location can lead to inappropriate treatment. Many experienced colorectal surgeons will repeat flexible sigmoidoscopy on any patient referred to them with a neoplasm anywhere in the left colon, to avoid the mistake of taking a patient with a rectal cancer directly to the operating room for resection.

Preoperative computed tomography (CT) may demonstrate the exact location of the tumor. However, often the tumor is too small to see definitively on CT, and thus other localization methods should be considered. When a tumor is encountered at colonoscopy, endoscopic tattoo placement should be considered. Tattooing of the tumor facilitates localization of the tumor intraoperatively, especially in cases where palpation of the tumor is not possible such as during minimally invasive colectomy. Effective tattooing has been

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shown to reduce operating times and ensure that the correct segment of colon is resected (6).

For most colonoscopically placed tattoos, India ink is used. The goal is to inject into the submucosal plane. Full-thickness injection results in inadvertent spraying of tattoo ink throughout the abdomen, which can make localization difficult. One technique to more accurately and reliably confine the injection to the submucosa is to first inject 0.5–1.0 mL of saline into the submucosa to create a bleb and then insert the India ink into the saline bleb (0.75–1.0 mL). It is helpful to repeat this procedure in three or more quadrants to avoid mesenteric injection only. It is also important to not inject directly into the tumor but rather the opposite wall or just distal to the tumor. One should note the placement of the tattoo relative to the tumor in the colonoscopy procedure note. It is preferable to inject tattoo only distal to the tumor, rather than both proximal and distal, as occasionally only one tattoo site can be identified intraoperatively. In addition, usually it is the distal extent of the lesion that is most critical for the surgeon when performing resection. An example of a laparoscopic view of a colonoscopic tattoo is shown in Fig. 25.1.

Even with tattoo placement, the location of the tumor and the tattoo can be sometimes difficult to discern, e.g., the tattoo ink is dispersed throughout the abdomen, or the surgeon is unable to visualize the tattoo marks due to mesenteric quadrant location placement, inadequate tattoo amount, obesity, or adhesions. Thus, when the tumor cannot be definitively identified on preoperative imaging, the patient and surgeon should always be prepared for the possibility of intraoperative colonoscopy for localization. Intraoperative colonoscopy should ideally be performed using carbon dioxide as the insufflation gas to limit bowel dilatation.

Another method of tumor localization is to place a metallic clip adjacent to the tumor at the time of colonoscopy. Plain radiographs in the supine position can be performed immediately post-colonoscopy. The colon is often still filled with gas and the location of the clip relative to the outline of the colon discernible. Alternatively, staging CT of the abdomen and pelvis can be performed shortly after colonoscopy and clip placement. If the clip remains in situ, then the anatomic location of the tumor should be readily visible on CT. This method may be especially important when tattoo ink is unavailable at the time of colonoscopy.

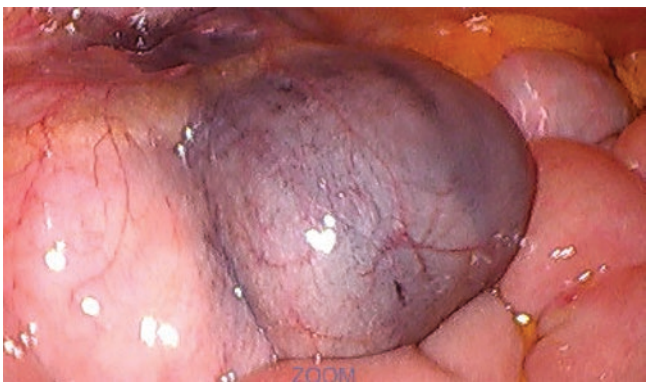

Fig. 25.1 Intraoperative localization of a hepatic flexure tumor by identification of tattoo

General Surgical Principles

Extent of Resection

In addition to removing the tumor itself, at least a 5-cm margin should be obtained both proximally and distally, and the feeding vessel should be taken at its origin. With high ligation of the vessel, it is unlikely not to obtain 5-cm margins due to resultant ischemia of the colon both proximally and distally. Adhering to 5-centimeter margins has been shown to minimize anastomotic recurrences (7). Proximal ligation of feeding vessels to the tumor should be performed to maximize lymphadenectomy. Colectomy specimens should have the non-peritonealized margins marked with ink to assess for completeness of resection, preferably by the surgeon, as is routine for proctectomy specimens for rectal cancer.

For the treatment of sigmoid colon cancer, the level of ligation of inferior mesenteric artery is controversial (high ligation versus low ligation). There is increased lymph node yield with high ligation over low ligation. However, studies have shown no functional or oncologic differences between high and low ligation (8–10). Unfortunately, there is not a universally agreed upon nomenclature regarding the inferior mesenteric artery (IMA) and its branches nor what is exactly meant by "high" versus "low" ligation. Many experienced surgeons consider the IMA to arise at the aorta and terminate when it branches into the superior hemorrhoidal artery and the left colic artery, which means that the average length of the IMA is only a few centimeters. Other surgeons consider the IMA to include what others would label the superior hemorrhoidal artery, claiming that the IMA becomes the superior hemorrhoidal artery when it crosses the common iliac artery. This latter designation is problematic as it ignores the principle of naming arteries based on their branch points and because it is difficult to ascertain exactly where an artery "crosses" another anatomically, especially after mobilization of the mesosigmoid.

No-Touch Technique

The no-touch technique was developed due to concern about dislodging tumor cells into the circulation during tumor manipulation. This technique showed initial promise in terms of prognosis (11). However, follow-up trials failed to recapitulate these results (12). For this technique, the vascular pedicle is ligated prior to mobilization of the colon. Garcia-Olmo et al. looked at blood samples to determine whether release of circulating tumor cells (CTCs) occurred during surgery and found no evidence of detachment with tumor manipulation (13). A recent randomized controlled trial of conventional colectomy versus no-touch for colon cancer resection found no difference in disease-free survival, overall survival, or recurrence-free survival in stages II and III colon cancer patients (14).

Lymphadenectomy

When considering the surgical treatment of colon cancer, a lymphadenectomy is considered adequate when feeding vessels are taken at their origin and at least 12 lymph nodes have been harvested and examined histologically. Examination of lymph nodes allows for accurate cancer staging. Adequate surgical staging is imperative for selection of patients for adjuvant therapy. The number of harvested lymph nodes and the ratio of involved versus harvested nodes can be used as markers of adequacy of surgical resection and are associated with patient outcomes (15). There is no doubt that lymph node excision is important to oncologic staging and outcomes; however, the extent of lymph node resection is debated. Even more controversial is the role of extended lymphadenectomy for synchronous extra-regional lymph node metastasis, such as para-aortic lymph node metastasis in colorectal cancer. One study demonstrated a benefit for highly selected patients, but this is not standard practice for most colorectal surgeons (16).

Mesocolic Excision

The aim of the mesocolic resection is to remove the tumor, its associated lymphovascular supply (including central vascular ligation), and mesocolon in an intact envelope of visceral peritoneum. There are no randomized controlled trials comparing complete mesocolic excision (CME) to "standard" colon surgery. The rationale for CME comes from the improvement in rectal cancer patient survival since the introduction of "total mesorectal excision." Initial retrospective studies have shown promising oncologic outcomes. Bertelsen et al. reported 5-year outcomes for right-sided colon cancer with CME versus standard resections and found a significant reduction in 5-year recurrence (9.7% versus 17.9%, respectively). Another difference was the number of lymph nodes harvested between the two groups (median 38 versus 21, respectively) (17). The main benefit of a CME is the increased lymph node yield (18, 19). Previous opinion on lymph node yield during lymphadenectomy was that it was mainly for prognostication; however, recent studies bring into question its ability to improve patient outcomes (survival) (20, 21). By performing a central ligation of the vessels, CME also obtains central and apical lymph nodes and thus captures "skip lesions," which can occur in 5% of cases on average (22–24). Completion of CME with an intact peritoneal lining has been demonstrated to improve survival by 15% (25). The other theoretical advantage of CME is that it standardizes surgical resection. Drawbacks include the technical difficulty of performing CME compared to a standard colectomy, leading to longer operative times. Further, given the increased dissection of critical vascular structures (superior mesenteric artery (SMA) and superior mesenteric vein (SMV)), there is a potential for damage and significant complications (26, 27). The most feared complication during CME is damage to the SMV, the main outflow to the small intestines, shown to occur in about 1.6% of right hemicolectomies (26). Several studies have shown that laparoscopic CME is feasible and safe (28–30). No functional differences have been noted between patients who have undergone CME versus conventional colon surgery (31). Critically evaluating different surgical techniques is challenging, as there is no precise definition of exactly what occurs during "conventional" surgery. It may be that some surgeons have been adhering to the basic principles of CME long before the introduction of the term. Ultimately, the major benefit of CME may be refocusing surgeons of the basic principles of colectomy for cancer–central ligation of vessels, removing the mesentery at greatest risk for metastatic lymph node spread in its envelope, and achieving negative circumferential negative margins–just as "TME" did for rectal cancer.

Adjacent Tissue or Organ Invasion

Larger colon cancers may invade adjacent structures/organs. The structures/organs most commonly involved are the abdominal wall, bladder, duodenum, omentum, ovaries, peritoneum, retroperitoneum, small bowel, stomach, ureters, and uterus. Surgical planning should include en bloc resection to achieve negative circumferential margins. Adhesions from the tumor to other structures are malignant in about 40% of cases. If there is an uncertainty if there is direct invasion or rather merely abutment, proceeding with en bloc resection is favored. Without en bloc resection, patients are at higher risk of recurrence and decreased survival (32).

For abdominal wall invasion, en bloc resection and then reconstruction of the abdominal wall are recommended. For other organ involvement, complete surgical resection should be attempted if feasible and reconstruction of critical structures (ureters, iliac, etc.) if it can be performed. There can be local invasion to the tail of the pancreas and spleen that necessitates distal pancreatectomy and splenectomy. For pancreatic or duodenal invasion, there are case reports of en bloc pancreaticoduodenectomy (33).

Neoadjuvant systemic therapy can be considered for locally advanced colon cancers. Data from the FOxTROT Collaborative Group showed significant tumor downstaging, less apical node involvement, and fewer positive margins, thus, favoring preoperative treatment in patients with locally advanced, resectable colon cancer (34). Neoadjuvant chemotherapy was noted to be well tolerated and safe, with no increase in perioperative morbidity and a trend toward fewer serious postoperative complications. Evidence of disease regression was noted in 59% of patients, including some pathologic complete responses. The Collaborative Group also noted a decrease in incomplete resection rate (abstract at GI ASCO). The National Comprehensive Cancer Network also recommends consideration of neoadjuvant therapy in clinical T4b colon cancer, as this may improve survival (35).

Neoadjuvant chemoradiotherapy can be considered for sigmoid tumors invading the bladder or other pelvic organs, provided that the radiation dose to surrounding small bowel can be limited. Neoadjuvant chemoradiotherapy has also been administered to select patients with more proximal colon tumors invading other vital structures such as duodenum and pancreas, although data are limited to case reports and small series, and thus no definitive conclusions can be made regarding relative efficacy.

Surgical Procedures Based on Anatomic Location

Cecum and Ascending Colon Cancer

For lesions of the cecum or ascending colon, a right hemicolectomy with ileocolic anastomosis is recommended. The anatomic boundaries of the resection include approximately 10-cm proximal to the ileocecal valve and the proximal transverse colon (Fig. 25.2).

Technical Aspects

Regardless of approach, most patients are positioned supine on the operating table, unless intraoperative colonoscopy is anticipated, whereas the patient should be in split leg position. It is helpful to tuck at least the patient's left arm to allow multiple individuals to stand on the left side, especially for laparoscopic cases. For a medial to lateral technique, regardless of approach (laparoscopic, robotic, or open), the operating surgeon stands on the left side of the table. For an open approach, a vertical midline or transverse/oblique incision is made, using a self-retaining retractor of choice. The abdomen should be thoroughly inspected, especially the liver, for evidence of metastatic disease. The tumor is assessed for resectability, taking into account invasion of disease into the duodenum or pancreas. The small bowel is retracted into the left half of the abdomen, facilitated by tilting the table right side up. The surgeon then identifies the ileocolic artery and performs a high ligation adjacent to the duodenum, after ensuring that the duodenum is dissected free and protected (Fig. 25.3). The mesentery is then dissected off the retroperitoneum through this window. The right colic artery, if present, and the right branch of the middle colic artery and vein are identified and ligated at their origins. The remaining mesentery to the transverse colon, including the marginal artery, is taken. The remaining mesentery next to the planned transection point of the terminal ileum is also taken. The right colon is dissected off the white line of Toldt to release the remaining lateral attachments. The lesser sac is often opened to mobilize the transverse colon and complete the mobilization of the hepatic flexure. The terminal ileum and proximal transverse colon are then divided, the specimen handed off the table, and the anastomosis constructed per surgeon preference. There are a variety of ways to perform the anastomosis (intracorporeal or extracorporeal, hand-sewn or stapled, side-to-side or end-to-side or end-to-end) with no one technique showing superiority over another. Closure of the mesenteric defect is controversial, as the defect is large and unlikely to cause obstruction. The omentum of the hepatic flexure and transverse colon that is being resected is typically taken with the specimen. Reliable data indicate that mobilization along anatomic planes is important and improves prognosis (36).

In a lateral to medial approach, the surgeon first transects the white line of Toldt, usually starting at the cecum and moving toward the hepatic flexure. Then the colon and mesocolon are mobilized off the retroperitoneum and duodenum. The hepatic flexure is freed from the liver superiorly and from the duodenum posteriorly. The ileocolic, right colic, and right branch of the middle colic vessels are then ligated at their origins. The remaining part of the procedure is similar to the procedure described above for a medial to lateral approach.

Hepatic Flexure Colon Cancer

For lesions in the hepatic flexure, a right hemicolectomy may be adequate if it is in the proximal hepatic flexure, but depending on location, an extended right hemicolectomy may be required. For an extended right hemicolectomy, the anatomic boundaries of resection are the terminal ileum to distal transverse colon.

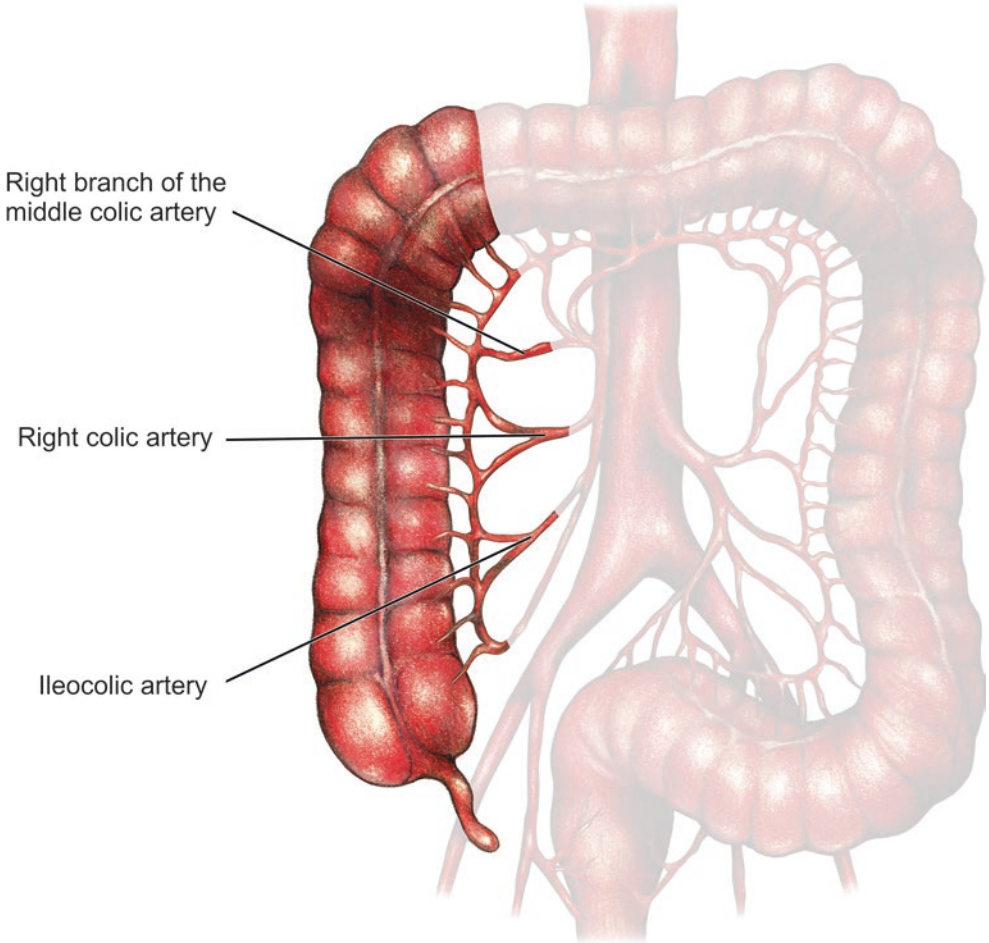

Fig. 25.2 Right hemicolectomy

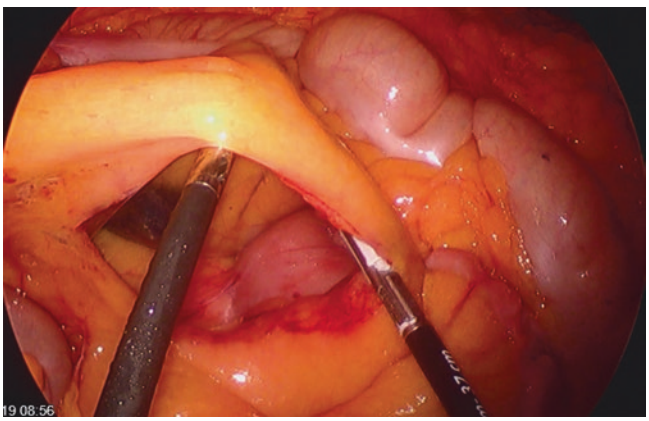

Fig. 25.3 Medial to lateral dissection of the right colon, identifying and protecting the duodenum

Technical Aspects

Please refer to cecal and right colon cancer resection (above) for a description of right hemicolectomy. In an extended right hemicolectomy, the procedure is performed similar to a right hemicolectomy, but the vascular division may include the main middle colic arterial trunk provided that there is adequate retrograde flow from the IMA to perfuse the splenic flexure (Fig. 25.4). The lesser sac is opened along its entire length, not just near the hepatic flexure and proximal transverse colon. This allows visualization and access to the blood supply. The splenic flexure may need to be mobilized to create a tension-free anastomosis. The colon and the mesentery are then resected according to the divided blood supply distribution. An ileocolic anastomosis is then created.

Removal of the spleen, either intentional or not, is associated with high morbidity and increased mortality (37). Inadvertent splenectomies are usually a consequence of capsular tear due to inadequate exposure and aggressive retraction. The incidence of required splenectomy during splenic flexure mobilization is less than 1% (38). Varty et al. conducted a case control study that compared cancers requiring splenectomy to cancers that did not. The authors found no influence on long-term survival but increased rates of postoperative sepsis (39).

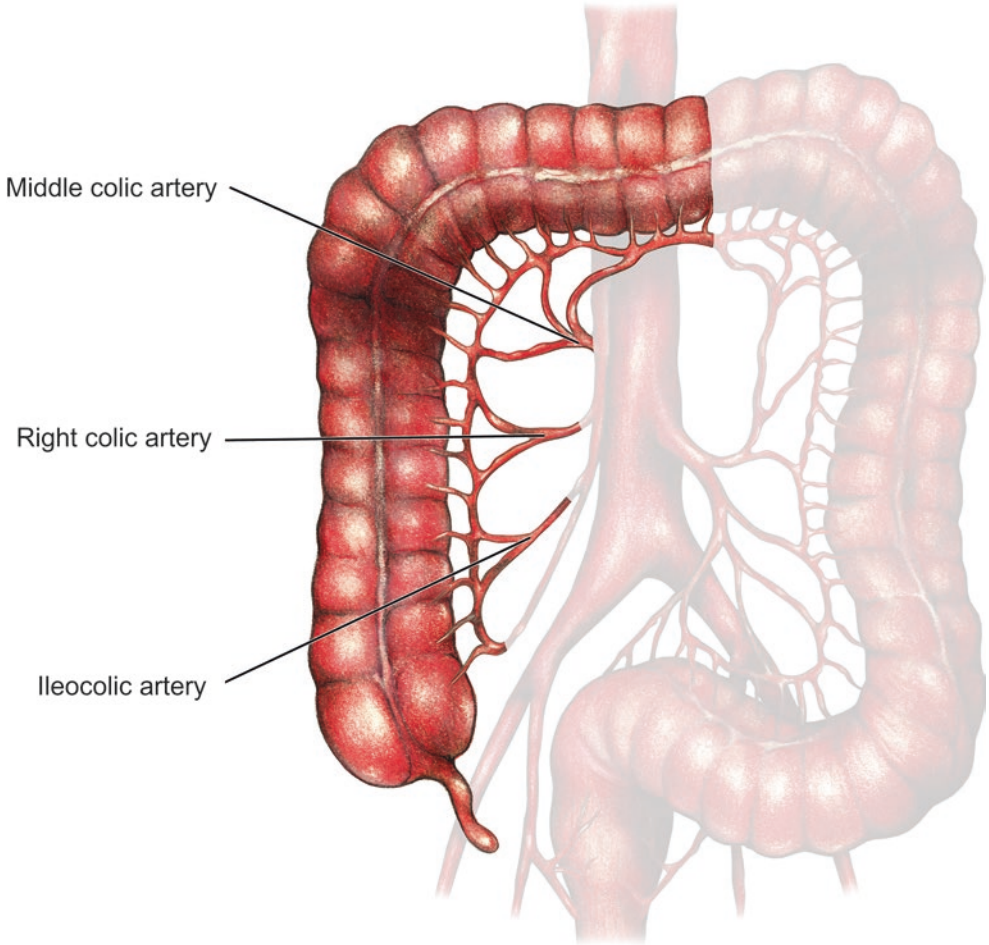

Fig. 25.4 Extended right hemicolectomy

Transverse Colon Cancer

It is often challenging to decide which surgical procedure to utilize for cancer of the transverse colon, as the blood supply comes from the middle colic, along with the right and left colic vessels. The best procedure is the one that removes the regional lymphatic drainage which is based on the arterial supply and corresponding mesentery. The decision is influenced by the location of the tumor within the transverse colon and the anatomy in that individual. The more common options include an extended right colectomy, extended left colectomy, or a subtotal colectomy. Segmental transverse colectomy is also sometimes utilized.

Technical Aspects

Proximal transverse colon cancers are typically managed with an extended right colectomy, which is described above. Lesions in the mid to distal aspect of the transverse colon may be offered an extended right colectomy, extended left colectomy, or segment transverse colectomy. An extended left colectomy requires ligation of the middle colic artery main branch in addition to the left colic artery as described below (Fig. 25.5). In the case of a mid-transverse colon cancer, a transverse colectomy may be considered. The principles of high ligation of the middle colic artery and drainage of regional lymphatics remain the cornerstone of care. In this case, the anastomosis is an ascending to descending colon anastomosis which requires mobilization of both segments and can be challenging or awkward technically. Segmental transverse colectomy is most appropriate for patients with a tumor in the mid-transverse colon with a redundant colon where mobility is not an issue. An end-to-end colo-colonic anastomosis is usually performed due to the risk of tension on a side-to-side anastomosis caused by the two sides of the colon mesentery retracting back toward their original position. There is also the concern regarding the adequacy of the lymphadenectomy that occurs with a segmental resection of the transverse colon. For these reasons, many surgeons treat mid-transverse colon lesions with an extended right colectomy which is easier for mobilization of the small bowel for an ileocolic anastomosis. A limited segmental transverse colectomy can be offered for palliative reasons or in frail patients that may not tolerate an extended resection.

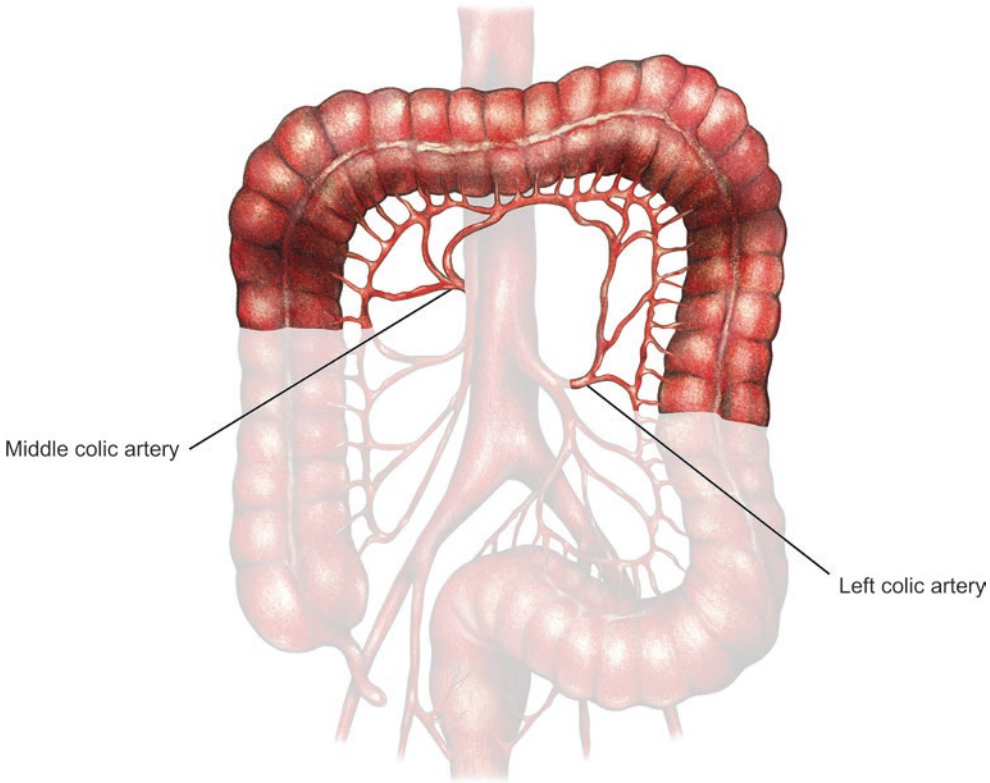

Fig. 25.5 Extended left hemicolectomy

Splenic Flexure and Descending Colon Cancer

Tumors of the splenic flexure and proximal descending colon are usually treated by a left colectomy. This procedure involves high ligation of the left colic artery and left branch of the middle colic artery (Fig. 25.6). The resultant mesenteric resection includes the areas drained by the distal half of the transverse colon and the descending colon. The resulting anastomosis is typically transverse colon to sigmoid colon. The root of the IMA and superior hemorrhoidal artery is preserved to maintain arterial flow to the remaining sigmoid colon. If colorectal anastomosis is performed, then the root of the IMA can be divided.

Technical Aspects

The patient should be positioned in split leg or low lithotomy position to facilitate stapled end-to-end anastomosis and/or leak testing of the anastomosis endoscopically. The small bowel should be positioned on the patient's right side so that exposure is gained to the base of the mesentery. Either before or after mobilization of the colon to its embryologic midline position, attention is directed to the mesentery. The inferior mesenteric vein is divided adjacent to the ligament of Treitz. A decision is made as to whether the sigmoid will be preserved, and then the IMA is divided at the aorta (sigmoid to be removed), or the left colic artery is ligated at its origin while preserving the root of the IMA and superior hemorrhoidal artery (sigmoid to be preserved). During these resections, the splenic flexure is completely mobilized, and the left side of the omentum is typically taken with the specimen. The proximal and distal colon transection lines are determined by the resected blood supply and the margin on the tumor. For some proximal splenic flexure lesions, an extended left colectomy with division of the main middle colic artery trunk divided is indicated.

For tumors located in the distal descending colon, a more formal left colectomy includes resection of the sigmoid colon and a colorectal anastomosis (Fig. 25.7). The IMA is isolated at its origin, making sure to identify and preserve the left ureter. The IMA is then ligated at its origin, and the inferior mesenteric vein (IMV) is taken near the ligament of Treitz at the inferior border of the pancreas. The mesentery is lifted off of the retroperitoneum, and the entire left colon from the distal transverse colon to the top of the rectum is removed. It is important to note that attempts at anastomosis can be difficult due to reach and tension. To facilitate reach, the IMV should be ligated proximally. The transverse colon should be mobilized and omentum released from the stomach. A retroileal anastomosis may be needed to allow reach of the colon to the rectum for anastomosis in select patients.

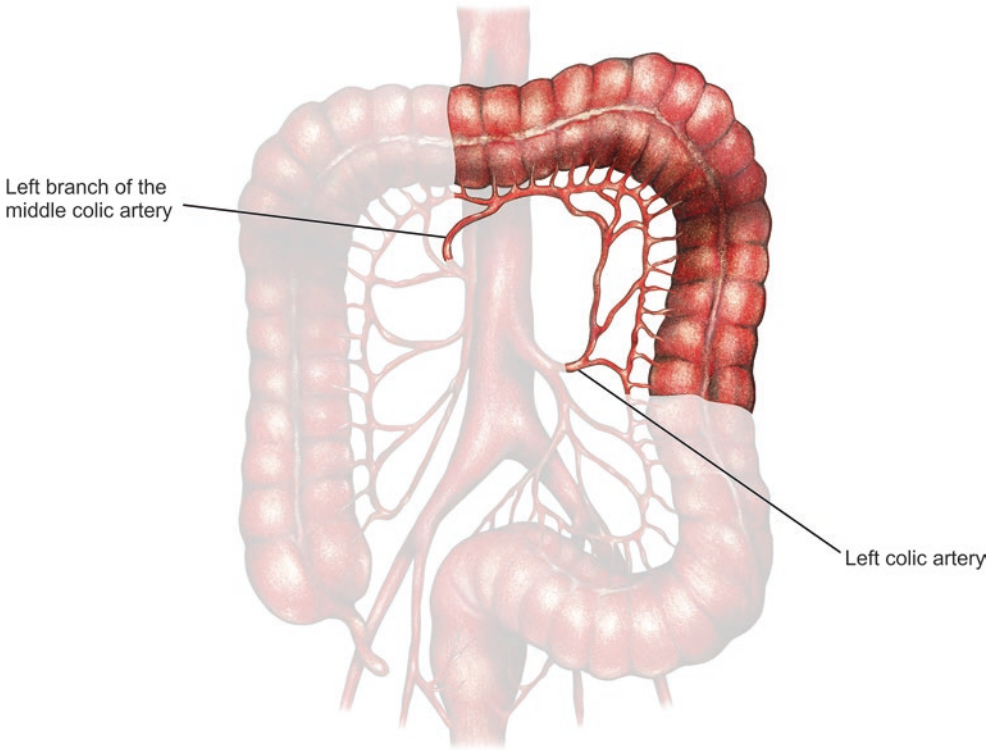

Fig. 25.6 Segmental left hemicolectomy for splenic flexure tumor

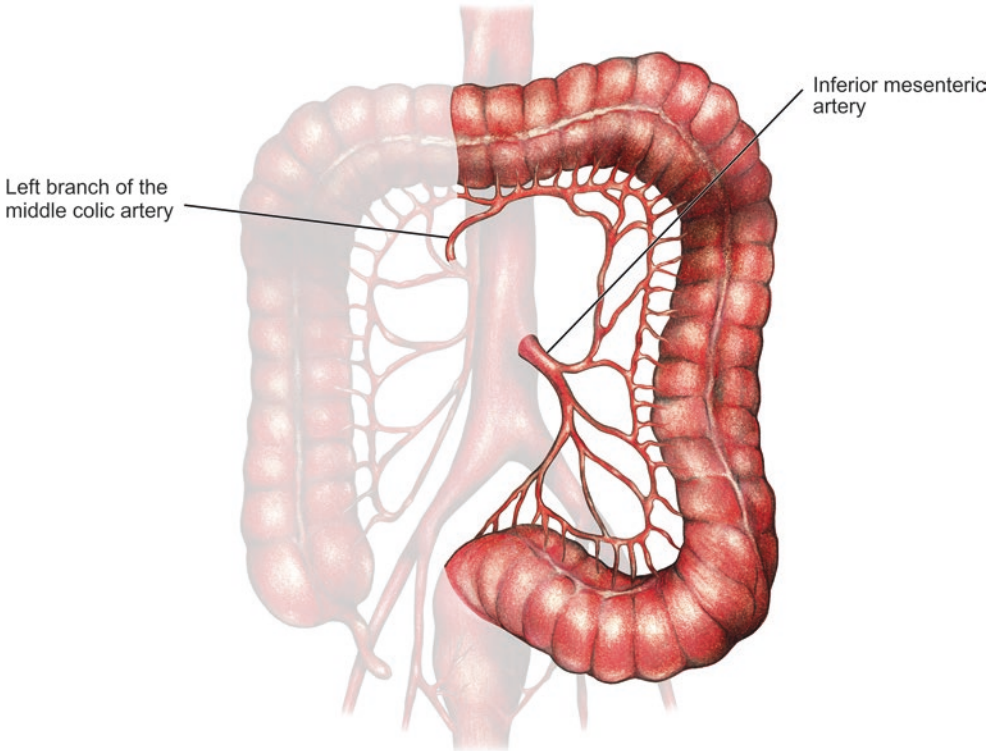

Fig. 25.7 Formal left hemicolectomy for descending colon tumor

Sigmoid Colon Cancer

Sigmoid colon cancer is treated with either a sigmoid colectomy or a left colectomy, depending on the location of the tumor in the sigmoid colon. More proximal lesions are best served with left colectomy (as outlined above) to ensure adequate lymph node harvest. Tumors in the mid to distal sigmoid colon are adequately treated with anterior resection of the rectosigmoid/sigmoid colectomy. There has not been a proven oncologic benefit for formal left colectomy for distal sigmoid colon tumors.

Technical Aspects

An anterior resection is performed for tumors of the mid and distal sigmoid colon. The patient is placed in low lithotomy position. For a medial to lateral approach, the peritoneum is incised along the root of the sigmoid mesocolon, from IMA origin to just distal to the sacral promontory. Dissection just deep to the arc of the superior hemorrhoidal vessels allows for identification and preservation of the hypogastric nerves, left ureter, and gonadal vessels. At this point, a decision is made as to whether to divide the IMA at the aorta or preserve the left colic artery and instead divide the superior hemorrhoidal artery at its origin (Fig. 25.8). As discussed previously, several studies have demonstrated that there is no survival advantage of "high" ligation of the IMA although lack of precise anatomic definitions makes it difficult to draw definitive conclusions (8, 40, 41). During mobilization of the sigmoid colon and the ligation of the vessels, the left ureter should be identified and preserved. Most injuries of the ureter occur at the level of the iliac artery. One then completes the dissection of the sigmoid and descending colon and its mesentery off of the retroperitoneum. The distal aspect of resection is the upper rectum, and the proximal aspect of resection is typically the junction of the descending and sigmoid colon, assuring appropriate margins and pulsatile arterial flow to the proximal colon conduit. One then determines if the descending colon will reach without tension to the rectal stump. If there is any tension, additional maneuvers to create length for the colon conduit include high ligation of the inferior mesenteric vein at the inferior border of the pancreas and complete splenic flexure mobilization. Some surgeons will routinely mobilize the splenic flexure, while some do so selectively. The anastomosis is then created, typically in an end-to-end fashion with an endoscopic stapler. As per routine, endoscopic inspection and pneumatic anastomotic leak testing, preferably with carbon dioxide as the instilled gas, should be performed.

Special Circumstances

Obstructing or Perforated Colon Cancer: Principles of Surgical Resection

About 15% of patients with colon cancer will present with acute obstruction or perforation. Management varies based on location of the tumor and the clinical presentation.

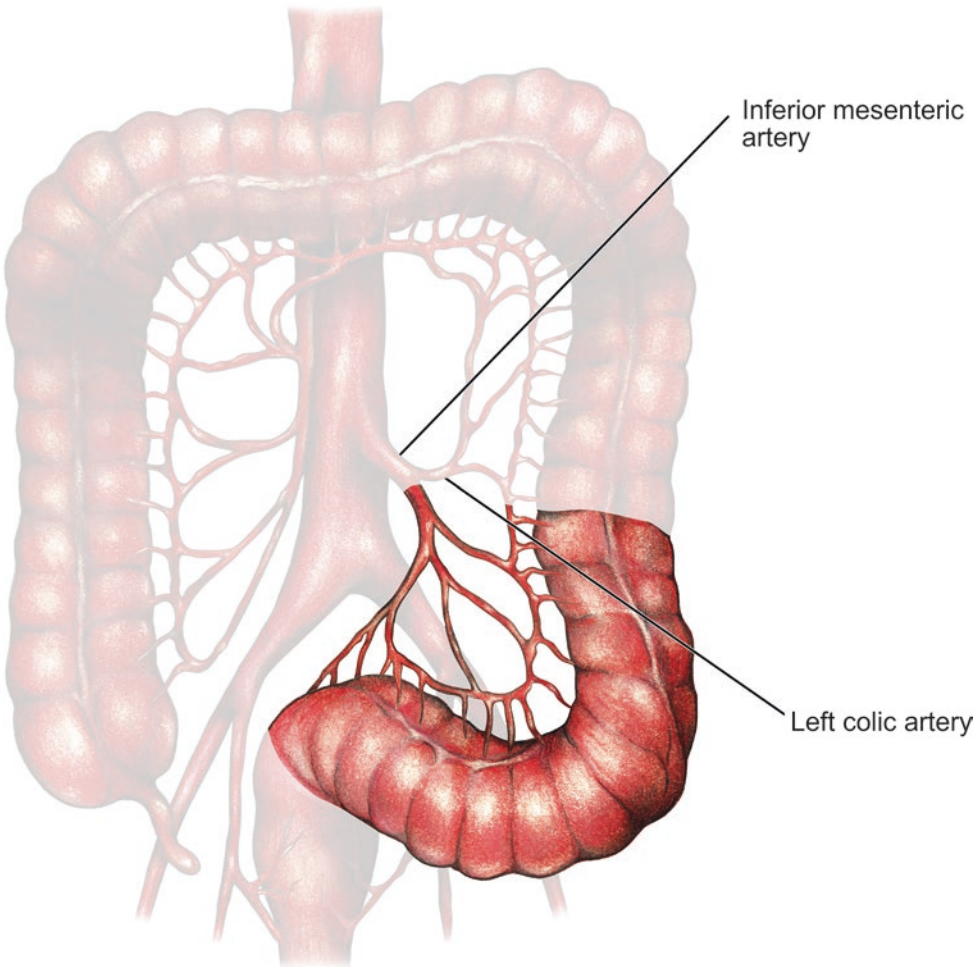

Fig. 25.8 Sigmoid colectomy

Patients who present with acute obstruction due to suspected colon malignancy typically undergo CT of the abdomen and pelvis ordered by the emergency room physician. Unless the patient has undergone recent colonoscopy, urgent water-soluble contrast enema should be considered as the next step in evaluation. Water-soluble contrast enema will typically confirm the diagnosis, evaluate for synchronous distal lesions, and prep the distal colon for possible intraoperative colonoscopy. For obstructing right colon tumors, right colectomy should be considered. The dilated colon proximal to the obstruction is removed during right colectomy, and if the ileocecal valve is competent, the ileum is usually of reasonable caliber, and the patient can thus be considered for primary anastomosis if doing well otherwise. If the ileum is dilated and edematous, resection with end ileostomy and mucus fistula using a corner of the transverse staple line in the ileostomy opening as a vent can be considered. Other options include leaving the closed distal colon segment in the abdomen (only if one can ensure that there are no synchronous large distal colon lesions), creation of formal colon mucus fistula in the contralateral abdomen, and creation of ileocolic anastomosis with proximal diverting ileostomy.

If the site of the obstruction is located more distally in the colon, more extensive resections are necessary. If there is evidence of proximal colon ischemia, then subtotal colectomy should be strongly considered (Fig. 25.9). The decision as to whether to perform anastomosis (ileosigmoid or ileorectal) should again be based on the condition of the bowel and the acute and chronic condition of the patient. If the proximal colon is dilated but not ischemic, then endoluminal stent as a bridge to formal resection can be considered. If this is not the favored approach or not possible, then Hartmann resection with proximal colostomy should be considered. Only in very rare cases should primary anastomosis, with or without proximal fecal diversion, be considered due to the risk of anastomotic leak. If primary anastomosis and proximal fecal diversion is performed, then intraoperative colonic lavage should be considered in order to clear the diverted segment of stool, which could otherwise slowly extrude out of a leaking anastomosis should this complication occur.

In cases of perforation, similar principles as discussed above are followed. One additional consideration for perforated tumors, however, is the high rate of recurrence and the need for adjuvant chemotherapy. In this situation, one should avoid creating a high-risk anastomosis that may leak and then delay or obviate adjuvant chemotherapy.

Surgical Resection for Colon Cancer in the Setting of Lynch Syndrome

Approximately 3% of all colorectal cancers develop within the setting of Lynch syndrome. These patients have an increased risk of developing metachronous colon cancers due to their genetic predisposition (42). When a curable colon cancer is diagnosed in the setting of Lynch syndrome, the American Society of Colon and Rectal Surgeons recommends total abdominal or subtotal colectomy as opposed to a

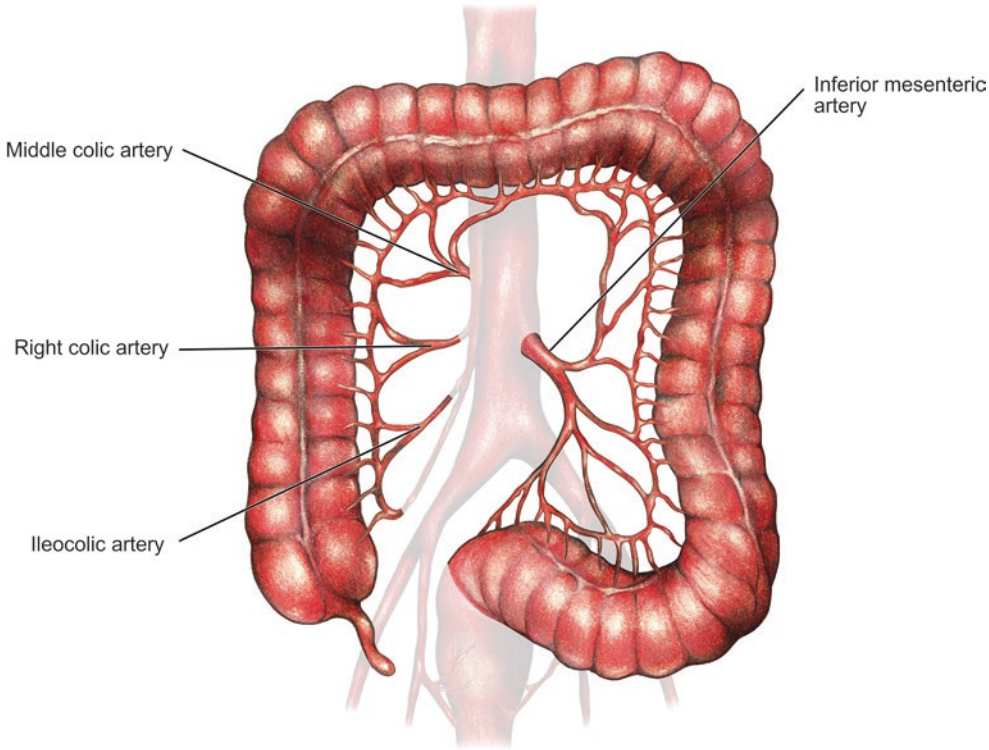

Fig. 25.9 Subtotal colectomy

segmental colectomy due to the reduced risk of metachronous cancer afforded by extended resection (43). This subject is covered in more detail in another chapter.

References

1. Available from: https://seer.cancer.gov/statfacts/html/colorect.html.
2. Stanciu C, Trifan A, Khder SA. Accuracy of colonoscopy in localizing colonic cancer. Rev Med Chir Soc Med Nat Iasi. 2007;111(1):39–43.
3. Piscatelli N, Hyman N, Osler T. Localizing colorectal cancer by colonoscopy. Arch Surg. 2005;140(10):932–5.
4. Cho YB, Lee WY, Yun HR, Lee WS, Yun SH, Chun HK. Tumor localization for laparoscopic colorectal surgery. World J Surg. 2007;31(7):1491–5.
5. Hilliard G, Ramming K, Thompson J Jr, Passaro E Jr. The elusive colonic malignancy. A need for definitive preoperative localization. Am Surg. 1990;56(12):742–4.
6. Trakarnsanga A, Akaraviputh T. Endoscopic tattooing of colorectal lesions: is it a risk-free procedure? World J Gastrointest Endosc. 2011;3(12):256–60.
7. Nelson H, Petrelli N, Carlin A, Couture J, Fleshman J, Guillem J, et al. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst. 2001;93(8):583–96.
8. Park SS, Park B, Park EY, Park SC, Kim MJ, Sohn DK, et al. Outcomes of high versus low ligation of the inferior mesenteric artery with lymph node dissection for distal sigmoid colon or rectal cancer. Surg Today. 2020;50(6):560–8.
9. Draginov A, Chesney TR, Quereshy HA, Chadi SA, Quereshy FA. Association of high ligation versus low ligation of the inferior mesenteric artery on anastomotic leak, postoperative complications, and mortality after minimally invasive surgery for distal sigmoid and rectal cancer. Surg Endosc. 2020;34(10):4593–600.
10. Olofsson F, Buchwald P, Elmstahl S, Syk I. High tie or not in resection for cancer in the sigmoid colon? Scand J Surg. 2019;108(3):227–32.
11. Turnbull RB Jr, Kyle K, Watson FR, Spratt J. Cancer of the colon: the influence of the no-touch isolation technic on survival rates. Ann Surg. 1967;166(3):420–7.
12. Wiggers T, Jeekel J, Arends JW, Brinkhorst AP, Kluck HM, Luyk CI, et al. No-touch isolation technique in colon cancer: a controlled prospective trial. Br J Surg. 1988;75(5):409–15.
13. Garcia-Olmo D, Ontanon J, Garcia-Olmo DC, Vallejo M, Cifuentes J. Experimental evidence does not support use of the "no-touch" isolation technique in colorectal cancer. Dis Colon Rectum. 1999;42(11):1449–56; discussion 54–6.
14. Takii Y, Shimada Y, Moriya Y, Nakamura K, Katayama H, Kimura A, et al. A randomized controlled trial of the conventional technique versus the no-touch isolation technique for primary tumor resection in patients with colorectal cancer: Japan Clinical Oncology Group Study JCOG1006. Jpn J Clin Oncol. 2014;44(1):97–100.
15. Sjo OH, Merok MA, Svindland A, Nesbakken A. Prognostic impact of lymph node harvest and lymph node ratio in patients with colon cancer. Dis Colon Rectum. 2012;55(3):307–15.
16. Ogura A, Akiyoshi T, Takatsu Y, Nagata J, Nagasaki T, Konishi T, et al. The significance of extended lymphadenectomy for colorectal cancer with isolated synchronous extraregional lymph node metastasis. Asian J Surg. 2017;40(4):254–61.
17. Bertelsen CA, Neuenschwander AU, Jansen JE, Tenma JR, Wilhelmsen M, Kirkegaard-Klitbo A, et al. 5-year outcome after complete mesocolic excision for right-sided colon cancer: a population-based cohort study. Lancet Oncol. 2019;20(11):1556–65.
18. West NP, Hohenberger W, Weber K, Perrakis A, Finan PJ, Quirke P. Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. J Clin Oncol. 2010;28(2):272–8.
19. Eiholm S, Ovesen H. Total mesocolic excision versus traditional resection in right-sided colon cancer - method and increased lymph node harvest. Dan Med Bull. 2010;57(12):A4224.
20. Chang GJ, Rodriguez-Bigas MA, Skibber JM, Moyer VA. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. J Natl Cancer Inst. 2007;99(6):433–41.
21. Le Voyer TE, Sigurdson ER, Hanlon AL, Mayer RJ, Macdonald JS, Catalano PJ, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. J Clin Oncol. 2003;21(15):2912–9.
22. Liang JT, Huang KC, Lai HS, Lee PH, Sun CT. Oncologic results of laparoscopic D3 lymphadenectomy for male sigmoid and upper rectal cancer with clinically positive lymph nodes. Ann Surg Oncol. 2007;14(7):1980–90.
23. Liang JT, Lai HS, Huang J, Sun CT. Long-term oncologic results of laparoscopic D3 lymphadenectomy with complete mesocolic excision for right-sided colon cancer with clinically positive lymph nodes. Surg Endosc. 2015;29(8):2394–401.
24. Siani LM, Lucchi A, Berti P, Garulli G. Laparoscopic complete mesocolic excision with central vascular ligation in 600 right total mesocolectomies: safety, prognostic factors and oncologic outcome. Am J Surg. 2017;214(2):222–7.
25. West NP, Kobayashi H, Takahashi K, Perrakis A, Weber K, Hohenberger W, et al. Understanding optimal colonic cancer surgery: comparison of Japanese D3 resection and European complete mesocolic excision with central vascular ligation. J Clin Oncol. 2012;30(15):1763–9.
26. Freund MR, Edden Y, Reissman P, Dagan A. Iatrogenic superior mesenteric vein injury: the perils of high ligation. Int J Color Dis. 2016;31(9):1649–51.
27. Wang C, Gao Z, Shen K, Shen Z, Jiang K, Liang B, et al. Safety, quality and effect of complete mesocolic excision vs non-complete mesocolic excision in patients with colon cancer: a systemic review and meta-analysis. Color Dis. 2017;19(11):962–72.
28. Storli KE, Sondenaa K, Furnes B, Eide GE. Outcome after introduction of complete mesocolic excision for colon cancer is similar for open and laparoscopic surgical treatments. Dig Surg. 2013;30(4–6):317–27.
29. Gouvas N, Pechlivanides G, Zervakis N, Kafousi M, Xynos E. Complete mesocolic excision in colon cancer surgery: a comparison between open and laparoscopic approach. Color Dis. 2012;14(11):1357–64.
30. Feng B, Sun J, Ling TL, Lu AG, Wang ML, Chen XY, et al. Laparoscopic complete mesocolic excision (CME) with medial access for right-hemi colon cancer: feasibility and technical strategies. Surg Endosc. 2012;26(12):3669–75.
31. Bertelsen CA, Larsen HM, Neuenschwander AU, Laurberg S, Kristensen B, Emmertsen KJ. Long-term functional outcome after right-sided complete mesocolic excision compared with conventional colon cancer surgery: a population-based questionnaire study. Dis Colon Rectum. 2018;61(9):1063–72.
32. Lopez MJ, Monafo WW. Role of extended resection in the initial treatment of locally advanced colorectal carcinoma. Surgery. 1993;113(4):365–72.
33. Curley SA, Carlson GW, Shumate CR, Wishnow KI, Ames FC. Extended resection for locally advanced colorectal carcinoma. Am J Surg. 1992;163(6):553–9.
34. Zhou Z, Nimeiri HS, Benson AB 3rd. Preoperative chemotherapy for locally advanced resectable colon cancer - a new treatment paradigm in colon cancer? Ann Transl Med. 2013;1(2):11.
35. Dehal A, Graff-Baker AN, Vuong B, Fischer T, Klempner SJ, Chang SC, et al. Neoadjuvant chemotherapy improves survival

in patients with clinical T4b colon cancer. J Gastrointest Surg. 2018;22(2):242–9.
36. Bokey EL, Chapuis PH, Dent OF, Mander BJ, Bissett IP, Newland RC. Surgical technique and survival in patients having a curative resection for colon cancer. Dis Colon Rectum. 2003;46(7):860–6.
37. Wakeman CJ, Dobbs BR, Frizelle FA, Bissett IP, Dennett ER, Hill AG, et al. The impact of splenectomy on outcome after resection for colorectal cancer: a multicenter, nested, paired cohort study. Dis Colon Rectum. 2008;51(2):213–7.
38. Langevin JM, Rothenberger DA, Goldberg SM. Accidental splenic injury during surgical treatment of the colon and rectum. Surg Gynecol Obstet. 1984;159(2):139–44.
39. Varty PP, Linehan IP, Boulos PB. Does concurrent splenectomy at colorectal cancer resection influence survival? Dis Colon Rectum. 1993;36(6):602–6.
40. Yang Y, Wang G, He J, Zhang J, Xi J, Wang F. High tie versus low tie of the inferior mesenteric artery in colorectal cancer: a meta-analysis. Int J Surg. 2018;52:20–4.
41. Dimitriou N, Felekouras E, Karavokyros I, Pikoulis E, Vergadis C, Nonni A, et al. High versus low ligation of inferior mesenteric vessels in rectal cancer surgery: a retrospective cohort study. J BUON. 2018;23(5):1350–61.
42. Parry S, Win AK, Parry B, Macrae FA, Gurrin LC, Church JM, et al. Metachronous colorectal cancer risk for mismatch repair gene mutation carriers: the advantage of more extensive colon surgery. Gut. 2011;60(7):950–7.
43. Herzig D, Hardiman K, Weiser M, You N, Paquette I, Feingold DL, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the management of inherited polyposis syndromes. Dis Colon Rectum. 2017;60(9):881–94.

Rectal Cancer: Neoadjuvant Therapy

26

Steven R. Hunt and Matthew G. Mutch

Key Concepts

- Standardized surgery using the total mesorectal excision concept remains paramount for achieving local control for rectal cancer.
- Addition of neoadjuvant therapy (short-course radiation, long-course chemoradiation) along with standardized surgery improves local control.
- Neoadjuvant short-course radiation therapy and long-course chemoradiation therapy have not improved DFS or OS for patients with LARC.
- Increased time interval between the completion of radiation therapy and surgery directly impacts the pathologic response of the primary tumor.
- The administration of systemic multidrug chemotherapy in the neoadjuvant setting as either induction or consolidation relative to radiation therapy has led to improved primary tumor response, improved tolerance, and improved delivery.

Introduction

As our understanding of the management of rectal cancer evolves, the tools available to stage and treat these patients are ever-increasing in number. Just a decade ago, staging and treatment were relatively straightforward. Patients were staged with endoscopy to assess tumor location, transrectal ultrasound (TRUS) to determine depth of tumor invasion (T stage) and lymph node status (N stage), and cross-sectional imaging (typically computed tomography, CT) to assess for distant metastatic disease (M stage). Based on these results, patients were offered one of two options for definitive therapy: patients with early stage tumors (cT1-2N0M0) went directly to surgery, and patients with locally advanced tumors (cT3-4N0 or cTXN1-2M0) received neoadjuvant therapy followed by surgery. The options for neoadjuvant therapy were limited to long-course radiation and chemotherapy, with short-course radiation therapy being used in parts of Europe and sparingly in the United States. Systemic chemotherapy was typically the last mode of therapy received by rectal cancer patients. Trimodal therapy combining pelvic radiation, surgery, and chemotherapy evolved into the current "standard of care" for patients with locally advanced rectal cancer (LARC).

Improvements in rectal cancer staging, systemic chemotherapy, and our understanding of the effects the components of trimodal therapy had on both local and systemic disease have allowed for significant changes in how we utilize these three modes of therapy. The treatment paradigm of long-course chemoradiation therapy followed by surgery, and then systemic chemotherapy is being challenged.

Historical rates of local pelvic failure for LARC were upward of 25%, but the introduction of strict surgical technique and neoadjuvant chemoradiation therapy has consistently lowered the rate to between 5% and 10% [1–4]. Despite these improvements in local control, neoadjuvant radiation and optimal surgery have not translated into consistently improved overall survival [5–7]. Patients with LARC (stage II and III) currently have a 30–40% risk of distant failure, which is the most frequent cause of cancer-related death in this population [8]. Many have hypothesized that the lack of improvement in survival is a result of the long time period between initiation of neoadjuvant therapy and the delivery of multidrug systemic chemotherapy, which can be up to 20 weeks. These issues have led to studies examining the most appropriate timing and sequence of the three treatment modalities. First, distant recurrence is a result of occult micrometastases, and the longer they are left untreated, the greater the chance they have of surviving and establishing growth in a distant site [9]. Second, in attempting to define the most appropriate timing of surgery after radiation therapy, it has become clear that longer "resting" intervals have

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led to a greater response rate of the primary tumor [10–13]. Third, the introduction of oxaliplatin to the systemic treatment of colorectal cancer has demonstrated an improvement in tumor response compared to 5-FU alone [14, 15]. Finally, the concept of organ preservation is becoming more accepted in patients who have a clinical complete response to neoadjuvant therapy [16]. As a result of these observations, there has been a dramatic change in rectal cancer treatment, namely, the utilization of multidrug systemic chemotherapy in the neoadjuvant setting and the introduction of the concept of total neoadjuvant therapy (TNT). This chapter will focus on the history of neoadjuvant therapy, the evolution of the use of systemic chemotherapy in the neoadjuvant setting, and the concept of total neoadjuvant therapy (TNT).

Rectal Cancer Staging

For the purposes of this chapter, staging will be discussed only in relation to determining the need for neoadjuvant therapy. Systemic staging is important, as knowledge of the presence of distant metastatic disease may impact decisions regarding the use and timing of all three modalities of therapy – surgery, radiotherapy, and chemotherapy. Locoregional staging in rectal cancer is important for planning operative therapy and for making the decision as to whether the patient should be treated with neoadjuvant therapy. TRUS had been used in rectal cancer staging for the better part of the last 30 years, but because of its operator dependence, technical challenges, and only moderate accuracy, it has been supplanted in the last decade by magnetic resonance imaging (MRI), especially for locally advanced tumors. Currently, pelvic MRI is the recommended imaging modality for accurate local staging of rectal cancer [17]. It provides information regarding tumor size and location, the relationship of the tumor to the sphincter complex and peritoneal reflection, evidence of extramural vascular invasion, and invasion of other pelvic structures. Most importantly, MRI defines the relationship of the tumor to the mesorectal fascia. This is often termed the "circumferential resection margin (CRM)" by radiologists, although obviously the true CRM can only be determined histologically. On MR, the CRM is defined as the closest distance of the tumor to the mesorectal fascia. It is thus assumed that the surgeon will be able to accurately mobilize the rectum and mesorectum in this plane. The CRM is considered threatened or involved when the tumor extends within 1 mm or less of the mesorectal fascia and breaches the mesorectal fascia or for lower tumors, when they invade the intersphincteric plane [18]. The significance of the CRM, and more specifically an involved CRM, to local recurrence and overall survival in rectal cancer patients has been elucidated with increasing clarity over the past three decades [18–21]. Local recurrence is significantly higher in patients with a positive CRM than without [18, 22]. Furthermore, with decreasing distance to the CRM, there is a dramatic increase in rates of local recurrence, metastasis, and death [18]. MRI has emerged as consistently superior to either TRUS or CT scan for CRM assessment, while offering comparable assessment of both T and N stage [23]. In patients who have contraindications to MRI, the combination of physical exam, TRUS, and a pelvic CT scan can provide adequate information to guide therapy.

There are no widely agreed upon recommendations for restaging the primary tumor following neoadjuvant therapy. Patients with a threatened or involved CRM on initial staging exam may benefit from restaging [17]. In these patients, treatment-related tumor retraction from the CRM portends an improved prognosis [21]. However, there have been very little data to support the concept that local restaging will change operative strategy in patients initially presenting with locally advanced tumors. Because neither radiotherapy nor chemotherapy kill in a "wave front" and isolated nests of viable tumor can persist in the original volume of tumor, the surgeon should plan on resecting all tissue that was originally involved with tumor. The major exception to this recommendation regarding restaging is when one is considering nonoperative management after neoadjuvant therapy (definitive chemoradiotherapy, "watch and wait").

The National Comprehensive Cancer Network (NCCN) provides a formal definition of the rectum as beginning at a virtual line between the sacral promontory and the top of the pubic symphysis and ending at the palpable upper border of the anorectal ring [17]. While this definition is important in differentiating rectal cancer from colon cancer, it is not intended to mandate which tumors should be treated with neoadjuvant therapy. Suitability for neoadjuvant radiation often depends on the nation in which the patient is presenting. In the United States, the NCCN guidelines recommend neoadjuvant radiation for all clinical stage II and III patients [17]. The European Society for Medical Oncology (ESMO) allows for patients with early cT3 cancers (invading less than 5 mm beyond muscularis propria) to be treated with proctectomy alone [24]. The ESMO guidelines even permit surgery alone for patients with clinical N1 disease in the upper and mid-rectum, provided that the circumferential resection margin appears free on imaging.

History of (Neo)Adjuvant Therapy

For over 100 years, radiation has been used to varying degrees in the treatment of rectal cancer. In the early twentieth century, surgery was used only for salvage, as it was extremely morbid. Over time, as operative and anesthetic techniques improved, surgery became the mainstay for the treatment of rectal cancer. In the early 1980s, William Heald published multiple papers describing his technique and excellent local control with what he described as "total

mesorectal excision" (TME), which emphasized the concept of removing the appropriate amount of mesorectum in its fascial envelope, using precise technique with good visualization [1]. This was not a novel concept, but not routinely practiced by many surgeons at the time, who often removed the rectum bluntly, potentially threatening the CRM and leaving involved mesorectal nodes in situ. Despite the publications of Heald and others, widespread adoption of TME technique was slow, and surgery at that time had a high local recurrence rate. This high local recurrence rate prompted multiple trials aimed at using radiation to improve local control.

Two competing schools of thought emerged on the use of radiation in rectal cancer. Advocates for preoperative radiation touted the ability of radiation to shrink tumors prior to surgery. This camp argued that tissue oxygenation, which is requisite for maximal radiation efficacy, was adversely impacted by scarring postoperatively. Additionally, neoadjuvant delivery would minimize radiation damage to the small bowel and neorectum, as pelvic adhesions would be fewer and small bowel fixation in the pelvis less, in the preoperative period. Those supporting the concept of selective postoperative radiotherapy noted that the inherent inaccuracies of staging would lead to overtreatment of many patients and also commit some patients with lower stage tumors to adjuvant chemotherapy because the true tumor stage would be difficult to differentiate. There was also significant fear that preoperative delivery would lead to increased anastomotic and wound complications. Delay of surgery, which was the mainstay of therapy, was also cited as a reason to delay radiation until after surgery. While early trials demonstrated the value of radiation in both the preoperative [25, 26] and postoperative setting [27–29], it would take years before the optimal timing of radiation would be established.

Adjuvant Radiation

The initial early large trials for rectal cancer used radiation alone in the adjuvant setting. The Medical Research Council Rectal Cancer Working Party in the United Kingdom found that radiation delivered in the postoperative setting decreased the local recurrence rate by 50% when compared to surgery alone [30]. Meanwhile, several in vitro and animal studies demonstrated that 5-fluorouracil (5-FU) enhanced the effectiveness of radiation on various tumor cell lines [31, 32]. Additionally, the Mayo Clinic demonstrated that combining 5-FU with radiation improved palliation in patients with recurrent or unresectable rectal cancer [33]. With this background, various groups began to explore the use of combined chemoradiation in trials.

In the United States, the Gastrointestinal Tumor Study Group performed a prospective randomized study comparing surgery alone to surgery plus adjuvant therapy with either chemotherapy, radiation, or combined chemoradiation [29]. While the study was small and likely underpowered, it did show that postoperative radiation combined with chemotherapy conferred a significant 24% survival advantage over surgery alone.

The North Central Cancer Treatment Group (NCCTG) set out to determine if chemotherapy and radiation were more effective than radiation alone in the adjuvant setting [34]. Patients were randomized to groups receiving radiation alone or chemotherapy and chemoradiation. The radiation was delivered over 5 weeks to a total dose of 45 Gy, and most patients received a 5.4 Gy boost to the tumor. The patients in the combined chemotherapy and chemoradiation group received systemic chemotherapy with 5-FU and semustine (methyl CCNU) for several cycles and then radiation combined with bolus 5-FU, administered early and late during the course of radiation. This group was also given more systemic chemotherapy after the chemoradiation. With 204 patients enrolled, the authors demonstrated significant improvements in disease-free survival, local recurrence, cancer-related death, and overall survival in the combined chemotherapy and chemoradiation group. While there was no difference in the severe side effects between groups, the chemoradiation group suffered more gastrointestinal and hematologic toxicities.

Following the release of these study results, the National Institute of Health convened a Consensus Conference on colorectal cancer. It was the overwhelming opinion of the conference that both adjuvant radiation and chemotherapy should be part of the treatment of locally advanced rectal cancer. This was released as a Consensus Statement in 1990, published in the Journal of the American Medical Association [35]. In the manuscript, the authors point out that semustine had significant leukemogenesis and nephrotoxicity, and they were emphatic that future studies should attempt to find adjuvant regimens that did not use semustine. Following release of the 1990 NIH consensus statement, many patients with rectal cancer were then given adjuvant chemoradiotherapy, although the vast majority of it was administered in the postoperative setting.

Seeking to deliver adjuvant chemoradiation in a more effective and more tolerable regimen, the Gastrointestinal Intergroup performed a 2 × 2 clinical trial comparing postoperative chemoradiation with bolus 5-FU to chemoradiation to chemoradiation with infusional 5-FU delivered over the entirety of the radiation treatment [36]. Additionally, they evaluated the use of semustine delivered before and after chemoradiation because of semustine's significant toxicities. This was a large multi-institute trial involving 660 patients with stage II and III rectal cancers. All patients received systemic chemotherapy with 5-FU (+/− semustine) both before and after chemoradiation. The trial showed that there was a significantly increased time to recurrence in the group that received the 5-FU as a constant infusion. Additionally, the

authors found no benefit to the addition of semustine to the systemic chemotherapy regimen. They concluded that infusional 5-FU was superior to bolus 5-FU and that semustine was not necessary in the adjuvant regimen for rectal cancer.

While it was clear that adjuvant therapy conferred a significant benefit to rectal cancer patients, it had not been definitively proven that the addition of radiation to adjuvant chemotherapy was more helpful than chemotherapy alone. The National Surgical Adjuvant Breast and Bowel Project (NSABP) R-02 was a large trial designed to address this question [37]. As with the trials discussed above, in the radiation group, systemic chemotherapy was given before and after postoperative chemoradiation. The authors demonstrated that the addition of radiation to systemic chemotherapy significantly improved local control but did not affect the incidence of distant disease or overall survival.

Neoadjuvant Radiation

Meanwhile, advocates for preoperative radiation had been working diligently to prove the value of administering radiation prior to surgery. Out of fear that radiation would lead to significant postoperative complications, early trials used relatively low doses (<20 Gy), and none of these studies showed significant improvement in local control or overall survival as compared to surgery alone [38–40].

Eventually, higher doses of preoperative radiotherapy were utilized. The European Organization for Research and Treatment of Cancer (EORTC) demonstrated that preoperative delivery of 34.5 Gy of radiotherapy reduced the local recurrence rate from 30% to 15% when compared to surgery alone. This was one of the first large prospective studies to show a benefit to neoadjuvant radiation. While there was a trend toward improved survival, it was not significant. The authors did caution that such a "large" dose of radiation in the neoadjuvant setting may have significant morbidity in elderly and medically frail individuals [41].

The Medical Research Council Rectal Cancer Working Party evaluated the use of neoadjuvant radiation for potentially operable fixed and tethered tumors [42]. These patients were chosen because the tumors were likely to be higher stage, minimizing the chance of overtreatment. Patients were randomized to surgery alone or radiation followed by surgery. Patients in the treatment group were given 40 Gy in 20 fractions, and surgery was delayed by at least 4 weeks. There was no difference in postoperative complications between the groups. The authors showed a significant improvement in local control and disease-free survival in the patients treated with neoadjuvant radiation followed by surgery as compared to patients treated with surgery alone.

The Uppsala Trial compared preoperative and postoperative radiation delivery in what was the largest comparative trial at that time [43]. Patients randomized to the preoperative radiation group were treated with 25.5 Gy over 5–7 days followed by immediate surgery. Patients assigned to the postoperative treatment group were given radiation only if their pathologic stage was stage II or III. They were then treated with 60 Gy over 8 weeks. Local recurrence rates were significantly better in the neoadjuvant group (12% vs 21%). Despite the improvement in local control, the study showed no survival advantage to preoperative radiation. The authors did note that half of the patients assigned to the postoperative treatment group had delayed radiation therapy due to prolonged recovery from surgery.

The Foundation Trials

The foundation for the use of neoadjuvant radiation that is commonly used today arises primarily from three sequential publications around the turn of the century in the New England Journal of Medicine. The first of these studies was the Swedish Rectal Cancer Trial [3]. Based on the results in the Uppsala Trial, the study designers compared surgery alone to neoadjuvant short-course radiation followed by immediate surgery. This large randomized trial was offered to patients with resectable rectal cancer for whom abdominal surgery was planned. All patients had a minimum of 5 years of follow-up. Nearly one-third of the patients in the trial had stage I disease. The results showed a significant and dramatic decrease in local recurrence in those treated with neoadjuvant short-course radiation (11% vs 27%). There was also a difference in overall and disease-free survival, favoring those in the neoadjuvant radiation group. Critics of the trial, many of whom believed that precise surgery alone was sufficient treatment for rectal cancer, argued that the local pelvic failure rate in the surgery alone group was too high. They contended that the trial only proved that radiation mitigated problems related to poor surgical technique. Moreover, there were significantly more stage I and stage II patients in the radiation/surgery group than in the surgery alone group. Even though patients were treated with short-course radiation and immediate surgery, the authors attributed these differences to tumor downstaging from radiation.

Soon after the Swedish trial was published, another large national study addressed some of its shortcomings. The Dutch Colorectal Cancer Group essentially repeated the Swedish Rectal Cancer Trial, randomizing patients to surgery alone versus preoperative short-course radiation followed by immediate surgery [2]. However, the trial designers recognized the importance of standardizing and optimizing surgical technique. Participating surgeons were required to attend workshops and symposia on "TME surgery" and watch instructional videos and were monitored by specially trained expert surgeons. Specifically, the first five proctectomy procedures at each institution were proctored. In addi-

tion, this study standardized pathologic examination of the specimen, and the histology slides were reviewed by supervisory pathologists. The rigor of the study succeeded in improving surgical outcomes, with an overall 2-year rate of local recurrence of 5.3%. However, even with the improved surgical technique, neoadjuvant radiation still significantly improved local control compared to surgery alone with local recurrences of 2.4% in the irradiated group, compared to 8.2% in the TME alone cohort at 2 years. These findings persisted at 10-year follow-up, with local recurrence rate of 5% in the group assigned to radiotherapy and surgery and 11% in the surgery-alone group ($p < 0{\cdot}0001$). Once again, despite the improvement in local control, there was no difference in overall survival between groups. There were significantly more perineal wound complications in the radiation treatment group, but other morbidities and mortality were no different between groups. The conclusion of this study was that even with optimal surgical technique, neoadjuvant radiation improved local control.

The German trial was designed to compare preoperative and postoperative chemoradiation [7]. Because some of the large American trials had shown a survival advantage with postoperative adjuvant chemoradiation [34, 36], the study designers chose to use long-course chemoradiation with infusional 5-FU. Patients were randomized to preoperative chemoradiation and delayed surgery or surgery followed by chemoradiation. Radiation was delivered as 50.4 Gy over 28 fractions, and the postoperative group also received an additional 5.4 Gy boost to the tumor bed. Proctectomy was standardized using TME principles in much the same fashion as in the Dutch trial. All patients were intended to be treated with four cycles of systemic 5-FU as the last therapy. The principle finding was that local recurrence was significantly better in the neoadjuvant therapy group (6% vs 13%). However, again, the local control advantage did not translate into an improvement in overall or disease-free survival. The postoperative group had significantly lower completion rates of chemoradiation (54% vs 92%) and full chemotherapy (50% vs 89%). Acute and chronic toxicities were significantly greater in the group treated with postoperative chemoradiation. The authors concluded that preoperative chemoradiation was superior to postoperative treatment with regard to local control and toxicity.

Short- vs Long-Course Radiation

In summation, the foundation studies and their predecessors allow two general conclusions. The first is that radiation provides improved local control for rectal cancer patients undergoing proctectomy. Secondly, preoperative radiation is superior to postoperative radiation for local control and is associated with less toxicity that postoperative radiation. Even prior to these studies, regional factions had aligned with either the short-course radiation or long-course chemoradiation factions. In most of the United States and parts of Europe, long-course chemoradiation was the "standard of care." In some parts of Northern and Western Europe, short-course radiation was the prevailing treatment. While the foundation studies provided clear evidence that preoperative radiation was superior, they did not provide any guidance on which method of delivery was better.

Practitioners who favored short-course radiation pointed to its decreased early toxicity, convenience for the patient, and decreased cost compared to long-course chemoradiation. Those who favored long-course chemoradiation felt that this modality afforded reduction of tumor bulk and was associated with a greater chance of anal sphincter preservation. Although reducing tumor bulk may make proctectomy easier, the same effect can be achieved by waiting longer to operate after short-course radiotherapy. The lack of downstaging seen in early trials of short-course radiotherapy was simply an artifact of the short-time interval between completion of radiotherapy and surgery (typically 1–2 weeks) typically employed. Secondly, there should be no effect of neoadjuvant therapy on anal sphincter preservation rates, because, as outlined above, nests of tumor cells can persist in the field of the original tumor, and surgeons should remove all tissue originally involved with tumor regardless of its appearance after neoadjuvant therapy, if they are to perform proctectomy. Some advocates for long-course chemoradiation also felt that the higher dose in each fraction of short-course radiation would lead to increased late toxicities, although there were no definitive data to support this contention.

The first comparative trial of short- and long-course chemoradiation was conducted in Poland [44]. Rather than a non-inferiority trial, the study was designed with the specific aim of determining if chemoradiation improved the rate of sphincter preservation. Patients with cT3 or cT4 tumors were randomized to the short-course arm received 25 Gy over 5 days followed by immediate surgery. The long-course patients were treated with 50.4 Gy over 28 days with bolus 5-FU and then delayed surgery. Postoperative systemic chemotherapy was not offered to patients that had a pathologic complete response (pCR). The authors found no difference in sphincter preservation rates, overall survival, or disease-free survival. Four-year actuarial local recurrence was 11% in the short-course group and 16% in the long-course group, which was not statistically different. Severe late toxicity was equal in both groups. The authors suggested that short- and long-course might be oncologically equivalent treatment options for advanced tumors. While practitioners of short-course treatment felt validated by the manuscript, the Polish trial did not convince many American oncologists that short course was a viable option and long-course chemoradiation continued to be the preferred option in the United States. Adding to the complexity of the decision-making process is

the fairly substantial financial incentive in the United States to utilize long-course radiotherapy for the radiation oncologist.

The Trans-Tasman study provided more evidence that short- and long-course preoperative regimens are oncologically equivalent [45]. The treatment arms were similar to the Polish trial except that inclusion was limited to cT3 tumors, and the radiosensitizing chemotherapy in the chemoradiation arm was delivered with infusional, rather than bolus 5-FU. Similar to the Polish trial, this study showed no difference in local recurrence or survival between groups. Again, there was no difference in severe late toxicities between short- and long-course regimens.

More recently, the Stockholm III trial provided guidance on the timing of radiation and surgery [46]. This noninferiority study set out to determine the optimal timing of surgery following neoadjuvant radiation. The study evaluated three radiotherapy treatment options – short-course radiation and immediate surgery, short-course radiation and delayed (4–8 weeks) surgery, and long-course radiation (without chemotherapy) and delayed surgery. While the comparative results of the study are muddled by some design flaws, the study did show significantly more frequent surgical complications with short course followed by immediate surgery. The authors concluded that surgery after short-course radiation should be delayed and that such a delay might allow for earlier neoadjuvant systemic chemotherapy.

Total Neoadjuvant Chemoradiation Therapy (TNT)

Rationale

As discussed above, the US "standard of care" trimodal regimen of neoadjuvant chemoradiation and surgery, followed by systemic chemotherapy, provides excellent local control for patients with LARC. However, distant recurrence remains the greatest pattern of failure for patients with T3,T4, or N+ tumors, with a risk as high as 30–40% [47, 48]. As a result, the vast majority of prospective randomized trials examining the various neoadjuvant regimens of radiation alone or with chemotherapy have failed to demonstrate any improvement in overall or disease-free survival [2, 4, 8]. These realizations have prompted a shift in treatment paradigms, focusing efforts to improve the rate of distant failure, while preserving strategies that result in excellent local control. The traditional treatment paradigm for LACR is clearly effective, but there are several shortcomings that may contribute to its failure to improve the survival for these patients. First, in the chemoradiation therapy, surgery, and systemic chemotherapy regimen, patients with advanced disease will not receive systemic multidrug cytotoxic therapy until a minimum of 21 weeks after the initiation of their treatment. This time interval can be further lengthened by any complications or delays in recovery from surgery. There are clear data demonstrating that timely delivery of adjuvant chemotherapy improves survival for patients with colorectal cancer [9]. It has been shown that for every month that adjuvant therapy is delayed, there is a relative decrease in overall survival by 14%. Thus, by extrapolation, delivering systemic chemotherapy at the beginning of the treatment regimen may lead to improvement in survival as the micrometastatic disease is being treated up to 5 months sooner than in the US "standard" treatment. Second, having systemic therapy at the end of the treatment sequence impacts patient compliance. Failure to receive adjuvant chemotherapy can result from complications associated with surgery, prolonged recovery resulting is poor performance status, and patient preference after an already long treatment course. Finally, neoadjuvant chemoradiation therapy is associated with a complete pathologic response rate of 15–19% and downstaging rate of 40–50% [49, 50]. However, with the introduction of newer regimens including agents such as oxaliplatin and its timing within the treatment regimen, there has been an increase in primary tumor response [51–53]. By altering the order of the three modes of therapy and exposing patients to systemic chemotherapy sooner, it may lead to improved compliance with therapy, improved tumor response, and ultimately improved survival. Therefore, several studies began to examine the use of systemic chemotherapy in the neoadjuvant setting, whether it by itself or as concurrent, induction, or consolidation treatment with radiation therapy.

Utilization of Systemic Chemotherapy in the Neoadjuvant Setting

Systemic Chemotherapy Alone

After the results of the MOSAIC trial were published demonstrating the addition of oxaliplatin to the standard 5-fluorouracil (5-FU)-based chemotherapy regimen improved disease-free survival for patients with stage III and selected stage II colon cancer, the FOLFOX (5-FU, folinic acid, oxaliplatin) regimen has become first-line therapy in the adjuvant setting [14]. The subsequent ADORE trial of adjuvant FOLFOX in patients with LARC treated with neoadjuvant chemoradiation therapy demonstrated a DFS benefit compared to 5-FU alone [54]. Further, studies examining the addition of oxaliplatin to 5-FU-based regimens for patients with metastatic disease have also shown up to a 70% improvement in tumor response compared to 5-FU alone [55, 56]. Based on these results and changes in clinical practice, clinicians began utilizing systemic FOLFOX therapy in the neoadjuvant setting for patients with LARC.

The Timing of Rectal Cancer Response to Chemoradiation Consortium was one of the first groups to publish their results of a multicenter trial demonstrating the response of the primary tumor to neoadjuvant FOLFOX therapy delivered after long-course chemoradiation, the sequence of which has been termed "consolidation" chemotherapy [52]. The primary goals of the study were to determine the primary tumor response, treatment toxicity, and surgical complications. This was a phase II trial that compared the outcomes for patients who underwent surgery 6 weeks after completion of chemoradiation therapy versus chemoradiation therapy followed by two cycles of FOLFOX therapy starting after 4 weeks with surgery within 3–5 weeks. With just two cycles of FOLFOX, the authors found there was a significant overall improvement in pathologic tumor response in the FOLFOX group vs the surgery group (P = 0.0217) and improvement in T stages (T0–31% vs 23%, T1–6% vs 5%, T2–28% vs 25%, T3–28% vs 43%, respectively) (P = 0.0008), but there was no improvement in N stage (0.0854). There was no difference in treatment-related toxicity and complications or perceived difficulty of surgery.

The improved pathologic response associated with FOLFOX then led some investigators to question the necessity of radiation therapy, which is associated with several toxicities such as sexual and bladder dysfunction, anal sphincter dysfunction, increased rate of pathologic pelvic fractures, and potential bone marrow suppression. The group from Memorial Sloan-Kettering Cancer Center performed a pilot study examining the feasibility of systemic FOLFOX therapy only before proctectomy for patients with LARC [57]. Thirty-two patients with tumors located between 5 and 12 cm from the anal verge were treated with six cycles of FOLFOX plus bevacizumab for cycles 1–4 only, followed by surgery. Patients who failed to respond to therapy defined as stable or progressive disease then received long-course chemoradiation therapy before surgery. The primary outcome of the study was R0 resection, which was accomplished in all 32 patients with only 2 patients receiving neoadjuvant radiation therapy due to chemotherapy-related toxicities. Ninety-four percent of patients completed all planned neoadjuvant therapy, and it was associated with 25% complete pathologic response rate, 0% 4-year local recurrence rate, and 84% disease-free survival rate. In this pilot study, 72% of the patients had clinically positive lymph nodes, so the authors concluded that in selected patients, neoadjuvant radiation therapy can be safely omitted. One caveat regarding patient selection is that all patients were cT3 (cT4 tumors were excluded) and there was no mention of circumferential radial margin status or depth of invasion into the mesorectum. However, given the high number of clinically node-positive patients, overall this was considered a high-risk group of patients.

This trial served as the template for the ongoing multicenter prospective randomized phase III trial Preoperative Radiation or Selective Preoperative Radiation and Evaluation Before Chemotherapy and TME (PROSPECT) [58]. The PROSPECT trial is a US-based multicenter trial comparing standard neoadjuvant chemoradiation therapy to neoadjuvant FOLFOX therapy with selective radiation for non-responding or progressing tumors. The protocol was amended to eliminate the use of bevacizumab because of the results of subsequent large-scale studies have not conferred a benefit for the inclusion of bevacizumab. Given the limited single institution phase II data available at the time the protocol was developed, the trial was designed as a seamless phase II/III trial, with the co-primary endpoints of local and distant recurrence. After enrollment of the first 366 patients, interim analysis showed that the predetermined stoppage requirements were not met. As a result, the study progressed to a phase III study, and enrollment was completed in the end of 2019 with a total of 1194 patients. Results from the study have not been published at the time of this writing.

The BACCHUS Trial is a UK prospective randomized phase II trial comparing FOLFOX plus bevacizumab versus FOLFOXFIRI (5-FU, oxaliplatin and irinotecan) plus bevacizumab followed by surgery 8–12 weeks after completion of the chemotherapy [59]. Enrollment began in 2016 for patients with rectal tumors from 4 to 12 cm from anal verge and high-risk features based on MRI. The high-risk features include cT3 tumors with >4 mm invasion into the mesorectum, tumors within 1 mm of the mesorectal fascia, or clinically node-positive disease. The target accrual was 30 patients in each arm, and the primary endpoint was complete pathologic response. Secondary endpoints included R0 resection status, downstaging, local recurrence, disease-free survival, and compliance and tolerance of therapy. Unfortunately, the study closed early due to poor enrollment, but they did publish their results in relation to the primary outcome of pCR. They accrued a total of 20 patients: 10 patients in each arm (Arm 1 FOLFOX and Arm 2 FOLFOXFIRI). In Arm 1, 80% of patients completed chemotherapy and went on to surgery, and in Arm 2, 90% of patients completed chemotherapy, but all patients underwent surgery. Because of the low accrual, they were not able to meet the primary endpoint. However, they reported the pCR for each arm was 0% and 20% (10% overall). Both groups demonstrated good tumor response based on the neoadjuvant rectal (NAR) scores, with no statistical difference between the groups. Treatment-related toxicity was greater in Arm 2, but overall was well tolerated with a high rate of completion. They also reported no difference in overall survival. These results are difficult to interpret given the failure to reach the endpoint, but the experience does provide support for using systemic chemotherapy in the neoadjuvant setting with regard to tumor response.

The Chinese FOWARC study was a randomized phase III, three-arm trial that compared standard chemoradiation therapy (Arm 1) versus five cycles of FOLFOX concurrent with long-course radiation therapy (Arm 2) versus 4–6 cycles of FOLFOX only (ARM 3), with all groups undergoing surgery 6–8 weeks after completion of neoadjuvant therapy [60]. Patients with tumors within 12 cm of the anal verge and any clinical stage II or III tumors were included in the study. A total of 495 patients were randomized, with the primary endpoint being 3-year disease-free survival. At the completion of the study, the numbers of patients in the final analysis were 130 in Arm 1, 141 in Arm 2, and 147 in Arm 3. The pCR rate was highest in Arm 2 (FOLFOX + chemo/XRT) at 27.5% vs Arm 1 at 14% and Arm 3 at 6.6% [OR 0.428 (95% CI 0.237 to 0.774) $P = 0.005$]. Neoadjuvant treatment compliance was equivalent across all three arms – 88.4%, 94.9%, and 94.5%, respectively. Interestingly, patients who received radiation therapy (Arms 1 and 2) had a higher rate of toxicity and surgical complications such as anastomotic leak and surgical infections compared to Arm 3 (chemotherapy alone). After a median follow-up of 45.2 months, the authors reported 3-year DFS of 72.9%, 77.2%, and 73.5% ($P = 0.709$ by log rank test), respectively [61]. The 3-year local recurrence rate was 8%, 7%, and 8.3% (log rank $P = 0.873$) and 3-year overall survival rate of 91.3%, 89.1%, and 90.7% (log rank $P = 0.971$). The results of this trial demonstrated no difference in tumor response (pCR and tumor downstaging) between traditional chemoradiation and chemotherapy alone, but despite improved response in the FOLFOX/radiation group, this did not translate into an improvement in DFS. This study had a high rate of compliance with adjuvant chemotherapy in all groups, which may have influenced the long-term outcomes. The authors concluded that neoadjuvant treatment with mFOLFOX6 concurrent with radiotherapy had acceptable tolerability and led to a higher rate of pCR compared with single-agent fluorouracil plus radiotherapy and that this was their preferred therapy. Another way of interpreting the data would be that disease-free and overall survival were not different, and thus the treatment with the lowest toxicity should be favored. At least in terms of anastomotic "fistula," this was the chemotherapy-alone group (8% vs 20% 5-FU radiotherapy, 18% FOLFOX radiotherapy).

The role of chemotherapy alone as neoadjuvant therapy alone remains unclear. The difficulties with accrual in some trials may reflect the perceived necessity of radiation therapy from both the clinician and patients' standpoint (bias). However, the PROSPECT trial was able to ultimately complete patient accrual and once the data mature, the study will be able to provide insight into which patients may benefit from neoadjuvant chemotherapy alone.

Radiation Therapy with Systemic Chemo Therapy (Concurrent)

The utilization of systemic chemotherapy concurrently with radiotherapy has several goals: maintaining local control, reducing distant failure, and improving the primary tumor's response to neoadjuvant therapy. The French Lyon R0-04 trial in the early 2000s was one of the first phase II trials to demonstrate the effectiveness of oxaliplatin and 5-FU when given concurrently with radiation therapy [62]. Forty patients with either cT3–4 or high-risk cT2 tumors received two cycles of oxaliplatin (weeks 1 and 5 during radiation), continuous infusion of 5-FU, and 50Gy of radiation over 5 weeks followed by surgery 5 weeks later. All patients completed the regimen but 17% suffered grade 3/4 toxicity. Six of the 40 (15%) had a complete pathologic response, and another 12 (30%) had only a few microscopic tumor cells remaining at the time of surgery. The Cancer and Leukemia Group B 89901 was a phase I/II US trial that confirmed that the addition of oxaliplatin in the neoadjuvant setting was able to achieve an improved pCR rate of 25% compared to historical data for 5-FU/radiation therapy [63]. In this trial, patients with clinical stage cT3–4,N0 tumors could receive up to six cycles of oxaliplatin during the radiation therapy. Once again, treatment-related toxicity was high with grade 3 or 4 diarrhea occurring in 38% of patients. The ECOG 3204 trial introduced bevacizumab along with oxaliplatin in the neoadjuvant setting in patients with nonmetastatic cT3–4 rectal cancers [64]. Fifty-four patients received five cycles of oxaliplatin and three cycles of bevacizumab along with 45 Gy of radiation therapy followed by surgical resection 6–8 weeks later. The primary endpoint of complete pathological response was achieved in 17% of patients, with 59% of patients experiencing downstaging. Ninety-one percent of patients completed therapy, but 36% patients experienced a grade 3 or 4 acute toxicity, with diarrhea being the most common.

These phase II trials set the foundation for several prospective randomized trials comparing neoadjuvant chemoradiation therapy with and without oxaliplatin. The STAR-01 Trial from Italy randomized 747 patients to 5-FU plus 50.4 Gy or six cycles of oxaliplatin plus 5-FU and 50.4 Gy followed by surgery 6–8 weeks later [50]. The primary endpoint of the study was to detect a 30% reduction in mortality with the addition of oxaliplatin. Compliance with the study protocol was good with 83% of patients in the oxaliplatin arm received at least five cycles of therapy. Acute toxicity was significantly higher in the oxaliplatin arm with 24% vs 8% ($P < 0.001$) having grade 3 or 4 adverse events. Diarrhea (15.3% vs 4.2%, $P < 0.001$), radiation dermatitis (4.5% vs 1.8%, $P < 0.037$), and asthenia (3.1% vs 0%, $P < 0.001$)

accounted for the differences between the groups. Sixteen percent of patients achieved a complete pathologic response in each group. To date the long-term results of this study have not been published.

The National Surgical Adjuvant Breast and Bowel Project Trial R-04 was a randomized trial of neoadjuvant 5-FU or capecitabine plus radiation therapy with or without oxaliplatin [65]. This study randomized 1608 patients with clinical stage II or III tumors to four arms – 5-FU/XRT, 5-FU + Oxaliplatin/XRT, capecitabine/XRT, and capecitabine+oxaliplatin/XRT, with the primary endpoint being locoregional failure. Complete pathologic response, sphincter-sparing procedure, downstaging, and pCR were secondary endpoints. The complete pathologic response was not different between any of the regimens; 5-FU vs capecitabine was 17.8% and 20.7% ($P = 0.17$), and oxaliplatin versus no oxaliplatin was 19.5% and 17.8% ($P = 0.42$). When examining the rate of sphincter-saving surgery, there was no statistical difference between all of the groups. Once again, patients treated with oxaliplatin experience significantly more grade 3 or 4 acute toxicity, and the incidence of diarrhea ($P < 0.001$) accounted for the differences between the groups. In 2015, the study group published the long-term and cancer-specific outcomes of the trial for the primary endpoint [66]. There was no difference in 3-year local recurrence between all groups; 5-FU versus capecitabine was 11.2% and 11.8% (HR = 1, $P = 0.98$), and oxaliplatin vs no oxaliplatin was 12.1% and 11.2% (HR = 0.94, $P = 0.7$). Similarly, there was no difference between the 5-year DFS and OS for all four arms. The DFS for the 5-FU vs capecitabine groups were 66.4% vs 67.7% (HR = 0.97, $P = 0.7$) and for the oxaliplatin vs no oxaliplatin groups were 64.2% vs 69.2% (HR = 0.91, $P = 0.34$). The 5-year OS for all groups were 79.9% vs 80.8% (HR = 0.94, $P = 0.61$) and 79% versus 81.3% (HR = 0.89, $P = 0.38$), respectively. Based on the results of these large prospective randomized trials, it was generally accepted that the addition of systemic oxaliplatin to concurrent 5-FU/long-course radiation therapy did not improve the complete pathologic response rate or long-term cancer-specific outcomes but was associated with an increased rate of grade 3 or 4 toxicities.

The German CAO/ARO/AIO-04 phase III trial sought to further understand the impact of oxaliplatin in the neoadjuvant and adjuvant setting [67]. This study randomized 1265 patients with clinical stage II or III patients into the control group (chemoradiation therapy with infusional 5-FU with 50.4 Gy, surgery, and 4 cycles of adjuvant infusional 5-FU) or the experimental group (chemoradiation with infusional 5-FU and 4 cycles of oxaliplatin with 50.4 Gy, surgery, and eight cycles of oxaliplatin and 5-FU), with a primary endpoint of DFS. Both groups had an equivalent and high compliance with therapy (83% vs 81%). There was no difference in grade 3 or 4 toxicities in the preoperative setting, but grade 3 or 4 GI toxicity was higher in the investigational group. There were no differences in operative morbidity, but they did report a small but significant improvement in pCR in the investigational group (17% vs 13%, OR 1.40, 95%CI 1.02–1.92, $P = 0.038$). After a median follow-up of 50 months, they demonstrated an improvement in 3-year DFS with addition of oxaliplatin in the treatment regimen (71.2% vs 75.9%, OR 0.79, 95%CI 0.64–0.98, $P = 0.03$) [68]. Compliance with adjuvant chemotherapy was similar between the groups, but it is worth noting the 5-FU only group received four cycles of adjuvant therapy and the 5-FU/oxaliplatin group received a total of eight cycles.

Pathologic Complete Response

Pathologic complete response (pCR) rate is often used as a surrogate for the relative effectiveness of neoadjuvant treatment regimens. However, it should be realized that pCR rate is primarily influenced by the amount of time that passes between completion of radiotherapy and surgery. Tumor cell death may be initiated immediately (during neoadjuvant therapy), but it takes time for the body to resorb dead cells. The pathologist cannot accurately distinguish between live and dead cells on histologic review of a resected specimen. Thus, the pCR rate can be manipulated by changing the duration of delay prior to proctectomy and one cannot assume that one neoadjuvant therapy regimen is superior to another based on pCR rate if proctectomy occurs at different intervals following neoadjuvant therapy.

We have also realized that extending the time interval between radiotherapy and surgery is associated with a higher rate of pCR, up to a limit, as all dead cells will eventually be resorbed and the histology will once again reflect the biologic activity of the tumor. It is less clear, however, whether patients exhibiting pCR after a longer treatment interval have the same good prognosis of those who are more rapidly sterilized. Along with assessing the relative effectiveness of neoadjuvant treatment regimens, the observation that neoadjuvant therapy regimens are associated with substantial pCR rates has led us to the concept of organ preservation. Variously termed "watch and wait," "definitive chemoradiotherapy," or "nonoperative management," treatment of highly select individuals with LARC without surgery has been employed.

Consolidation vs Induction Chemotherapy

Historically, the pCR after traditional long-course chemoradiation therapy has ranged from 15% to 20% after a 6–8 week resting period before surgery [1–4]. As noted above, it has also been demonstrated that longer waiting periods are associated with a higher pCR rate [10–13]. Rather than having

resection, clinicians began investigating the potential benefits of adding systemic chemotherapy durging this "waiting" period. As previously discussed, the hypothesis is to provide ongoing treatment to the primary tumor and to occult micrometastatic disease while allowing the body to completely resorb cells rendered nonviable after radiotherapy. The goals are to improve the potential for organ preservation, local control, and disease-free survival.

In 2004, Dr. Angelita Habr-Gama published the first reports of managing patients with rectal cancer who had a complete pathologic response nonoperatively [16]. At that time, their neoadjuvant regimen consisted of 50.4 Gy over 6 weeks with concurrent infusional 5-FU/leucovorin with tumor assessment 8 weeks after completion of therapy was able to achieve a pCR rate of 26%. As their experience with "watch and wait" evolved, they refined their neoadjuvant regimen to include an additional boost of radiation to the primary tumor and the addition of systemic chemotherapy during the rest period. This newer regimen consisted of 45 Gy over 5 weeks followed by an additional boost of 9 Gy to the primary tumor and mesorectum. Patients would also receive three cycles of infusional 5-FU/leucovorin during the radiation and an additional three cycles after the completion of radiation therapy. They treated 70 consecutive patients with T2–4,N0–2 tumors with this regimen and demonstrated that 68% had an initial complete clinical response at 8 weeks after completion of neoadjuvant therapy [69]. In their most recent report of their series, in 197 select patients with a complete clinical response who were treated nonoperatively, the 5 year DFS was 60% (95% CI 53%–67%) [70]. These investigations set the stage for the development of novel neoadjuvant therapy strategies aimed at improving the primary tumor response, as well as control distant metastatic spread, which will hopefully improve disease-free survival while limiting toxicity of therapy, possibly via organ preservation.

The Timing of Rectal Cancer Response to Chemoradiation Consortium sought to define the optimal time for surgery after long-course chemoradiation therapy in patients with clinical stage II or III rectal cancer. In 2011, they initiated a multicenter, nonrandomized, phase II trial to evaluate tumor response, treatment-related toxicity, and surgical outcomes for extended intervals between chemoradiation therapy and surgery, with the administration of systemic FOLFOX therapy during the extended waiting period (consolidation therapy). The initial study compared patients who underwent surgery 6–8 weeks after completion of chemoradiation to patients who received chemoradiation therapy followed by two cycles of FOLFOX therapy with surgery 3–5 weeks later [52]. The addition of two cycles of FOLFOX resulted in a significant improvement in pCR (25% vs 18%, $P = 0.0217$). There was no associated difference in surgical complications between the groups, but the additional time interval of 37 days between completion of chemoradiation and surgery in the FOLFOX group was associated with more significant pelvic fibrosis. The next iteration of this study expanded the cycles of FOLFOX therapy before surgery and was designed as a series of four sequential phase II study groups for patients with clinical stage II or III rectal cancer [53]. Group 1 received chemoradiation therapy followed by surgery 6–8 weeks later. Once Group 1 was filled, patients were then enrolled into Group 2 consisting of chemoradiation, two cycles of FOLFOX therapy followed by surgery. Patients were then sequentially enrolled in Groups 3 and 4, where they received four and six cycles of FOLFOX, respectively. Patients were allowed to receive a complete course of adjuvant chemotherapy, but it was not mandated in the study protocol. The primary endpoint was pCR. The study enrolled 259 patients with 60 in Group 1, 67 in Group 2, 67 in Group 3, and 65 in Group 4. The pCR rate increased with each additional two cycles of FOLFOX therapy (Group 1–18%, Group 2–25%, Group 3–30%, and Group 4–38%, $P = 0.0036$), and there was no significant difference in overall treatment-related toxicity between the groups. In 2018, they published the final results from the study and conferred that the addition of FOLFOX therapy in the neoadjuvant setting was associated with improved 5-year DFS [71]. Interestingly, the improvement in survival was seen in patients receiving at least one cycle of systemic therapy. The 5 year DFS for Group 1 versus Groups 2–4 was 50% vs 81% ($P = 0.0005$). There was no difference in DFS between Groups 2, 3, and 4. This is the first large-scale trial to demonstrate an improvement in survival for patients with rectal cancer receiving neoadjuvant consolidation chemotherapy, but there are several issues that need to be considered. For example, this was not a randomized trial, it was not powered for DFS as an endpoint, and adjuvant chemotherapy was not standardized. Regardless, this was a high-quality study that has shaped subsequent clinical trials examining total neoadjuvant therapy.

The Korean Society of Coloproctology established the KONCLUDE trial in 2018 [72]. This is a multicenter randomized trial comparing consolidation chemotherapy to adjuvant chemotherapy. Patients with mid to low rectal cancers with cT3N0 or cT1-3N1-2 were randomized after chemoradiation therapy to eight cycles of FOLFOX then surgery or surgery then eight cycles of FOLFOX. The primary endpoints are pCR and 3-year DFS. The study was powered to show 15% improvement in both outcomes, so 179 patients are expected to be enrolled in each arm.

While neoadjuvant systemic chemotherapy given after the completion of chemoradiation/radiation therapy has been termed consolidation therapy, "induction chemotherapy" describes systemic chemotherapy delivered prior to neoadjuvant chemoradiation/radiation therapy. As discussed above, systemic chemotherapy appears to be beneficial in the neoadjuvant setting, but questions remain regarding whether its

timing relative to chemoradiation/radiation impacts its effectiveness. Potential benefits of induction chemotherapy have been hypothesized to be better compliance, better tolerance, and omission of radiation therapy with a good tumor response, and the shorter time interval between completion of radiotherapy and surgery may limit pelvic fibrosis. Potential benefits of consolidation chemotherapy include prolonging the time interval between radiotherapy and surgery so as to allow for better assessment of primary tumor response, which may allow for better selection of patients for possible nonoperative therapy (organ preservation).

The Spanish GCR-3 phase II randomized trial compared the use of concurrent and adjuvant chemotherapy to induction chemotherapy in patients with LARC in patients with stage II or III tumors of the mid to lower rectum [73]. Fifty-two patients in Arm A received concurrent capecitabine oxaliplatin (CAPOX) and radiation therapy, surgery, and four cycles of adjuvant CAPOX, and 56 patients in Arm B received four cycles of CAPOX followed by radiation therapy and surgery. The final results did not demonstrate any difference in pCR, (13.5% vs 14.3%), 5-year DFS (64% vs 62%, $P = 0.85$), or 5-year local recurrence (2% vs 5%, $P = 0.61$). However, they did demonstrate better compliance and tolerance in Arm B (the induction chemotherapy arm). More patients completed treatment per the study protocol in Arm B than Arm A (91%A vs 54%, $P < 0.001$), and more patients in Arm A discontinued the study protocol because of treatment-related adverse events (17% vs 2%, $P = 0.006$).

The publication of these data was then followed by a publication from the group at Memorial Sloan Kettering Cancer Center, describing a large cohort retrospective study of their experience with total neoadjuvant therapy (TNT) [74]. They compared 320 patients who received neoadjuvant chemoradiation therapy followed by adjuvant oxaliplatin/5-FU-based chemotherapy to 331 patients who received eight cycles of oxaliplatin/5-FU-based induction chemotherapy followed by chemoradiation therapy. Patients in both regimens were then offered nonoperative management if they had a complete clinical response or surgery if there was persistent disease. At 12 months, the combined raw clinical complete response rates and pCR were 21.3%% and 35.7%, respectively. The most significant finding of the study was the compliance and tolerance of the systemic chemotherapy. The TNT group received more total doses of systemic chemotherapy, had fewer dose reductions, and was more likely to receive more than six cycles of therapy. The long-term survival data has not been published to date.

There are currently two multicenter randomized trials comparing induction vs consolidation chemotherapy for the treatment of LARC. The first is a US-based trial by the Rectal Cancer Consortium [75]. Patients with rectal cancers staged by MRI to be cT2-3N0 or cT1-3N1-2 were randomized to Arm 1 (induction) or Arm 2 (consolidation). The induction arm received eight cycles of FOLFOX or six cycles of CAPOX followed by chemoradiation therapy, and the consolidation arm received chemoradiation therapy followed by the same courses of FOLFOX or CAPOX. Patients were then restaged at the completion of TNT. Those patients with persistent disease underwent resection with total mesorectal excision, and those with a complete clinical response were then allocated to nonoperative therapy. The nonoperative patients were then followed regularly with digital rectal exam, endoscopy, and cross-sectional imaging. The primary endpoints for the study are 3-year recurrence-free survival. The study is closed to accrual and is awaiting follow-up data at this point. The second trial is the CAO/ARO/AIO-12 from the German Rectal Cancer Study Group [76]. They randomized 306 patients with stage II or III rectal cancer to Group A (3 cycles FOLFOX → chemoradiation therapy → surgery) or Group B (chemoradiation therapy → 3 cycles FOLFOX → surgery), with the primary endpoint of pCR. The study hypothesis was that TNT (either arm) would achieve pCR of 25% compared to 15% for traditional chemoradiation therapy. Initial results published in 2019 found the pCR in the consolidation group was higher (25% vs 17%). With regard to the primary endpoint of the study, Group B ($P < 0.001$) and not Group A ($P = 0.210$) fulfilled the predefined study hypothesis. Additionally, there were differences in the tolerance associated with the chemoradiation therapy and the FOLFOX therapy. Ninety seven percent of patients treated with upfront chemoradiation therapy received the full dose of radiation versus 91% who received upfront chemotherapy. Conversely, more patients in Group A received all three cycles of oxaliplatin (93%) and 5-FU (92%) compared to Group B (90% and 85%, respectively). Long-term oncologic outcomes are pending.

Based on aforementioned studies, there appears to be clear benefit to the utilization of systemic chemotherapy in the neoadjuvant setting. Whether given as induction or consolidation, the reported benefits to date include increased compliance, better tolerance, and improved primary tumor response, but it is unclear if this will translate into improved long-term survival. The final results of ongoing trials will help to answer this question as well as to delineate the relative effectiveness of induction versus consolidation chemotherapy. Finally, the impact of TNT on the practice of organ preservation should be better elucidated.

Short-Course Radiation Therapy with Systemic Chemotherapy

As discussed above, there are substantial data demonstrating that neoadjuvant short-course radiation therapy (SCRT) is as effective as neoadjuvant long-course chemoradiation therapy for achieving local pelvic control after proctectomy [2, 44,

45]. Additionally, short-course radiation therapy can provide significant tumor downstaging when surgery is delayed for an extended period of time [77]. The difference in time for delivery of a full course of radiation (1 week for short course vs 5–6 weeks for chemoradiation) makes it a very appealing alternative for patients and third-party payors, because of reduced cost and reduced time away from home for patients who live remote from their treatment center. In recent years, these two concepts (TNT and SCRT) have been united, and clinical trials initiated to examine the use of SCRT with either consolidation or induction chemotherapy. The Swedish RAPIDO trial randomized patients to Arm A (traditional long-course chemoradiation therapy with surgery 8–10 week later and optional adjuvant CAPOX) or Arm B [short-course radiation (5Gy × 5 days), a 2-week rest period, six cycles of CAPOX, and surgery 4 weeks later] [78]. Only patients with very high-risk tumors, defined as having at least one of the following characteristics, were included: cT4a-b and/or cN2, extramural vascular invasion, involved mesorectal fascia, and metastatic lateral lymph nodes. The primary endpoint for the study was 3-year DFS with immediate secondary endpoints being pCR and R0 resection rates. The trial has completed patient accrual but the results have yet to be published.

Washington University completed a pilot study of short-course radiation therapy followed by four cycles of FOLFOX with surgery 4 weeks later [79]. The rationale for the pilot study was that short-course radiation is not widely utilized in the United States, so the authors sought to demonstrate safety and effectiveness prior to participating in RAPIDO. Seventy-six patients with cT3–4NXMX rectal cancers were enrolled to receive this regimen, examining the rate of tumor downstaging and gastrointestinal toxicity. There were two interim analyses after 25 and 50 cases with stopping criteria of <50% T stage downstaging or a rate of grade 3 GI toxicity >20%. After completion of the study, the authors reported an overall downstaging rate of 70% with a pCR rate of 29%. All nonhematologic grade 3 or 4 toxicity was 21% with only 9% being related to gastrointestinal toxicity. For the long-term outcomes, they compared the patients with cM0 disease from this trial to a matched group of patients with clinical stage II or III tumors treated with traditional chemoradiation therapy [80]. The only difference between the two cohorts was total cycles of FOLFOX received with the short-course group receiving 11 cycles vs eight ($P < 0.0001$) in the long-course chemoradiation group. There was no difference in 3-year local recurrence rates (92% vs 96%, $P = 0.36$, respectively), but the short-course group had a better 3-year distant metastasis-free rate (88% vs 70%, $P = 0.028$) and DFS (85% vs 68%, $P = 0.032$).

A phase II single-arm trial from the United Kingdom examined the role of short-course radiation therapy after induction chemotherapy with four cycles of oxaliplatin/5-FU [81]. Sixty patients with T3 tumors without threatened circumferential radial margin were treated with this regimen and underwent surgical resection with planned adjuvant chemotherapy. The primary endpoint was feasibility assessed by completion of the treatment protocol. Fifty seven of the 60 patients made it through the protocol including surgery. However, when comparing the chemotherapy received in the neoadjuvant versus adjuvant setting, they reported a median percent dose intensity of 100% vs 63% for 5-FU and 100% vs 45% for oxaliplatin (this is a measure of actual dose received divided the by the protocol dose) demonstrating patients were more likely to receive and tolerate systemic chemotherapy in the neoadjuvant period than after surgery. There was reasonable tumor response as downstaging occurred in 73% of cases, but the pCR rate was only 12%. It should be noted that surgery occurred within 7 days of completing the radiation therapy, which could bias the results against pCR.

The Polish Colorectal Study Group has published the only long-term data comparing short-course radiation plus consolidation chemotherapy versus traditional chemoradiation therapy [82]. Two hundred sixty-one patients with cT4 or fixed cT3 tumors were randomized to Group A (short course +3 cycles of FOLFOX) and 254 patients to Group B (long-course chemoradiation) with primary endpoints of R0 resection rate and DFS. Patients in Group A had less toxicity related to the neoadjuvant therapy (75% vs 83%, $P = 0.006$), but there was no difference in the rates of grade III or IV toxicity. The R0 resection rate (77% vs 71%, $P = 0.07$) and pCR (16% vs 12%, $P = 0.17$) were similar in both groups. Interestingly, Group A had better 3-year overall survival rate (73% vs 65%, $P = 0.046$), but there was no difference in DFS (53% vs 52%, $P = 0.86$). Finally, there was no difference in postoperative complications (29% vs 25%, $P = 0.18$), which suggests that the extended period of time between completion of short course and surgery does not make the surgery more difficult. After 7 years of follow-up, there was no difference in OS, DFS, or LR between these groups [83]. Both the RAPIDO and POLISH II trials examined very high-risk patients where there was either a threatened circumferential margin, clinically positive lymph nodes, or other high-risk MRI-based features. Despite these adverse features, the utilization of short-course radiotherapy along with neoadjuvant chemotherapy was well tolerated and provided results equivalent to those achieved with long-course chemoradiation therapy. There are little data comparing short-course radiation-based TNT with long-course radiation based TNT, but both modes of radiation therapy have demonstrated effectiveness in providing excellent local control, improving compliance with systemic chemotherapy, and improving rates of pCR and tumor downstaging. We continue to wait for long-term survival data to determine if the change in the order of delivery of trimodal therapy will ultimately prove beneficial.

Conclusion

The management of rectal cancer continues its evolution, as investigators continually seek to find treatment strategies that will improve outcomes and reduce toxicity. Historically, pelvic failure rates following surgery alone were high, so investigators focused on the importance of surgical technique and the utility of adjuvant radiation therapy. These efforts demonstrated that preoperative treatment, whether delivered as long-course radiation alone, chemoradiation or short-course radiation, improved outcomes when compared to surgery alone and when compared to postoperative adjuvant therapy. Neoadjuvant therapy and optimal surgery have improved local control, but, unfortunately, they have not been translated into consistently improved overall survival. This has been puzzling to many investigators, although one must conclude that there is an adverse impact of pelvic radiotherapy on overall survival; otherwise the improvement in local control should translate into a similar improvement in overall survival, all else being equal. The addition of oxaliplatin to the systemic chemotherapy regimen has made chemotherapy for colorectal cancer markedly more effective than it was in the past. As a result, systemic chemotherapy has been shifted into the neoadjuvant setting to treat micrometastatic disease early. This adjustment has also led to improved response of the primary tumor to neoadjuvant therapy and improved compliance and tolerance of systemic chemotherapy. Evidence is emerging that this will improve survival for rectal cancer patients. With the improved tumor response, the option of nonoperative management of rectal cancer is being explored. To date, there is no widely accepted regimen for TNT. This is because of the heterogeneity of the available data, as each study examines different patient populations, utilizes different regimens, and examines different clinical endpoints. Based on the available data, it is clear that TNT will offer some advantages over conventional trimodal therapy. The National Collaborative Cancer Network (NCCN) has recognized the importance of TNT and the heterogeneous approaches to TNT, and the new NCCN guidelines allow for almost any combination of trimodal therapy – both in the traditional delivery method and as part of a TNT protocol. As the efficacy of immunotherapy is better defined, it may also be added to neoadjuvant treatment regimens.

References

1. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet. 1986;1(8496):1479–82.
2. Kapiteijn E, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345(9):638–46.
3. Swedish Rectal Cancer Trial, et al. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med. 1997;336(14):980–7.
4. Bosset JF, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med. 2006;355(11):1114–23.
5. Breugom AJ, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol. 2015;16(2):200–7.
6. Breugom AJ, et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. Ann Oncol. 2015;26(4):696–701.
7. Sauer R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351(17):1731–40.
8. Sauer R, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol. 2012;30(16):1926–33.
9. Biagi JJ, et al. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. JAMA. 2011;305(22):2335–42.
10. Francois Y, et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. J Clin Oncol. 1999;17(8):2396.
11. Pettersson D, et al. Tumour regression in the randomized Stockholm III trial of radiotherapy regimens for rectal cancer. Br J Surg. 2015;102(8):972–8; discussion 978.
12. Cotte E, et al. Pathologic response, when increased by longer interval, is a marker but not the cause of good prognosis in rectal cancer: 17-year follow-up of the Lyon R90-01 randomized trial. Int J Radiat Oncol Biol Phys. 2016;94(3):544–53.
13. Probst CP, et al. Extended intervals after neoadjuvant therapy in locally advanced rectal cancer: the key to improved tumor response and potential organ preservation. J Am Coll Surg. 2015;221(2):430–40.
14. Andre T, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009;27(19):3109–16.
15. Hong YS, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. Lancet Oncol. 2014;15(11):1245–53.
16. Habr-Gama A, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg. 2004;240(4):711–7; discussion 717–8.
17. Benson AB, et al. Rectal cancer, version 2.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2018;16(7):874–901.
18. Adam IJ, et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. Lancet. 1994;344(8924):707–11.
19. Birbeck KF, et al. Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. Ann Surg. 2002;235(4):449–57.
20. Cawthorn SJ, et al. Extent of mesorectal spread and involvement of lateral resection margin as prognostic factors after surgery for rectal cancer. Lancet. 1990;335(8697):1055–9.
21. Taylor FG, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. J Clin Oncol. 2014;32(1):34–43.
22. Wibe A, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. Br J Surg. 2002;89(3):327–34.
23. Bipat S, et al. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging--a meta-analysis. Radiology. 2004;232(3):773–83.

24. Glynne-Jones R, et al. Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv22–40.
25. Rider WD, et al. Preoperative irradiation in operable cancer of the rectum: report of the Toronto trial. Can J Surg. 1977;20(4):335–8.
26. Jones DJ, et al. Predicting local recurrence of carcinoma of the rectum after preoperative radiotherapy and surgery. Br J Surg. 1989;76(11):1172–5.
27. Balslev I, et al. Postoperative radiotherapy in Dukes' B and C carcinoma of the rectum and rectosigmoid. A randomized multicenter study. Cancer. 1986;58(1):22–8.
28. Fisher B, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. J Natl Cancer Inst. 1988;80(1):21–9.
29. Gastrointestinal Tumor Study Group. Prolongation of the disease-free interval in surgically treated rectal carcinoma. N Engl J Med. 1985;312(23):1465–72.
30. Randomised trial of surgery alone versus surgery followed by radiotherapy for mobile cancer of the rectum. Medical Research Council Rectal Cancer Working Party. Lancet. 1996;348(9042):1610–4.
31. Byfield JE, et al. Pharmacologic requirements for obtaining sensitization of human tumor cells in vitro to combined 5-fluorouracil or ftorafur and X rays. Int J Radiat Oncol Biol Phys. 1982;8(11):1923–33.
32. Vietti T, Eggerding F, Valeriote F. Combined effect of x radiation and 5-fluorouracil on survival of transplanted leukemic cells. J Natl Cancer Inst. 1971;47(4):865–70.
33. Moertel CG, et al. Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. Lancet. 1969;2(7626):865–7.
34. Krook JE, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med. 1991;324(11):709–15.
35. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA. 1990;264(11):1444–50.
36. O'Connell MJ, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med. 1994;331(8):502–7.
37. Wolmark N, et al. Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02. J Natl Cancer Inst. 2000;92(5):388–96.
38. The evaluation of low dose pre-operative X-ray therapy in the management of operable rectal cancer; results of a randomly controlled trial. Br J Surg. 1984;71(1):21–5.
39. Roswit B, Higgins GA, Keehn RJ. Preoperative irradiation for carcinoma of the rectum and rectosigmoid colon: report of a National Veterans Administration randomized study. Cancer. 1975;35(6):1597–602.
40. Stevens KR Jr, Allen CV, Fletcher WS. Preoperative radiotherapy for adenocarcinoma of the rectosigmoid. Cancer. 1976;37(6):2866–74.
41. Gerard A, et al. Preoperative radiotherapy as adjuvant treatment in rectal cancer. Final results of a randomized study of the European Organization for Research and Treatment of Cancer (EORTC). Ann Surg. 1988;208(5):606–14.
42. Randomised trial of surgery alone versus radiotherapy followed by surgery for potentially operable locally advanced rectal cancer. Medical Research Council Rectal Cancer Working Party. Lancet. 1996;348(9042):1605–10.
43. Pahlman L, Glimelius B. Pre- or postoperative radiotherapy in rectal and rectosigmoid carcinoma. Report from a randomized multicenter trial. Ann Surg. 1990;211(2):187–95.
44. Bujko K, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg. 2006;93(10):1215–23.
45. Ngan SY, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol. 2012;30(31):3827–33.
46. Erlandsson J, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. Lancet Oncol. 2017;18(3):336–46.
47. Peeters KC, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg. 2007;246(5):693–701.
48. Zhao L, et al. Oxaliplatin/fluorouracil-based adjuvant chemotherapy for locally advanced rectal cancer after neoadjuvant chemoradiotherapy and surgery: a systematic review and meta-analysis of randomized controlled trials. Colorectal Dis. 2016;18(8):763–72.
49. Bosset JF, et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results--EORTC 22921. J Clin Oncol. 2005;23(24):5620–7.
50. Aschele C, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol. 2011;29(20):2773–80.
51. Fernandez-Martos C, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol. 2010;28(5):859–65.
52. Garcia-Aguilar J, et al. Optimal timing of surgery after chemoradiation for advanced rectal cancer: preliminary results of a multicenter, nonrandomized phase II prospective trial. Ann Surg. 2011;254(1):97–102.
53. Garcia-Aguilar J, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. Lancet Oncol. 2015;16(8):957–66.
54. Hong YS, et al. Oxaliplatin-based adjuvant chemotherapy for rectal cancer after preoperative chemoradiotherapy (ADORE): long-term results of a randomized controlled trial. J Clin Oncol. 2019;37(33):3111–23.
55. Giessen C, et al. A randomized, phase III trial of capecitabine plus bevacizumab (Cape-Bev) versus capecitabine plus irinotecan plus bevacizumab (CAPIRI-Bev) in first-line treatment of metastatic colorectal cancer: the AIO KRK 0110 trial/ML22011 trial. BMC Cancer. 2011;11:367.
56. Rothenberg ML, et al. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) as second-line therapy in metastatic colorectal cancer: a randomized phase III noninferiority study. Ann Oncol. 2008;19(10):1720–6.
57. Schrag D, et al. Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. J Clin Oncol. 2014;32(6):513–8.
58. Schrag D, et al. Challenges and solutions in the design and execution of the PROSPECT phase II/III neoadjuvant rectal cancer trial (NCCTG N1048/Alliance). Clin Trials. 2019;16(2):165–75.
59. Glynne-Jones R, et al. Bevacizumab and Combination Chemotherapy in rectal cancer Until Surgery (BACCHUS): a phase II, multicentre, open-label, randomised study of neoadjuvant chemotherapy alone in patients with high-risk cancer of the rectum. BMC Cancer. 2015;15:764.
60. Deng Y, et al. Modified FOLFOX6 with or without radiation versus fluorouracil and leucovorin with radiation in neoadjuvant treatment of locally advanced rectal cancer: initial results of the Chinese FOWARC multicenter, open-label, randomized three-arm phase III trial. J Clin Oncol. 2016;34(27):3300–7.

61. Deng Y, et al. Neoadjuvant modified FOLFOX6 with or without radiation versus fluorouracil plus radiation for locally advanced rectal cancer: final results of the Chinese FOWARC trial. J Clin Oncol. 2019;37(34):3223–33.
62. Gerard JP, et al. Preoperative concurrent chemoradiotherapy in locally advanced rectal cancer with high-dose radiation and oxaliplatin-containing regimen: the Lyon R0-04 phase II trial. J Clin Oncol. 2003;21(6):1119–24.
63. Cancer and Leukemia Group B 89901, et al. Phase I/II study of preoperative oxaliplatin, fluorouracil, and external-beam radiation therapy in patients with locally advanced rectal cancer: Cancer and Leukemia Group B 89901. J Clin Oncol. 2006;24(16):2557–62.
64. Landry JC, et al. Phase 2 study of preoperative radiation with concurrent capecitabine, oxaliplatin, and bevacizumab followed by surgery and postoperative 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX), and bevacizumab in patients with locally advanced rectal cancer: ECOG 3204. Cancer. 2013;119(8):1521–7.
65. O'Connell MJ, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. J Clin Oncol. 2014;32(18):1927–34.
66. Allegra CJ, et al. Neoadjuvant 5-FU or capecitabine plus radiation with or without oxaliplatin in rectal cancer patients: a phase III randomized clinical trial. J Natl Cancer Inst. 2015;107(11):djv248.
67. Rodel C, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol. 2012;13(7):679–87.
68. Rodel C, et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2015;16(8):979–89.
69. Habr-Gama A, et al. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? Dis Colon Rectum. 2013;56(10):1109–17.
70. Habr-Gama A, et al. Organ preservation in cT2N0 rectal cancer after neoadjuvant chemoradiation therapy: the impact of radiation therapy dose-escalation and consolidation chemotherapy. Ann Surg. 2019;269(1):102–7.
71. Marco MR, et al. Consolidation mFOLFOX6 chemotherapy after chemoradiotherapy improves survival in patients with locally advanced rectal cancer: final results of a multicenter phase II trial. Dis Colon Rectum. 2018;61(10):1146–55.
72. Kim CW, et al. Korean Society of Coloproctology (KSCP) trial of cONsolidation Chemotherapy for Locally advanced mid or low rectal cancer after neoadjUvant concurrent chemoraDiothErapy: a multicenter, randomized controlled trial (KONCLUDE). BMC Cancer. 2018;18(1):538.
73. Fernandez-Martos C, et al. Chemoradiation, surgery and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: long-term results of the Spanish GCR-3 phase II randomized trial†. Ann Oncol. 2015;26(8):1722–8.
74. Cercek A, et al. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. JAMA Oncol. 2018;4(6):e180071.
75. Smith JJ, et al. Organ preservation in rectal adenocarcinoma: a phase II randomized controlled trial evaluating 3-year disease-free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy, and total mesorectal excision or nonoperative management. BMC Cancer. 2015;15:767.
76. Fokas E, et al. Randomized phase II trial of chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for locally advanced rectal cancer: CAO/ARO/AIO-12. J Clin Oncol. 2019;37(34):3212–22.
77. Lee SW, et al. The impact of surgical timing on pathologic tumor response after short course and long course preoperative chemoradiation for locally advanced rectal adenocarcinoma. Cancer Res Treat. 2018;50(3):1039–50.
78. Nilsson PJ, et al. Short-course radiotherapy followed by neoadjuvant chemotherapy in locally advanced rectal cancer--the RAPIDO trial. BMC Cancer. 2013;13:279.
79. Myerson RJ, et al. Five fractions of radiation therapy followed by 4 cycles of FOLFOX chemotherapy as preoperative treatment for rectal cancer. Int J Radiat Oncol Biol Phys. 2014;88(4):829–36.
80. Markovina S, et al. Improved metastasis- and disease-free survival with preoperative sequential short-course radiation therapy and FOLFOX chemotherapy for rectal cancer compared with neoadjuvant long-course chemoradiotherapy: results of a matched pair analysis. Int J Radiat Oncol Biol Phys. 2017;99(2):417–26.
81. Gollins S, et al. A prospective phase II study of pre-operative chemotherapy then short-course radiotherapy for high risk rectal cancer: COPERNICUS. Br J Cancer. 2018;119(6):697–706.
82. Bujko K, et al. Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Ann Oncol. 2016;27(5):834–42.
83. Cisel B, et al. Long-course preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for clinical T4 and fixed clinical T3 rectal cancer: long-term results of the randomized Polish II study. Ann Oncol. 2019;30(8):1298–303.

Rectal Cancer: Local Excision

27

John R. T. Monson and Rebecca Hoedema

Key Concepts

- Local excision of biopsy-proven rectal cancer requires en bloc full-thickness dissection.
- Predictors of lymph node metastases include tumor depth, lymphovascular invasion, poor differentiation, and tumor budding.
- Local recurrence rates for T2 rectal cancers treated with neoadjuvant therapy and local excision appear similar to those of T1 cancers treated with local excision alone.
- Transanal endoscopic surgery techniques including transanal endoscopic microsurgery (TEM) and transanal minimally invasive surgery (TAMIS) may improve surgical outcomes as compared to standard transanal excision techniques.

Introduction

Local excision for rectal tumors dates back to the early 1800s, with a report by Dr. Jacques Lisfranc describing excision of a benign rectal mass in the lower rectum [1]. Sir Alan Parks described a more modern version of transanal excision in the 1960s [2]. Conventional transanal excision techniques can be limited by the location of the tumor, anatomy of the rectum, and the tumor characteristics. This approach is ideal for lesions within 8 cm from the anal verge, <3 cm in size and occupying <40% of the rectal circumference [3]. Tumors located more proximally in the rectum can be more challenging. "Transanal endoscopic microsurgery" (TEM) using an operating proctoscope with continuous gas insufflation was developed by Buess in the early 1980s to overcome some of these anatomic constraints [4]. Although there were certainly enthusiasts of the TEM approach, high capital costs, limited mobility of the operating instruments, a formidable learning curve, and issues with the insufflation system limited enthusiasm. In 2010, Atallah described the transanal use of a single-port laparoscopic platform with the use of insufflation to perform transanal minimally invasive surgery (TAMIS) which has overcome some of the limiting factors associated with TEM and allowed for the utilization of standard laparoscopic instruments with which surgeons are familiar [5].

Patient Selection

The local excision technique was initially described for presumed benign tumors in the distal rectum, as an alternative to proctectomy. Local excision allowed the patient to avoid major abdominal surgery and could be curative, providing that negative margins could be obtained and there was no invasive cancer. Local excision for known rectal cancer was first described by Morson et al. in 1977 at St. Mark's Hospital, who reported a low rate of local recurrence after excision with negative margins [6].

The typical treatment for locally advanced rectal cancer includes neoadjuvant treatment followed by proctectomy using the principles of total mesorectal excision (TME) [7]. Variations in treatment algorithms arise primarily from differences in the sequence and dosing of neoadjuvant/adjuvant therapy elements (radiotherapy and chemotherapy). Decision-making for patients with clinically staged early rectal cancers can be more complex, as the best chance for

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cure (proctectomy, with or without neoadjuvant therapy) is associated with the greatest morbidity [8], while organ preservation strategies risk undertreatment and cancer-related mortality. Reports of reasonable oncologic outcomes following local excision, and patient interest in rectal preservation has driven the continued enthusiasm for local excision [9].

Patient selection is critical when patients are being considered for local excision. Current staging modalities include digital rectal examination to assess tumor character, fixation, and relation to the anorectal muscular ring. Anal sphincter bulk and tone should also be assessed, as full-thickness local excision can adversely impact rectal compliance and/or remove a portion of the internal anal sphincter for very distal tumors. In addition to baseline carcinoembryonic antigen level (CEA), patients should be evaluated for distant metastatic spread with computed tomography (CT) of the chest, abdomen, and pelvis. Local tumor staging can be assessed with either rectal cancer protocol magnetic resonance imaging (MRI) or transrectal ultrasound (TRUS). MRI is an important tool to help differentiate cT1/cT2 tumors from cT3/cT4 tumors, which can significantly alter initial treatment plans. MRI can also be helpful in assessing the relationship of the tumor to the mesorectal fascia. However, MRI is less accurate for estimating lymph node status, although certain findings (heterogeneous signal intensity and irregular margins) are usually indicative of lymph node involvement with tumor [10]. Tang et al. demonstrated that other MRI findings, namely, the diameter of the largest lymph node and the tumor percent enhancement on the arterial phase were independent risk factors of lymph node positivity in early rectal cancer patients ($p = 0.005$ vs 0.021, respectively) [11]. Hopefully with improvements in radiographic assessment of mesorectal lymph node status and the involvement of dedicated radiologists who review all rectal cancer MRIs and participate in multidisciplinary tumor discussions, the decision-making process for patients with clinically early stage rectal cancer will be more refined.

It should be remembered that local staging provides only *estimates* of tumor stage, and there is a substantial rate of inaccuracy with any staging test, especially when estimating mesorectal nodal involvement. Treatment decisions for patients with rectal cancer occur in prospective fashion (preoperatively), when stage of the tumor cannot be known with certainty. In addition, decisions regarding initial treatment may adversely impact subsequent therapy. For example, local excision of an anterior tumor may create substantial scarring and adjacent organ adherence that may compromise future attempts at proctectomy. Thus, it is critical that the surgeon consider not only whether local excision is appropriate as the initial mode of treatment but how local excision may impact subsequent care if the clinical stage was inaccurate, negative margins were not obtained, or local pelvic failure occurs.

In the following sections, we discuss outcomes for various stage tumors thought to be suitable for local excision. This is somewhat disingenuous because, as noted above, histologic stage cannot be known with certainty until *after* operation. Unfortunately, much of the published literature on local excision reports outcomes of select patients who meet certain histologic criteria, rather than including all patients undergoing local excision on an intention-to-treat basis. This will obviously bias the results in favor of local excision. In addition to the aforementioned problem of retrospective patient selection for inclusion in studies of local excision outcomes, there are other issues with the published literature on local excision. Firstly, there has been a paucity of prospective randomized trials (RCTs) comparing local excision with proctectomy. The vast majority of reports are retrospective analyses, in which selection bias is inherent to the study design. Secondly, many published studies have heterogeneous study populations. Lastly, many trials do not report time-to-event (Kaplan-Meier) calculations of survival and/or recurrence, instead inappropriately using crude fractions, which may artifactually improve outcomes. These problems further limit our ability to rigorously compare treatment outcomes.

T1N0

In general, local excision as a sole definitive treatment for rectal cancer should be reserved for histologically favorable T1 cancers, confined to the submucosa. However, T1 cancers with unfavorable histologic features, i.e., presence of lymphovascular invasion, poor differentiation, and tumor budding, should be strongly considered for proctectomy given the risk of lymph node metastasis. Adherence to these strict criteria may produce equivalent survival for local excision when compared to radical surgery. An analysis of retrospective data from the Surveillance, Epidemiology, and End Results database reported that local excision of a T1 rectal cancer produced similar cancer-specific survival when compared to radical surgery [12]. Two meta-analyses, comparing local excision and radical surgery for T1 rectal cancer, demonstrated similar 5-year overall survival when comparing outcomes of the TEM subgroup and proctectomy [13, 14]. However, it should be noted that these meta-analyses only included one underpowered RCT; the remainder of the studies were retrospective cohort studies. In addition, one of the meta-analyses found inferior oncologic results with local excision overall [13].

If a patient undergoes local excision and final pathology unexpectedly reveals high-risk features, patients should be

considered for completion proctectomy or adjuvant chemoradiotherapy. As noted above, patients should understand prior to undergoing local excision that these are potential scenarios once final histology is reviewed. Another consideration that may drive shared decision-making preoperatively is that patients undergoing local excision typically undergo more frequent surveillance examinations [15]. This may be of importance to patients with limited resources and/or difficulty in traveling to the treating facility.

Predicting Lymph Node Metastasis

The ideal candidate for local excision is a patient who has a primary tumor that can be excised completely with negative margins and has no lymph node metastasis. In this ideal patient, local excision can be curative. However, our ability to predict lymph node metastasis is not ideal, and occult lymph node metastases may be the primary driver of the higher local recurrence rates observed following local excision as compared to radical surgery. Estimates of lymph node status in rectal cancer patients thus dramatically affect treatment recommendations.

Predicting lymph node metastasis for rectal cancer is a multifactorial calculation. The use of the preoperative staging workup, imaging modalities, and histologic findings can help determine the risk and benefit of local excision. Unfavorable histologic features in the primary tumor can predict lymph node metastasis and change the direction of cancer care. Chang et al. found multiple unfavorable histologic features, primarily lymphovascular invasion (LVI), had an additive risk for lymph node metastasis [16]. According to the American Society of Colon and Rectal Surgeons practice parameters for the management of rectal cancer last published in 2013, local excision is an appropriate treatment modality for carefully selected T1 rectal cancers without high-risk features [17].

Depth of Invasion

T1 lesions are further classified according to the depth of invasion of the tumor by dividing the submucosal layer into thirds according to Kikuchi [18]. They noted an incremental increase in risk of lymph node metastasis and/or local recurrences with a deeper depth of invasion. The risk of lymph node metastasis is 3% for lesions invading the superficial 1/3 of the submucosa (SM1), but it rises up to 23% for deeply invading lesions (SM3), and therefore local excision should be reserved for superficial or middle lesions for the best curative and oncologic results [19–21]. Tumors with a depth invading to the SM3 level were found to be similar to T2 rectal cancers in relation to lymph node metastasis and local recurrence rates [17].

The T stage and SM level of the tumor are important predictors of lymph node metastasis which in turn, significantly affects the risk for local recurrence and the long-term survival in those patients with rectal cancer treated with local excision. Analysis of the Swedish Rectal Cancer Registry demonstrated that the risk of lymph node metastasis in T1 lesions is 6% in the absence of adverse histologic features [22]. It has also been reported that histologically favorable T1 lesions with a low risk of lymph node metastasis can be potentially cured with local excision surgery alone.

Unfortunately, SM level can only be accurately assessed *after* excision of the tumor, either by full- or partial-thickness local excision or endoscopic submucosal dissection (ESD). Although occasionally SM level can be assessed in a routine polypectomy specimen, this is relatively uncommon, as there is the need for a significant portion of the submucosa within the resected specimen in order to define the deepest border of the submucosa. Therefore, SM level calculation is typically only useful after local excision to make decisions regarding recommendations for completion proctectomy or adjuvant chemoradiotherapy.

Lymphovascular Invasion and Poor Differentiation

Lymphovascular invasion is found to be the most consistent histologic feature associated with metastatic disease. Chang retrospectively reviewed 943 patients with pT1 or pT2 rectal cancers at a single institution and found lymphovascular invasion was the variable that was most strongly associated with the risk of lymph node metastasis, with an odds ratio of 11.5 and risk of 68.8% (Table 27.1) [16]. Lymphovascular invasion has recently been reported to be associated with systemic recurrence in rectal cancer patients, which is less

Table 27.1 Lymph node metastasis in relation to risk factors in patients with pT1–2 rectal cancer

Cancer	LV1	PD	LNM, n	LNM, %
pT1	–	–	18/241	7.5
	–	+	1/5	20
	+	–	9/15	60
	+	+	3/3	100
pT2	–	–	87/569	15.3
	–	+	5/16	31.3
	+	–	59/88	67.0
	+	+	6/6	100

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+ presence, absence, *LV1* lymphovascular invasion, *PD* poor differentiation, *LNM* lymph node metastasis

Table 27.2 Analysis of independent association between LV1+ and LR/SR in RC

	Locoregional recurrence			Systemic recurrence		
Parameter	*p*	HR	95% CI	*p*	HR	95% CI
Age	0.37	1.02	0.98–1.07	0.49	0.99	0.95–1.03
Male	0.88	1.09	0.37–3.21	0.42	0.68	0.24–1.80
Stage III	0.05	2.57	1.01–6.93	0.05	1.66	0.69–4.32
Total LN	0.09	0.92	0.83–1.01	0.76	0.99	0.91–1.07
LV1	0.40	1.57	0.55–4.49	0.04	2.57	1.04–6.39

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Established prognostic factors and LV1 were incorporated into a Cox proportional hazards multivariate model to evaluate the independent association between LV1+ and LR/SR
LV1+ was an independent predictor of adverse LR in CC ($p = 0.02$) but not RC ($p = 0.40$). LV1+ was an independent predictor of adverse SR in RC ($p = 0.04$) but not CC ($p = 0.88$) and CRC ($p = 0.31$)
CC colon cancer, *CRC* colorectal cancer, *LR* locoregional, *LN* lymph node, *LV1* lymphovascular invasion, *LV1+* lymphovascular invasion positive, *LV1-* lymphovascular invasion negative, *RC* rectal cancer, *SR* systemic recurrence

amenable to curative surgical interventions and associated with reduced overall survival [23, 24]. Hogan et al. found that lymphovascular invasion in rectal cancer patients portended an increase in systemic recurrence and therefore an adverse effect on survival (Table 27.2) [25].

In addition, poor differentiation on histology is associated with lymph node metastasis in rectal cancer [16, 21, 26, 27]. Bosch et al. performed a meta-analysis of 17 studies and further confirmed that poor differentiation, among other adverse histologic findings, is a strong predictor of lymph node metastasis with a relative risk of 4.9 (95% confidence interval 3.3–6.9) [28].

Tumor Budding

Tumor budding was initially described by Hase in 1993 and defined as small clusters of undifferentiated cancer cells ahead of the invasive front of the lesion [29]. A review of 663 patients who underwent curative resection of colorectal cancer found that tumors with substantial budding had more aggressive behavior than tumors without budding. Initially reported primarily in the Japanese literature as a predictor and prognostic indicator of lymph node metastasis [30, 31], more recent reports from Western centers have supported this concept [28, 32]. It has now been adopted in the reporting system and is well-established as an independent adverse prognostic factor in colorectal carcinoma that can then allow for stratification of patients into risk categories more meaningful than just the TNM staging and potentially help guide treatment decisions, especially in early rectal cancers. Consensus statements and recommendations have been put forth by the International Tumor Budding Consensus Conference (ITBCC) that support tumor budding as an independent predictor of lymph node metastasis in T1 colorectal cancer. The authors clarify that tumor budding and tumor grade are not the same and that tumor budding should be included in synoptic reporting, guidelines and protocols for colorectal cancer reporting (Table 27.3) [33].

Table 27.3 Statements of the ITBCC 2016 based on the GRADE System

	Statement	Recommendation	Evidence
1	Tumor budding is defined as a single tumor cell or a cell cluster consisting of four tumor cells or less	Strong vote: 22/22 (100%)	High
2	Tumor budding is an independent predictor of lymph node metastasis in pT1 colorectal cancer	Strong vote: 23/23 (100%)	High
3	Tumor budding is an independent predictor of survival in stage II colorectal cancer	Strong vote: 23/23 (100%)	High
4	Tumor budding should be taken into account along with other clinicopathological features in a multidisciplinary setting	Strong vote: 23/23 (100%)	High
5	Tumor budding is counted on H&E	Strong vote: 19/22	Moderate
6	Intramural budding exits in colorectal cancer and has been shown to be related to lymph node metastasis	Strong vote: 22/22	Low
7	Tumor budding is assessed in one hotspot (in a field measuring 0.785 mm^2) at the invasive front	Strong vote: 22/22 (100%)	Moderate
8	For tumor budding assessment in colorectal cancer, the hotspot method is recommended	Strong vote: 22/22 (100%)	Moderate
9	A three-tier system should be used along with the budding count in order to facilitate risk stratification in colorectal cancer	Strong vote: 23/23 (100%)	Moderate
10	Tumor budding should be included in guidelines/ protocols for colorectal cancer reporting	Strong vote: 23/23 (100%)	High
11	Tumor budding and tumor grade are not the same	Strong vote: 23/23 (100%)	High

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T2

To date, local excision has been a plausible option in early rectal cancers, namely, T1 tumors, but what about T2 lesions? Proctectomy for patients with T2 rectal cancers is associated

with high cure rates at the cost of high morbidity, risk of permanent colostomy, and significant impairment to anorectal, sexual, and urinary function with an associated effect on quality of life [34–37]. However, the standard recommendation for T2 lesions remains radical resection due to the high risk of lymph node metastases, unless patient comorbidities are prohibitive or the patient refuses radical surgery and/or the possibility of a colostomy. Locoregional recurrence rates for T2 tumors after local excision alone are unacceptably high, ranging from 13% to 30%, which may be partially due to the 30–40% incidence of occult nodal involvement [9, 38, 39]. However, recent evidence suggests that local excision with adjuvant chemoradiotherapy may be effective in treating occult nodal disease and minimize recurrence [40, 41].

Techniques

Transanal Excision

A thorough surgical history and physical examination including bowel function and continence are important prior to scheduling. The examination includes a digital rectal examination along with office proctoscopy to determine the location and characteristics of the mass. Standard transanal excision technique can be a viable option if the rectal cancer is palpable with digital examination and specifically if the top of the mass can be palpated. Optimal visualization during surgery is imperative, so a mechanical bowel preparation is recommended in most circumstances, but a simple enema preparation may suffice in the appropriate patient. Typically, preoperative intravenous antibiotics are given within 1 hour of the start of the surgery. General anesthesia is most commonly used for these cases, although spinal anesthesia and MAC sedation can also be viable options in the appropriate patient.

Patient positioning is based on the location of the tumor and surgeon preference. Many surgeons would want the tumor in the dependent position. For example, if the tumor is anteriorly based, the patient would be in the prone position. A myriad of anoscopes, retractors, proctoscopes, and other self-retaining tools can be used for optimal exposure. Electrocautery is then used to mark approximately 5–10 mm around the tumor. Stay sutures can be helpful in these circumstances and dissection continues with a combination of both sharp dissection and electrocautery. For known or strongly suspected cancer, a full-thickness dissection is typically performed. For benign appearing lesions, partial-thickness resection is usually the best option, as it can be curative if the tumor is benign, damage to the rectal wall is avoided, and all future treatment options are preserved if indeed an occult carcinoma is found. Partial-thickness resection can also be performed using endoscopic ESD techniques (see Chap. 23). Closure of the defect should be completed in a transverse fashion to avoid stricture formation. If closure is not possible and the peritoneal cavity has not been entered, then leaving the wound open to heal by secondary intention can be considered (Fig. 27.1).

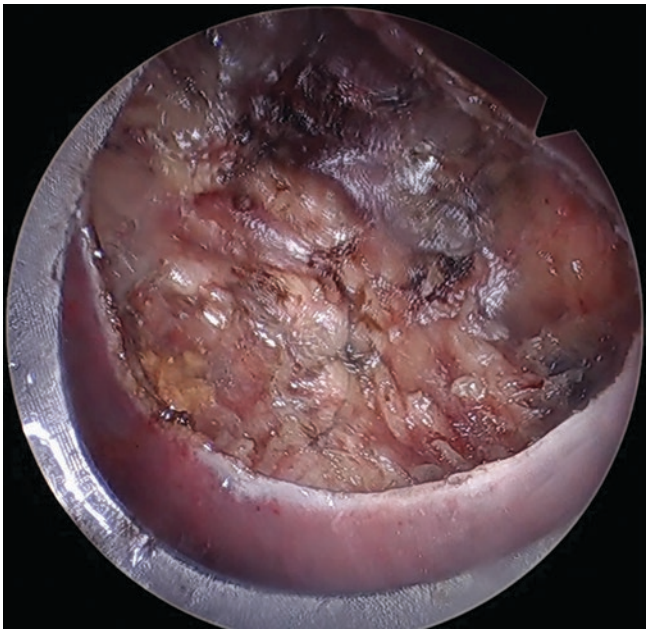

Fig. 27.1 Transanal endoscopic microsurgery defect

Transanal Endoscopic Microsurgery

Preoperative preparation is similar as for standard local excision, with the exception that some surgeons prefer the patient be positioned so that the tumor is "towards the sky," so that is naturally falls away from the rectal wall during dissection. The operating proctoscope is gently inserted into the anal canal and then attached to the table mount (Fig. 27.2). Pneumorectum is established allowing the proctoscope to visualize the target tumor. Three instrument ports are placed, and electrocautery is used to demarcate 5–10 mm around the target tumor. The tumor is removed and the defect closed. If intraperitoneal entry occurs or is suspected during a TEM procedure, laparoscopic assistance may be necessary for closure of the defect and to perform pneumatic leak testing, as one would perform following colorectal anastomosis.

Implementation of the TEM technique has broadened the application of local excision for rectal cancers and has allowed for removal of more proximal tumors compared to the standard transanal technique. As noted above, there are several limitations associated with the TEM technique, namely, cost and a steep learning curve, and many surgeons have migrated to the TAMIS technique for mid and proximal rectal tumors.

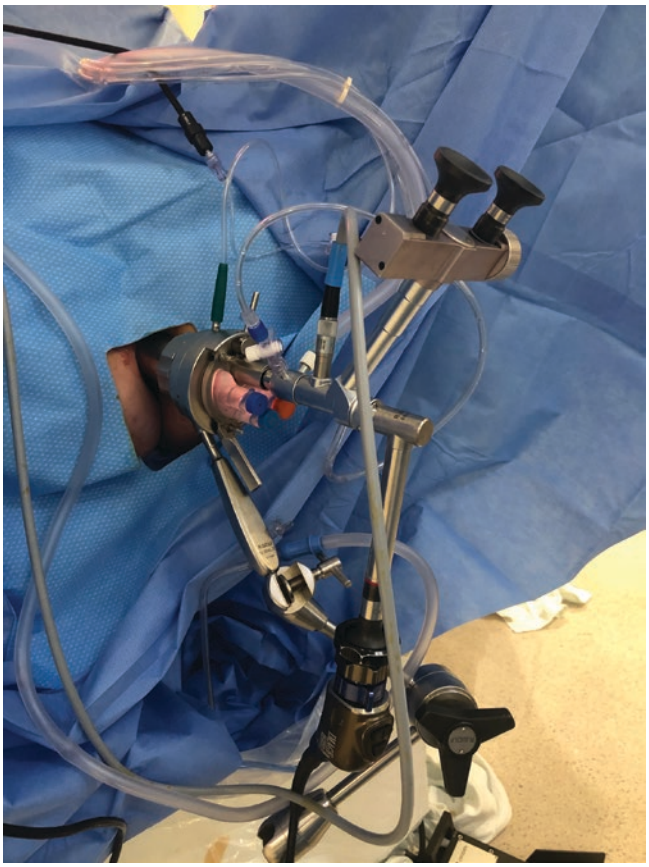

Fig. 27.2 Transanal endoscopic microsurgery device

Transanal Minimally Invasive Surgery (TAMIS)

TAMIS was first introduced in 2009 as an alternative to TEM, offering similar visibility and versatility but at a significant cost advantage [5]. Dissection can be performed in multiple quadrants, and there are fewer restrictions on patient positioning. This technique uses a flexible, disposable single-port minimally invasive platform placed transanally. Laparoscopic insufflation, camera, and tools are utilized. Dissection occurs in a similar fashion to TEM. Insufflation occurs and the tumor marking occurs in a similar way using cautery (Fig. 27.3). Closure of the defect occurs with varying techniques [42]. If the tumor is near the top of the anal sphincter, a hybrid approach using TAMIS and transanal approaches may be necessary. As noted above for TEM, if intraperitoneal entry occurs or is suspected during a TAMIS procedure, laparoscopic assistance may be necessary for closure of the defect and to perform pneumatic leak testing, as one would perform following colorectal anastomosis.

Complications

Each of the described techniques for local excision of early distal rectal cancers has limitations: incomplete resection, conversion to an alternative approach, or the need for staged

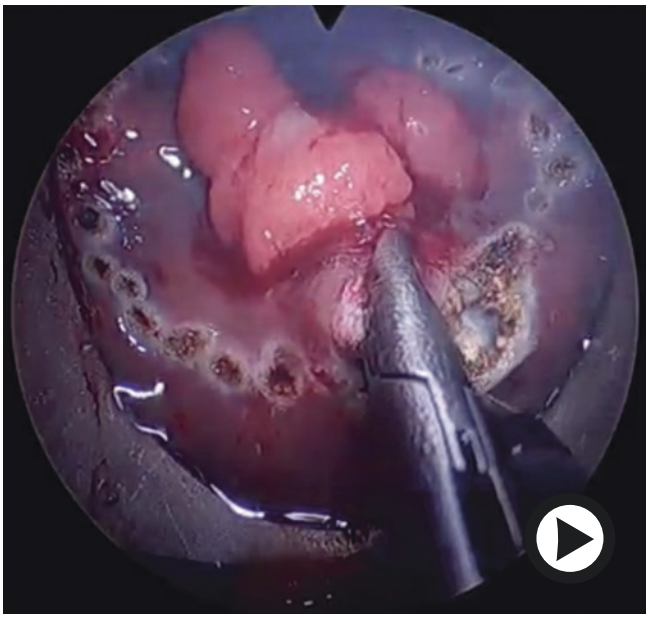

Fig. 27.3 Insufflation occurs and the tumor marking occurs in a similar way using cautery. https://doi.org/10.1007/000-33e

procedures to name a few. These events are more likely to occur if the tumor is too bulky or if the working environment/space is too tight, incomplete visualization of the entire tumor due to a fold, uncontrolled bleeding occurs, or poor bowel preparation.

Overall, the complication rate for local excision, regardless of the technical approach, is lower than for radical surgery [9, 43]. Common complications after local excision include urinary retention/urinary tract infections, bleeding, and other gastrointestinal complaints. Uncommon complications include wound infections, thromboembolic events, rectal strictures, or rectovaginal fistulas [9]. The most common complication with local excision is postsurgical urinary retention. This can occur up to 5% of patients and secondary to pressure on the urethra, anal stretch, edema, and pain [44]. This is usually self-limited and treated by either self-catheterization or placement of an indwelling catheter.

Postoperative bleeding can also occur up to 5% and tends to occur several days post-op and usually corresponds to a suture line dehiscence if the wound was closed, sloughing of any scab formation, or anticoagulation medication. Minor bleeding can oftentimes be self-limited, but frank hemorrhage warrants resuscitation, endoscopic evaluation, and treatment. After stabilization, it can usually be addressed with monopolar cautery, sutures, and/or epinephrine injection. Major intraoperative bleeding, however, is a rare event.

Pelvic abscess can also occur. It is unclear whether abscess is more frequent when an extraperitoneal defect is left open versus closed, and this is the subject of much debate. Tumors that cause a defect breaching the peritoneum necessitate closure, but there is conflicting evidence for those lesions located in the extraperitoneal rectum that do not vio-

late the peritoneal cavity. A single randomized trial showed no difference in early or late complications and determined that there is no difference in the approach to the open wound [45]. However, there were only 44 patients randomized, and the study may have been underpowered to detect a true difference. Other observational studies have equivocal outcomes. Some surgeons favor defect closure; others favor leaving the defect open [46–48]. A recent multi-institutional matched analysis at a high-volume center consisting of 991 eligible patients found no difference in 30-day postoperative morbidity in those undergoing closure of the defect versus leaving the defect open after local excision [49]. Thus, the management of the rectal wall defect after local excision is at the surgeon's discretion.

Oncologic Results

Local excision is an acceptable oncologic treatment strategy for patients with T1 rectal cancers, and local excision with chemoradiation treatment has gained some interest and can be an acceptable oncologic treatment for certain patients with T2 distal rectal cancers.

T1 Cancer

Approximately 15% of rectal cancers present at stage I. Since the first report of local excision as an acceptable alternative to radical resection, local excision without additional therapy has been offered as a treatment alternative for early distal T1 tumors [6]. This oncologic approach can be a viable option in appropriately selected patients with favorable clinical and histological features. Local excision can also be viewed as a palliative treatment for patients with more advanced disease who are medically unfit for radical surgery. The main drawback of local excision as curative therapy is the inability to excise and accurately stage mesorectal lymph nodes. T1 rectal tumors have a 6–11% risk of nodal metastasis overall, pending additional histologic information [38].

Criteria for local excision include well to moderately differentiated T1 cancer, the absence of lymphovascular or perineural invasion, and tumors less than 3 cm in diameter occupying less than one-third of the circumference of the bowel lumen [38]. In order to achieve a good oncologic outcome, optimal surgical technique is imperative. It has been shown that a positive margin following local excision of a T1 rectal cancer is associated with a higher risk of recurrence and concomitant lower 5-year overall survival [9, 50]. Hopefully, advancements and improvements in surgical techniques will greatly improve the rates of en bloc resection with negative margins in rectal cancer patients treated with local excision. As noted previously, this has been a substantial problem in prior trials of local excision. Even using more modern techniques, achieving negative margins can be challenging. Prospectively collected data from a 21-center collaborative in the United Kingdom regarding 424 patients undergoing TEM +/− adjuvant/neoadjuvant radiotherapy revealed that positive margins were found in 11%, 23%, and 42% of patients with pT1, pT2, and pT3 tumors.

Data from that same report revealed that local recurrence rates following local excision by TEM in patients with T1 rectal cancer were 10%, 13%, and 19% at years 2, 3, and 5 [51]. Local recurrence was found to be associated with three histopathologic factors: depth of invasion, tumor maximum diameter, and lymphovascular invasion. For favorable tumors (no lymphovascular invasion, SM1), local recurrence rates ranged from 3% to 8% depending on tumor size. The rates of local recurrence were found to be 18–42% for unfavorable tumors (lymphovascular invasion positivity, SM2–3).

Junginger et al. published their long-term oncologic outcomes for T1 rectal cancers after local excision [52]. Median follow-up was 8.6 years. Low-risk tumors compared with high-risk tumors had 5- and 10-year local recurrence rates of 7% and 12% versus 32% and 35%, respectively. In addition, the 5- and 10-year cancer-specific survival rates for low-risk patients were 98% and 91% compared with high-risk patients at 84.3% and 74.3% ($p = 0.05$). These studies have shown that to minimize the risk of local recurrence, it is advisable to limit local excision to T1 rectal cancers with favorable histology as mentioned previously [17, 25, 28].

T2 Cancer

Traditionally, the substantial rates of metastatic nodal disease associated with T2 rectal cancers have swayed most surgeons from treating T2 rectal cancers with local excision alone as this approach can lead to local recurrence rates of 10–66% [51]. High rates of local failure and compromise in survival outcomes have been shown, with 5-year local recurrence rates of 47% in patients undergoing local excision alone compared to 6% with proctectomy and overall survival of 65% versus 81%, respectively [53]. Despite these sobering numbers, there has been increasing emphasis on organ preservation techniques, and some surgeons have recommended expanding the indications for local excision to include some T2 rectal cancers.

Data and evidence from the Surveillance, Epidemiology, and End Results program reveal that more than 20% of patients with T2 cancer are being treated by local excision, although those treated with local excision alone had a suboptimal overall survival [54]. In an attempt to improve outcomes following local excision for T2 tumors, recent clinical trials have evaluated local excision combined with neoadjuvant or adjuvant treatment with the hope of improving outcomes and expanding eligibility for organ-sparing surgery.

Local Excision and Adjuvant Therapy

The Cancer and Leukemia Group B 8984 trial (CALGB 8984) compared oncologic outcomes in patients with T1 rectal cancer treated with local excision alone and T2 rectal cancer treated with local excision followed by adjuvant chemoradiotherapy [50]. They found that despite adjuvant therapy, the T2 group experienced worse 10-year overall survival and disease-free survival and were at higher risk of local recurrence (18% vs. 8%). A meta- analysis of oncologic outcomes for patients with T1 or T2 rectal cancers undergoing local excision followed by either adjuvant chemoradiotherapy or completion surgery included 14 studies [55]. It was found that, among patients originally undergoing local excision for T2 tumors, local recurrence occurred in 15% (range: 11–21%) of patients treated with adjuvant chemoradiation and 10% (range: 4–22%) of patients treated with completion proctectomy.

A systematic review by Cutting et al. found local recurrence rates of 6% for T1, 14% for T2, and 34% for T3 rectal cancers [56]. These studies suggest that adjuvant therapy after local excision for T2 or greater rectal cancers is inferior to radical surgery but better than local excision alone.

Neoadjuvant Therapy and Local Excision

Traditionally, locally advanced rectal cancer was treated with chemoradiotherapy followed by radical surgery with the benefit of tumor downsizing and improvement in local recurrence rates in large randomized controlled trials [57, 58]. It has been shown that up to 30% of patients will experience a complete pathologic response after neoadjuvant chemoradiation [59]. In the hope that occult tumor in mesorectal nodes could be sterilized with neoadjuvant chemoradiotherapy, some surgeons explored the concept of local excision following neoadjuvant therapy in select patients.

The American College of Surgeons Oncology Group Z6041 study was a phase II trial by Garcia-Aguilar et al. with a single arm of 84 patients with T2 rectal cancer that were treated with neoadjuvant chemoradiation and local excision [60]. Downstaging occurred in 64% of patients. Lezoche et al. compared local excision with laparoscopic proctectomy in a randomized controlled trial [61]. All patients had an R0 resection, and local recurrence rates were similar for the local excision and proctectomy groups, 8% versus 6%, respectively. The cancer-related survival rate was 89% for local excision and 94% for proctectomy ($p = 0.609$).

Another randomized controlled trial, GRECCAR 2, published in 2017 by Rullier et al. investigated patients with cT2–3 rectal cancer treated with neoadjuvant chemoradiation and then randomized to either local excision or radical surgery [62]. In a total of 145 patients, there were no statistically significant differences in oncologic outcomes between the groups, and 3-year local recurrence rates were similar for the local excision group and the proctectomy group (6% vs. 3%, $p = 0.63$). Overall survival rates were 89% and 95% respectively ($p = 0.40$). Only 8% of patients treated by completion radical surgery had nodal involvement, suggesting that radical surgery may have been unnecessary for most of them.

The recently published CARTS study investigated oncologic and functional outcomes of patients with T1–3 rectal cancers treated with neoadjuvant chemoradiation followed by local excision [63]. Of those patients recruited, 35 patients underwent local excision, and 16 patients underwent radical resection. Results showed a 5-year local recurrence rate of 8%, with 5-year disease-free survival and overall survival rates of 82% and 83%, respectively. These reports suggest that local excision after completion of chemoradiation may be an option in selected patients.

One of the major downsides of local excision following neoadjuvant radiotherapy is the problem of wound healing, as it is not uncommon for the rectal wall closure to break down in the radiated field. There is also the question as to whether local excision is even necessary in complete clinical responders (see Chap. 28). Local excision would only be helpful if there were viable tumor remaining in the rectal wall, but not in the mesorectal nodes. If there is no remaining tumor in either location, or in both locations, then local excision would not be anticipated to be of benefit to the patient.

Quality of Life

One of the goals of organ preservation with local excision is better functional outcomes with a better quality of life. Although resection of the rectal wall can have functional consequences, several studies have shown that those patients with early rectal cancers who undergo local excision compared with those who undergo radical resection have a better quality of life and better bowel function overall [64]. Pucciarelli et al. found that anorectal function 1 year after local excision with neoadjuvant chemoradiation had minimal impact on function and overall quality of life [65, 66]. As reported in the CARTS study, health-related quality of life was equal to that at baseline, with improved emotional well-being for patients treated with local excision compared to radical surgery [63].

Salvage Surgery

Population-based studies have shown that the treatment of early distal rectal cancers by various local excision techniques has more than doubled over the last two decades [9, 54]. This is likely due to advancements in local excision sur-

gical platforms, patient preference, and publication of outcome data. The increase in the use of local excision techniques for early stage rectal cancer relies on the desire for sphincter preservation and maintaining bowel continuity if the risk of lymph node metastasis is low. Local recurrence is the most common pattern of failure, ranging from 20% to 30% [43, 51, 67–70]. When patients develop a local recurrence, what surgical options are available and what are the prognosis and long-term oncologic outcomes?

Bikhchandani et al. reported an R0 resection rate of 93% on 27 patients who underwent multimodal salvage surgery for local recurrence of rectal cancer after local excision [71]. The 5-year recurrence-free survival rate was 47%, and the 5-year overall survival rate was 50%. The majority of re-recurrences were distant metastases. The long-term survival rates were disappointing and grim compared with published rates of 92–97% disease-free survival at 5 years after radical surgery for early rectal cancer [9]. This was consistent with other previously published studies that found that salvage resection for recurrence after local excision is associated with only modest success [72, 73].

You et al. performed extended resections for patients suffering local failure after local excision, with an R0 resection rate of only 80% [72]. With a median follow-up of 33 months, 3-year re-recurrence-free survival was 43%, and 5-year overall survival was 63%. Friel et al. reported outcomes following salvage surgery for recurrence after local excision and found that the results were inferior to those of initial radical treatment [74]. They stressed the importance of appropriate patient selection for local excision and cautioned against assuming that salvage surgery would be successful for patients with local failure.

The practice of local excision seems to exchange the increased risk of disease recurrence for the benefit of improved function and sphincter preservation. It is imperative to counsel patients regarding the oncologic risks of local excision and explain that salvage therapy is not always associated with good outcome.

Conclusion

Local excision alone can be offered to patients with early T1 rectal cancers in the absence of adverse histopathologic features, such as poor differentiation, lymphovascular invasion, tumor budding, or close margins. Patients with low-risk T2 tumor should be considered for local excision only in the context of palliative intent or enrolment in a clinical trial. Patients with T3 tumors should only undergo local excision as palliation (usually for bleeding). Salvage surgery for local recurrence in those treated initially by local excision is possible in some patients, but oncologic results appear to be inferior to those that would be obtained by proctectomy at initial diagnosis. All patients managed with organ preservation usually undergo intensive posttreatment multimodality surveillance, as it is assumed (but not proven) that identifying local failure early will lead to improved outcomes (See Chap. 30).

References

1. Corman ML. Jacques Lisfranc 1790-1847. Dis Colon Rectum. 1983;26(10):694–5.
2. Parks AG. A technique for excising extensive villous papillomatous change in the lower rectum. Proc R Soc Med. 1968;61(5):441–2.
3. Althumairi AA, Gearhart SL. Local excision for early rectal cancer: transanal endoscopic microsurgery and beyond. J Gastrointest Oncol. 2015;6(3):296–306.
4. Buess G, Hutterer F, Theiss J, Bobel M, Isselhard W, Pichlmaier H. A system for a transanal endoscopic rectum operation. Chirurg. 1984;55(10):677–80.
5. Atallah S, Albert M, Larach S. Transanal minimally invasive surgery: a giant leap forward. Surg Endosc. 2010;24(9):2200–5.
6. Morson BC, Bussey HJR, Samoorian S. Policy of local excision for early cancer of the colorectum. Gut. 1977;18:1045–50.
7. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery-the clue to pelvic recurrence? Br J Surg. 1982;69:613–6.
8. Peters KC, can de Velde CJ, Leer JW, Martin H, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer; increased bowel dysfunction in irradiated patients-a Dutch colorectal cancer group study. J Clin Oncol. 2005;23:6199–206.
9. You YN, Baxter NN, Stewart A, et al. Is the increasing rate of local excision for stage I rectal cancer in the United States justified? Ann Surg. 2007;245:726–33.
10. Moreno CC, Sullivan PS, Mittal PK. MRI evaluation of rectal cancer: staging and restaging. Curr Probl Diagn Radiol. 2017;46(3):234–41.
11. Tang Y, Shengxiang R, Yang C, Yabin H, et al. Value of MRI morphologic features with pT1-2 rectal cancer in determining lymph node metastasis. J Surg Oncol. 2018;118(3):544–50.
12. Bhangu A, Brown G, Nicholls RJ, Wong J, et al. Survival outcome of local excision versus radical resection of colon or rectal carcinoma: a Surveillance, Epidemiology, and End Results (SEER) population-based study. Ann Surg. 2013;258(4):563–9.
13. Kidane B, Chadi SA, Kanters S, Colquhoun PH, et al. Local resection compared with radical resection in the treatment of T1N0M0 rectal adenocarcinoma: a systematic review and meta-analysis. Dis Colon Rectum. 2015;58(1):122–40.
14. Lu JY, Lin GL, Qiu HZ, Xiao Y, et al. Comparison of transanal endoscopic microsurgery and total mesorectal excision in the treatment of T1 rectal cancer: a meta-analysis. PLoS One. 2015;10(10):e0141427.
15. Brunner W, Widmann B, Marti L, et al. Predictors for regional lymph node metastasis in T1 rectal cancer: a population-based SEER analysis. Surg Endosc. 2016;30:4405–15.
16. Chang HC, Huang SC, Chen JS, Tang R, et al. Risk factors for lymph node metastasis in pT1 and pT2 rectal cancer: a single-institute experience in 943 patients and literature review. Ann Surg Oncol. 2012;19(8):2477–84.
17. Monson JR, Weiser MR, Buie WD, Change GJ, et al., Standards Practice Task Force of the American Society of Colon and Rectal Surgeons. Practice parameters for the management of rectal cancer (revised). Dis Colon Rectum. 2013;56:535–50.
18. Kikuchi R, Takano M, Takagi K, Fujimoto N, et al. Management of early invasive colorectal cancer. Risk of recurrence and clinical guidelines. Dis Colon Rectum. 1995;38:1286–95.
19. Kitajima K, Fujimori T, Fujii S, et al. Correlations between lymph node metastasis and depth of submucosal invasion in submucosal

invasive colorectal carcinoma: a Japanese collaborative study. J Gastroenterol. 2004;39:534–43.
20. Kudo S. Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. Endoscopy. 1993;25:455–61.
21. Nascimbeni R, Burgart LJ, Nivatvongs S, Larson DR. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. Dis Colon Rectum. 2002;45:200–6.
22. Saraste D, Gunnarsson U, Janson M. Predicting lymph node metastases in early rectal cancer. Eur J Cancer. 2013;49(5):1104–8.
23. Beaton C, Twine CP, Williams GI, Radcliffe AG. Systematic review and meta-analysis of histopathological factors influencing the risk of lymph node metastasis in early colorectal cancer. Color Dis. 2013;15:788–97.
24. Anannamcharoen S, Boonya-Ussadol C. Identification of patients with high-risk for pulmonary metastasis after curative resection for colorectal cancer. J Med Assoc Thai. 2012;95:86–91.
25. Hogan MB, Chang KH, Duff G, Samaha MB, et al. Lymphovascular invasion: a comprehensive appraisal in colon and rectal adenocarcinoma. Dis Colon Rectum. 2015;58(6):547–55.
26. Rasheed S, Bowley DM, Aziz O, Tekkis PP, et al. Can depth of tumour invasion predict lymph node positivity in patients undergoing resection for early rectal cancer? A comparative study between T1 and T2 cancers. Color Dis. 2008;10(3):231–8.
27. Kobayashi H, Mochizuki H, Kato T, Mori T, et al. Is total mesorectal excision always necessary for T1-T2 lower rectal cancer? Ann Surg Oncol. 2010;17(4):973–80.
28. Bosch SL, Teerenstra S, de Wilt JH, Cunningham C, et al. Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. Endoscopy. 2013;45(10):827–34.
29. Hase K, Shatney C, Johnson D, Trollope M, et al. Prognostic value of tumor "budding" in patients with colorectal cancer. Dis Colon Rectum. 1993;36(7):627–35.
30. Okuyama T, Oya M, Ishikawa H. Budding as a risk factor for lymph node metastasis in pT1 or pT2 well-differentiated colorectal adenocarcinoma. Dis Colon Rectum. 2002;45(5):628–34.
31. Masaki T, Sugiyama M, Atomi Y, Matsuoka H, et al. The indication of local excision for T2 rectal carcinomas. Am J Surg. 2001;181(2):133–7.
32. Glasgow SC, Bleier JI, Burgart LJ, Finne CO, et al. Meta-analysis of histopathological features of primary colorectal cancers that predict lymph node metastases. J Gastrointest Surg. 2012;16(5):1019–28.
33. Lugli A, Kirsch R, Ajioka Y, Bosman F, et al. Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Mod Pathol. 2017;30(9):1299–311.
34. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicenter, randomized trial. Lancet. 2009;373:811–20.
35. Scheele J, Lemke J, Meier M, Sander S, et al. Quality of life after sphincter-preserving rectal cancer resection. Clin Colorectal Cancer. 2015;14:33–40.
36. Hendren SK, O'Connor BL, Liu M, Asano T, et al. Prevalence of male and female sexual dysfunction is high following surgery for rectal cancer. Ann Surg. 2005;242:212–23.
37. Emmertsen KJ, Laurberg S, Rectal Cancer Function Study G. Impact of bowel dysfunction on quality of life after sphincter-preserving resection for rectal cancer. Br J Surg. 2013;100:1377–87.
38. Garcia-Aguilar J, Mellgren A, Sirivongs P, Buie D, et al. Local excision of rectal cancer without adjuvant therapy: a word of caution. Ann Surg. 2000;231:245–51.
39. Gopaul D, Belliveau P, Vuong T, Trudel J, et al. Outcome of local excision of rectal carcinoma. Dis Colon Rectum. 2004;47:1780–8.
40. Lawrence L, Kelly J, Nassif G, Atallah S, et al. Chemoradiation and local excision for T2N0 rectal cancer offers equivalent overall survival compared to standard resection: a national cancer database analysis. J Gastrointest Surg. 2017;21:1666–74.
41. Melnitchouk N, Fields A, Lu P, Scully RE, et al. Local versus radical excision of early distal rectal cancers: a national cancer database analysis. Ann Surg Oncol. 2020;27(7):2169–76.
42. Albert MR, Atallah SB, de Beche-Adams TC, Izfar S, et al. Transanal minimally invasive surgery (TAMIS) for local excision of benign neoplasms and early-stage rectal cancer: efficacy and outcomes in the first 50 patients. Dis Colon Rectum. 2013;56(3):301–7.
43. You N. Local excision: is it an adequate substitute for radical resection in T1/T2 patients? Semin Radiat Oncol. 2011;21(3):178–84.
44. O'Neill CH, Platz J, Moore JS, Callas PW, et al. Transanal endoscopic microsurgery for early rectal cancer: a single-center experience. Dis Colon Rectum. 2017;60(2):152–60.
45. Ramirez JM, Aquilella V, Arribas D, Martinez M. Transanal full-thickness excision of rectal tumours: should the defect be sutured? A randomized controlled trial. Color Dis. 2002;4(1):51–5.
46. Brown C, Raval MJ, Phang PT, Karimuddin AA. The surgical defect after transanal endoscopic microsurgery: open versus closed management. Surg Endosc. 2017;31(3):1078–82.
47. Noura S, Ohue M, Miyoshi N, Yasui M. Significance of defect closure following transanal local full-thickness excision of rectal malignant tumors. Mol Clin Oncol. 2016;5(4):449–54.
48. Hahnloser D, Cantero R, Salqado G, Dindo D, et al. Transanal minimal invasive surgery for rectal lesions: should the defect be closed? Color Dis. 2015;17(5):397–402.
49. Lee L, Althoff A, Edwards K, Albert MR, Atallah SB, et al. Outcomes of closed versus open defects after local excision of rectal neoplasms: a multi-institutional matched analysis. Dis Colon Rectum. 2018;61(2):172–8.
50. Greenberg JA, Shibata D, Herndon JE, Steele GD, et al. Local excision of distal rectal cancer: an update of cancer and leukemia group B 8984. Dis Colon Rectum. 2008;51(8):1185–91.
51. Bach SP, Hill J, Monson JR, et al. A predictive model for local recurrence after transanal endoscopic microsurgery for rectal cancer. Br J Surg. 2009;96:280–90.
52. Junginger T, Goenner U, Hitzler M, et al. Long-term oncologic outcome after transanal endoscopic microsurgery for rectal carcinoma. Dis Colon Rectum. 2016;59:8–15.
53. Mellgren A, Sirivongs P, Rothenberger DA, et al. Is local excision adequate therapy for early rectal cancer? Dis Colon Rectum. 2000;47:1773–9.
54. Stitzenberg KB, Sanoff HK, Penn DC, Meyers MO, Tepper JE. Practice patterns and long-term survival for early-stage rectal cancer. J Clin Oncol. 2013;31:4276–82.
55. Borstlap WA, Coeymans TJ, Tanis PJ, et al. Meta-analysis of oncological outcomes after local excision of pT1–2 rectal cancer requiring adjuvant (chemo)radiotherapy or completion surgery: oncological outcomes after local excision of rectal cancer. Br J Surg. 2016;103:1105–16.
56. Cutting JE, Hallam SE, Thomas MG, Messenger DE. A systematic review of local excision followed by adjuvant therapy in early rectal cancer: are pT1 tumors the limit? Color Dis. 2018;20:854–63.
57. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al., on behalf of the Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345:638–46.
58. Sauer R, Becker H, Hohenberger W et al., on behalf of the German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351:1731–40.
59. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy. Ann Surg. 2004;240:711–7.

60. Garcia-Aguilar J, Renfro LA, Chow OS, et al. Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial. Lancet Oncol. 2015;16:1537–46.
61. Lezoche E, Baldarelli M, Lezoche G, Paganini AM, Gesuita R, Guerrieri M. Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy. Br J Surg. 2012;99:1211–8.
62. Rullier E, Rouanet P, Tuech JJ, et al. Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial. Lancet. 2017;390:469–79.
63. Stijns RCH, de Graaf EJR, Punt CJA, et al. Long-term oncological and functional outcomes of chemoradiotherapy followed by organ-sparing transanal endoscopic microsurgery for distal rectal cancer: the CARTS study. JAMA Surg. 2019;154:47–54.
64. Pucciarelli S, Giandomenico F, De Paoli A, Gavaruzzi T, et al. Bowel function and quality of life after local excision or total mesorectal excision following chemoradiotherapy for rectal cancer. Br J Surg. 2017;104(1):138–47.
65. Lynn PB, Renfro LA, Carrero XW, Shi Q, et al. Anorectal function and quality of life in patients with early stage rectal cancer treated with chemoradiation and local excision. Dis Colon Rectum. 2017;60(5):459–68.
66. Halverson AL, Morris AM, Cleary RK, Chang GJ. For patients with early rectal cancer, does local excision have an impact on recurrence, survival, and quality of life relative to radical resection? Ann Surg Oncol. 2019;26(8):2497–506.
67. Nash GM, Weiser MR, Guillem JG, et al. Long-term survival after transanal excision of T1 rectal cancer. Dis Colon Rectum. 2009;52:577–82.
68. Madbouly KM, Remzi FH, Erkek BA, et al. Recurrence after transanal excision of T1 rectal cancer: should we be concerned? Dis Colon Rectum. 2005;48:711–9.
69. Bentrem DJ, Okabe S, Wong WD, et al. T1 adenocarcinoma of the rectum: transanal excision or radical surgery? Ann Surg. 2005;242:472–7.
70. Paty PB, Nash GM, Baron P, et al. Long-term results of local excision for rectal cancer. Ann Surg. 2002;236:522–9.
71. Bikhchandani J, Ong GK, Dozois EJ, Mathis KL. Outcomes of salvage surgery for cure in patients with locally recurrent disease after local excision of rectal cancer. Dis Colon Rectum. 2015;58(3):283–7.
72. You YN, Roses RE, Chang GJ, Rodriquez-Bigas MA, et al. Multimodality salvage of recurrent disease after local excision for rectal cancer. Dis Colon Rectum. 2012;55(12):1213–9.
73. Weiser MR, Landmann RG, Wong WD, et al. Surgical salvage of recurrent rectal cancer after transanal excision. Dis Colon Rectum. 2005;48:1169–75.
74. Friel CM, Cromwell JW, Marra C, Madoff RD, et al. Salvage radical surgery after failed local excision for early rectal cancer. Dis Colon Rectum. 2002;45(7):875–9.

Rectal Cancer: Nonoperative Management

28

Julio Garcia-Aguilar and Rodrigo Oliva Perez

Key Concepts

- A proportion of patients with rectal cancer managed by neoadjuvant chemoradiation may achieve complete disappearance of the primary tumor (complete clinical response) during assessment of response after treatment completion.
- Establishing a complete clinical response requires the combination of clinical, endoscopic, and radiological findings consistent with the absence of residual cancer at the site of the original cancer.
- Patients that achieve a complete clinical response have been considered for organ preservation strategy with strict surveillance and no immediate surgery (Watch and Wait) to avoid the potential morbidity, mortality, requirement for stomas, and functional consequences of a proctectomy.
- Patients that achieve a complete clinical response and are managed by the Watch and Wait strategy have a 25% risk for developing local regrowth of the primary tumor.
- The majority of local regrowths are amenable to successful salvage proctectomy with negative resection margins (R0).
- Patients that achieve a cCR and are managed by Watch and Wait have similar overall survival rates when compared to patients with pCR managed by radical proctectomy. Disease-free survival rates are superior for patients undergoing radical proctectomy due to the 25% risk of local regrowth following WW requiring salvage proctectomy.
- Functional outcomes and quality of life appear to be improved among patients with complete clinical response managed by Watch and Wait when compared to proctectomy.

Introduction

The introduction of neoadjuvant therapy has led to significant changes in the management of rectal cancer. The observation of a variable degree of tumor response to neoadjuvant therapy has challenged the previously standard practice of proctectomy and has prompted the introduction of new treatment algorithms. The assessment of tumor response after neoadjuvant therapy, previously considered unnecessary, is now an integral part of contemporary rectal cancer management algorithms. Patients found to have clinical, endoscopic, and radiological evidence of complete disappearance of the primary tumor are considered candidates for deferral of surgery and active surveillance, with the ultimate goal of achieving sustained organ preservation, a strategy known as Watch and Wait (WW). In this chapter we will review rectal cancer management with an emphasis on baseline staging, neoadjuvant treatment regimens, timing and methods for assessment of tumor response, and surveillance protocols relevant for the effective and safe implementation of WW strategies that will result in optimal organ preservation. We will also provide an overview of the evidence supporting the WW strategy for rectal cancer patients who achieve a clinical complete response to neoadjuvant therapy.

Terminology and Definitions

Organ preservation strategies in the management of rectal cancer require new terms and definitions.

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The final histologic stage of the tumor after neoadjuvant therapy should follow the nomenclature of the AJCC/IUCC TNM classification [1]. ypT0 indicates no residual tumor in the bowel wall in the primary tumor bed (within the rectal wall), whereas ypN0 means negative nodes in the mesorectum when part of the surgical specimen. The term pathologic complete response (pCR) should be reserved for ypT0N0 tumors in patients who had a proctectomy or for ypT0 tumors after a full-thickness local excision (LE) without radiological evidence of mesorectal positive nodes or deposits.

Patients without evidence of tumor on clinical, endoscopic, and radiological exams are considered to have a clinical complete response (cCR) [2]. The key to determining whether a WW strategy will likely be successful is based on the assumption that cCR after neoadjuvant therapy correlates with pCR after proctectomy [3].

The goal of the WW strategy is to identify patients who have no residual disease in the bowel wall after neoadjuvant therapy who can avoid surgery and preserve the rectum [4]. Therefore, the term Watch and Wait was originally used exclusively for patients *who achieved a cCR and were offered no immediate surgery with strict and close surveillance* [4]. This means that achieving a cCR is a prerequisite for entering a WW program.

Considering the lack of a "perfect" correlation between cCR and pCR, some patients with a cCR entering a WW program are at risk of local regrowth during follow-up [5]. The reappearance of the tumor in the rectal wall or in the regional lymph nodes after an apparent cCR is called local regrowth [6]. Regrowths occur more often in the bowel wall compared to the regional lymph nodes and therefore are more easily detected by digital rectal examination (DRE) and/or flexible sigmoidoscopy. Most local regrowths are potentially salvageable by surgery [7–12]. Any tumor reappearance in the pelvis after a curative-intent surgery is considered "local recurrence." Distant metastases can occur in patients with a sustained cCR but are more frequent in patients with tumor regrowth.

Historically, most rectal cancer patients entered in a WW protocol had received standard long-course chemoradiation therapy (CRT) [4, 12, 13]. As treatment strategies evolved over time, systemic chemotherapy was progressively added to standard neoadjuvant CRT regimens. Chemotherapy that is given before CRT is called *induction chemotherapy*, and chemotherapy given during and after CRT (before surgery) is called *consolidation chemotherapy* [14–17]. The full regimen of induction or consolidation chemotherapy (eight cycles of FOLFOX [leucovorin, fluorouracil, oxaliplatin] or five cycles of CapeOX [capecitabine, oxaliplatin]) in combination with CRT is called *total neoadjuvant therapy* [18].

Radiation therapy delivery has also evolved over time. Originally, most treatment regimens included external beam radiotherapy (EBRT), with or without intensity modulation techniques (IMRT). In addition to the mode of delivery, fractionation of doses may encompass two different regimens: long-course with hyperfractionation or short-course with hypofractionation. Even though a detailed description of these different approaches is beyond the scope of this chapter, suffice to say that both regimens may result in pCR and/or cCR [19, 20]. In an attempt to increase the total dose of radiation delivery, techniques have been developed to provide maximal dose (dose escalation) with minimal toxicity. Therefore, additional doses (boosts) to the primary tumor may be delivered by EBRT, endorectal high-dose-rate brachytherapy (HDBRT) or contact radiation (Papillon technique) [16, 17, 21, 22].

Rationale

The possibility of a permanent stoma has always been one of the main concerns of patients diagnosed with rectal cancer. Even though patients' perspectives may vary across different geographical areas and cultures, a permanent end-colostomy impacts body image and impairs quality of life [23]. The concept of avoiding surgery in rectal cancer patients treated with neoadjuvant chemoradiation was driven by the observation of pCR in patients treated with abdominal-perineal resection (APR) with permanent colostomy [4]. Following similar observations from anal cancer treatment, where patients with complete tumor regression after neoadjuvant chemoradiation (nCRT) avoided radical surgery with surprisingly favorable oncological outcomes, initial attempts were made to identify rectal cancer patients who had achieved a pCR, by means of clinical, endoscopic, and radiological examination [24]. However, most rectal cancer patients have more surgical options than anal cancer patients, for whom APR is the main radical surgical alternative. Depending on tumor stage, anatomy, and relation to the anal sphincter complex, many rectal cancer patients are candidates for sphincter preserving procedures. Although avoiding a permanent stoma, restorative proctectomy is often associated with significant bowel dysfunction, particularly worsened by previous exposure to ionizing radiation to the pelvis. A sizeable fraction of patients who undergo a restorative procedure with their temporary diverting stoma reversed are left with variable degrees of fecal incontinence and a constellation of symptoms known as "low anterior resection syndrome," some requiring conversion to a permanent stoma or creation of cecostomy/appendicostomy for anterograde colon lavage [25–27]. In addition, proctectomy, with or without sphincter preservation, has significant consequences in terms of sexual and urinary function [28, 29].

Despite recent advances in minimally invasive approaches to the surgical management of rectal cancer, proctectomy is also associated with immediate postoperative morbidity and mortality [30]. One of the main drivers of postoperative mor-

bidity among these patients is the risk of postoperative anastomotic leak. Prospective randomized clinical trials have shown the benefits of diverting stomas in decreasing the risk of clinically relevant leaks and the need for urgent reoperations among these patients [31]. However, the creation of a diverting stoma often results in direct morbidity associated with high-output syndromes (with ileostomy) and with subsequent stoma reversal [32]. Altogether, avoidance of potentially unnecessary proctectomy among patients with complete tumor regression after nCRT could have the potential benefits of sparing patients from the need of a permanent or temporary stoma, risk of immediate and late morbidity, chance of postoperative mortality, and negative functional consequences in bowel, urinary, and sexual functions [30–35]. In addition, patients undergoing proctectomy for rectal cancer will have potentially significant long-term financial and social burdens beyond the clinical aspects of the disease and its treatment. These patients will need resources to finance surgical treatment as well as its potential complications, the cost of supplies for the stoma, and assistance dealing with the impact of proctectomy on the activities of daily living and professional life [36].

Primary Tumor Assessment and Selection Criteria

Baseline tumor assessment for patients being considered for organ preservation is of paramount importance and is based primarily on clinical findings of DRE, endoscopic features, and radiological imaging. Neoadjuvant therapy should only be instituted after these studies are complete, and confirmatory biopsies of adenocarcinoma have been obtained and properly documented.

Accidental Versus Intentional WW

The occasional eradication of rectal cancer by radiation therapy has been known for decades. Attempts to cure rectal cancer with radiation alone were popular at the beginning of the twentieth century, when the mortality and morbidity of rectal cancer surgery were prohibitive [37]. The difficulty in identifying patients with a true complete response and increased safety of surgery ultimately led to the abandonment of the idea of treating cancer with radiation alone. Over the years, some surgeons have omitted surgery in some patients with an apparent complete or near-complete response because of advanced age, high surgical risk from comorbid conditions, or patient refusal of a permanent stoma. This "accidental" approach to WW, still the only one accepted at many institutions, should be distinguished from the systematic or "intentional" approach, in which patients with distal rectal cancer likely requiring restorative proctectomy with low colorectal anastomosis or non-restorative proctectomy with permanent colostomy are treated with optimal neoadjuvant therapy, restaged, and selectively entered in a WW protocol with the intention of achieving permanent organ preservation [38]. Chances of achieving a cCR are now anticipated, and consideration of WW is discussed prior to treatment with nCRT. The intentional WW approach is relatively straightforward in patients with locally advanced rectal cancer requiring nCRT before proctectomy for oncological purposes. However, patients with less advanced disease, not necessarily requiring nCRT before proctectomy for oncological reasons, may also be considered for WW and undergo nCRT for the primary purpose of achieving a cCR [38].

Baseline Stage

Baseline tumor stage is an important predictor of tumor response to nCRT. In general, more advanced tumors are less likely to completely respond to nCRT compared to early-stage tumors. Therefore, clinical stage has potential implications for the selection of patients for WW. Current guidelines recommend nCRT for patients with locally advanced tumors that have baseline features indicative of high risk of local recurrence following proctectomy alone [39]. A distance of the primary tumor to the mesorectal fascia of ≤1 mm (mrCRM≤1 mm including T3c,d or T4), extramural venous invasion (EMVI), extensive nodal disease (N1c/N2), or lateral pelvic sidewall nodes (LPNM) have been associated with the risk of local recurrence after proctectomy alone and therefore are currently indications for nCRT. While the presence of these features is not a contraindication for WW, a cCR is less likely in patients with such advanced tumors. In addition, clinical and radiological identification of a cCR may be quite challenging in the presence of extensive disease, where it may be difficult to ascertain whether palpable or radiographic extraluminal abnormalities are due to fibrotic changes versus remaining tumor following neoadjuvant therapy.

The indication for nCRT in patients with intermediate disease—those with mrT3a,b or N0/1 and no additional high-risk features (CRM≤1 mm, EMVI+, LPNM+)—is controversial. While such patients are still considered candidates for nCRT in international guidelines that use the TNM classification system as the basis for risk stratification (such as the guidelines of the National Comprehensive Cancer Network; www.nccn.org), data from the MERCURY trial suggest that these patients are at low risk for local recurrence after proctectomy, casting doubt on the need for nCRT [40]. While the debate about the benefits of nCRT for all intermediate-risk rectal cancer patients is beyond the scope of this chapter, offering nCRT to patients with more distal intermediate stage tumors offers the possibility of a cCR and potential organ preservation [41].

A similar treatment algorithm may be considered for patients with early-stage disease (mrT1/T2N0). As the local recurrence rate with proctectomy alone is very low, early-stage tumors are typically not considered candidates for nCRT. However, nCRT followed by local excision has been proposed as an alternative for patients with early-stage distal rectal cancer who otherwise would need a coloanal anastomosis or a permanent colostomy. Several phase II trials have shown that the rate of pCR for these patients is higher than in patients with more advanced disease [3, 42]. It is therefore reasonable to offer WW to patients with early-stage rectal cancer who seek to avoid a permanent stoma and start treatment with nCRT in an attempt to achieve a cCR.

Tumor Location

Tumor location is also important when selecting patients for WW. While any rectal cancer patient with a cCR after CRT is a potential candidate for WW, those more likely to benefit from a WW approach that may result in organ preservation are patients with tumor located in the distal rectum who may otherwise need a low colorectal or coloanal anastomosis or a permanent colostomy. Tumors in this location are also more likely to be accessible to monitoring by DRE [2].

Tumor location in the distal rectum is particularly important when considering nCRT with the goal of achieving cCR in early-stage tumors. mrT2 cancers beyond the reach of DRE are probably surrounded by mesorectal fat and are less likely to have CRM positivity and local recurrence if treated by up-front proctectomy. As most of these patients are candidates for sphincter-saving surgery, they are less likely to benefit from organ preservation. However, an exception to this rule is an obese patient with a long anal canal in whom a tumor located immediately above the anorectal ring may be just beyond the reach by DRE but who may still be a candidate for a WW strategy.

Magnetic resonance imaging using dedicated rectal cancer protocols provides valuable information about the location of the tumor in relation to other anatomical structures, such as the sphincter complex, the levator muscles, the prostate and seminal vesicles, the vaginal wall and cervix, as well as the anterior peritoneal reflection and helps the surgeon anticipate the need for a permanent stoma, the ability to perform a sphincter-saving procedure and even the type of anastomosis in case proctectomy is undertaken. This information is also very useful for the selection of patients for WW [43]. In summary, patients with lower tumors requiring a low colorectal or a hand-sewn coloanal anastomosis or an APR are more likely to benefit from a WW strategy and organ preservation. Patients with more proximal tumors that carry a low risk of local recurrence and unlikely to benefit from CRT will derive minimal benefit from organ preservation and may be better treated with up-front proctectomy.

Endoscopic Features

Some endoscopic features such as pit pattern and submucosal vascular architecture can help identify benign lesions or even superficially invasive rectal cancers that fulfill the criteria for endoscopic submucosal resection (see Chap. 23) or transanal local excision (see Chap. 27) without the need for proctectomy or nCRT [44].

Endoscopic and some DRE features related to tumor morphology have not been associated with differences in response rates to neoadjuvant treatment. Therefore, qualities commonly associated with more advanced disease, such as ulceration and tethered lesions, are not necessarily exclusion criteria for entering WW. Size has been associated with response, suggesting that smaller tumors are more likely to respond completely to treatment [45]. Still, even patients with large circumferential tumors may also achieve a cCR and successfully undergo WW. Proper documentation of the endoscopic characteristics of the tumor at baseline—ideally through endoscopic images—is important for subsequent evaluations during the assessment of tumor response. Some large, circumferential, ulcerated tumors develop a concentric scar that narrows the lumen of the rectum and prevents proper endoscopic evaluation of tumor response. Patients with such tumors may not be ideal candidates for WW because complete endoscopic assessment and surveillance are not possible.

In summary, patients being considered for nCRT with the hope of entering a WW program should have confirmation of invasive adenocarcinoma, a tumor that is (preferably) accessible to DRE, endoscopic features consistent with invasive cancer not suitable for endoscopic submucosal dissection, and an MRI showing a tumor located in the distal rectum. Baseline staging features may be useful for estimating the probability of a tumor achieving a cCR and selecting a treatment plan that will potentially include a WW strategy to achieve organ preservation.

Assessment of Tumor Response

Most rectal cancers respond to some degree to chemotherapy and radiation. The degree of response depends on intrinsic tumor characteristics, such as size, stage, and some genomic features and treatment variables, including the fractionation dose of the radiation and the time from completion of radio-

therapy to assessment of response. In a WW program, tumor response is assessed with the same diagnostic tools as for the initial staging: DRE, endoscopy, and radiology (preferably MRI).

The 6-week interval between the end of the neoadjuvant therapy and surgery in patients with stage II-III rectal cancer treated with CRT and proctectomy has been proven to be effective in terms of surgical technical difficulty and perioperative morbidity and is associated with a pCR rate of approximately 18% [46]. Retrospective studies have suggested that longer intervals between the end of radiotherapy and surgery result in higher pCR rates [47, 48]. These data, along with the growing body of evidence from patients entered in WW protocols, suggest that tumor response is time-dependent and probably nonlinear [49–51]. These findings have implications for the design of WW strategies: tumors that have responded significantly but have not achieved a cCR at the time of the initial evaluation 6–8 weeks after completion of CRT may still achieve a cCR with longer observation. Several prospective studies suggest that adding chemotherapy during the longer observation period increases the likelihood of cCR and the probability of organ preservation [15, 18].

Our current WW strategy is to assess tumor response 6–8 weeks after completion of neoadjuvant therapy. Based on the degree of tumor response, patients are stratified in one of three treatment groups (Table 28.1) [52]. Patients with an incomplete clinical response (iCR) and a clearly visible tumor, even if the tumor has decreased in size significantly from baseline, typically undergo surgery (Table 28.1, Fig. 28.1). Patients with a cCR can enter a standard WW surveillance protocol with repeat assessments every 3–4 months (Table 28.1, Fig. 28.2). Patients with a very significant response that does not meet all criteria of a cCR—termed a near-complete clinical response (nCR)—can be entered in an intensive surveillance protocol, with a repeat exam after 6–8 additional weeks (Table 28.1, Fig. 28.3). Continued observation at similar intervals may be appropriate as long as the tumor continues showing signs of ongoing response until all strict criteria of a cCR are achieved. Most patients should achieve all strict criteria within 28–34 weeks following completion of radiotherapy. While not the norm, it may take up to a year (52 weeks) for some tumors to achieve a cCR. A lack of evidence of continued response in any of the three diagnostic modalities or any sign of tumor regrowth is an indication for surgery.

Criteria for a Complete Clinical Response

The criteria of a complete clinical response are based on three pillars of assessment. Clinical evaluation with DRE should reveal a regular mucosal surface, with only minor induration of the rectal wall and no significant abnormalities. Endoscopic assessment is typically characterized by whitening of the mucosa with telangiectasias and absence of ulceration, mass, or stenosis of the rectum (Figs. 28.4 and 28.5). Radiological assessment should include the presence of an area of low-signal intensity at the original tumor location on MRI-T2W [magnetic resonance tumor regression grade 1 (mrTRG1)] (Fig. 28.6); restriction to diffusion on MRI-DW should be absent, corresponding to the area of low-signal intensity on T2-weighted images (Fig. 28.7).

Given the random distribution of cancer cells in the different layers in the rectal wall after nCRT [53, 54], endoscopic biopsies are not very useful in the assessment of rectal cancer response to CRT. A negative biopsy is not a requirement for patients with a cCR entering a WW protocol. Conversely, a negative endoscopic biopsy cannot exclude residual tumor in patients with near-complete or incomplete clinical response. Therefore, endoscopic biopsy in patients with an incomplete

Table 28.1 Clinical response and suggested management

Clinical response	Endoscopic features	Clinical features	Radiological features (MR)	Suggested management
Incomplete	Deep ulcerations, elevated borders, significant distortion of rectal wall	Hard palpable mass, significant stenosis	mrTRG3-5, mixed or high-signal intensity, restriction to diffusion in the corresponding area of the primary tumor	Surgical management
Near-complete	No visible mass, only superficial/shallow ulcer	Minimal/questionable irregularity	mrTRG 2	Reassessment in 8–12 weeks; further response should be documented in subsequent reassessment
Complete	Only whitening of the mucosa and/or telangiectasias	Smooth surface in DRE	Low-signal intensity (T2-weighted images), absence of diffusion restriction (corresponding area), mrTRG1	WW, reassessment in 12 weeks

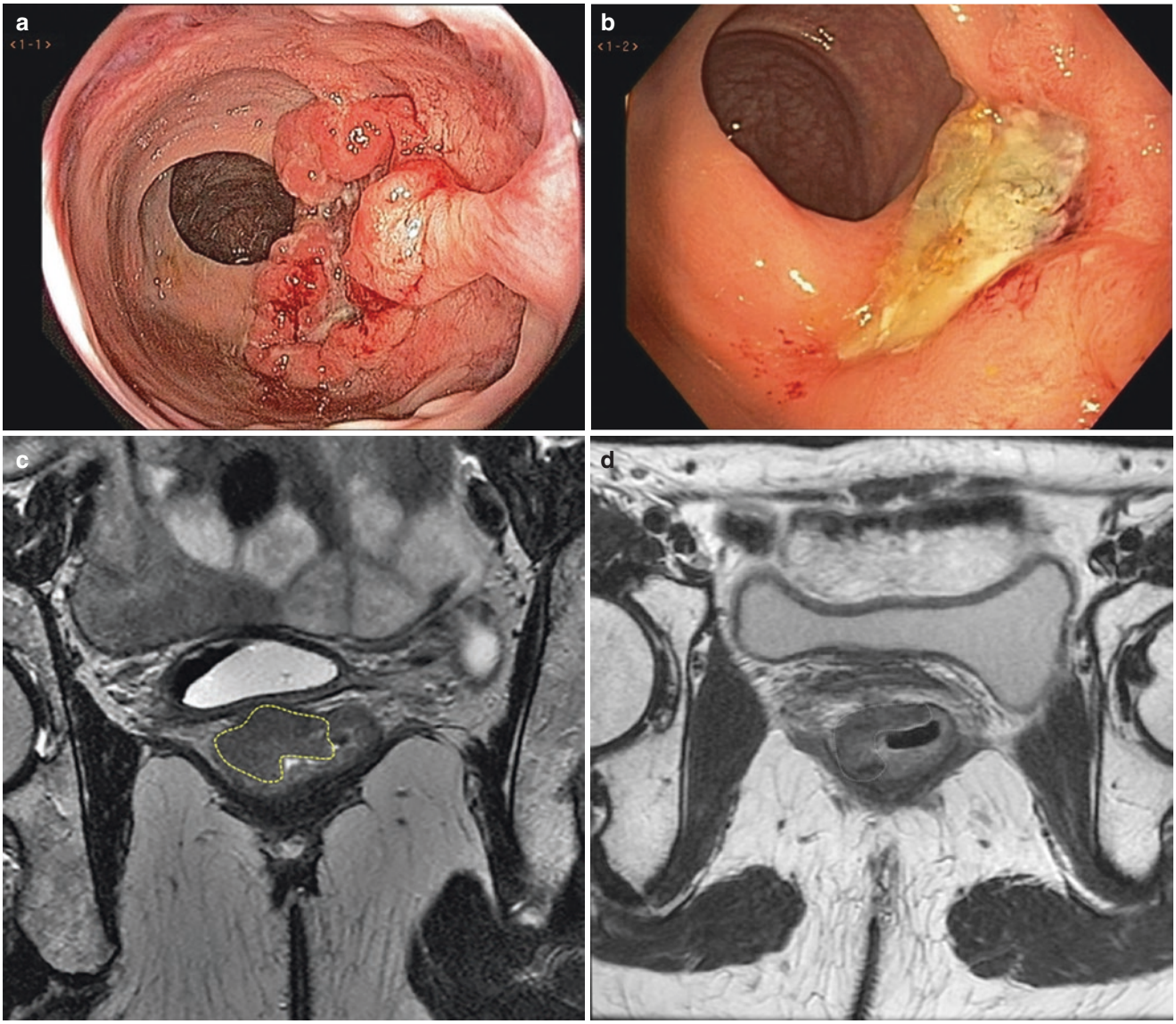

Fig. 28.1 Partial response (*not* near-complete). Endoscopic view of a rectal cancer at baseline (**a**) and exhibiting a clear large and necrotic residual ulcer (≤70% response) by endoscopy at 6 weeks (**b**). Similar findings can be seen in baseline MR showing a mrT3N0 (**c**, dotted yellow line) and ≤70% response (mrTRG3, dotted yellow line) at 6 weeks (**d**). Achievement of a cCR is unlikely

response, for the purpose of convincing patients that they have residual cancer in the setting of incomplete clinical response, is risky because a negative biopsy may give the patient a false sense of security and an argument to refuse a recommended operation [55].

One of the challenges for broad implementation of WW is establishing uniform and reproducible criteria for tumor response. Each modality is accurate but imperfect. Combining modalities increases accuracy [56]. In their investigation of the accuracies of DRE, endoscopy, and MRI in predicting pCR or sustained cCR, Maas et al. found that clinical assessment was the most accurate. When all three modalities were consistent with absence of residual tumor, the accuracy of predicting complete response was 98% [56]. A three-tiered response assessment schema currently being tested in the OPRA trial (organ preservation in rectal adenocarcinoma) consists of DRE, endoscopy, and T2- and diffusion-weighted MRI [52]. Based on that assessment, patients are considered complete responders, incomplete responders, or near-complete responders. Studies aimed at validating the reproducibility of that response assessment schema are underway.

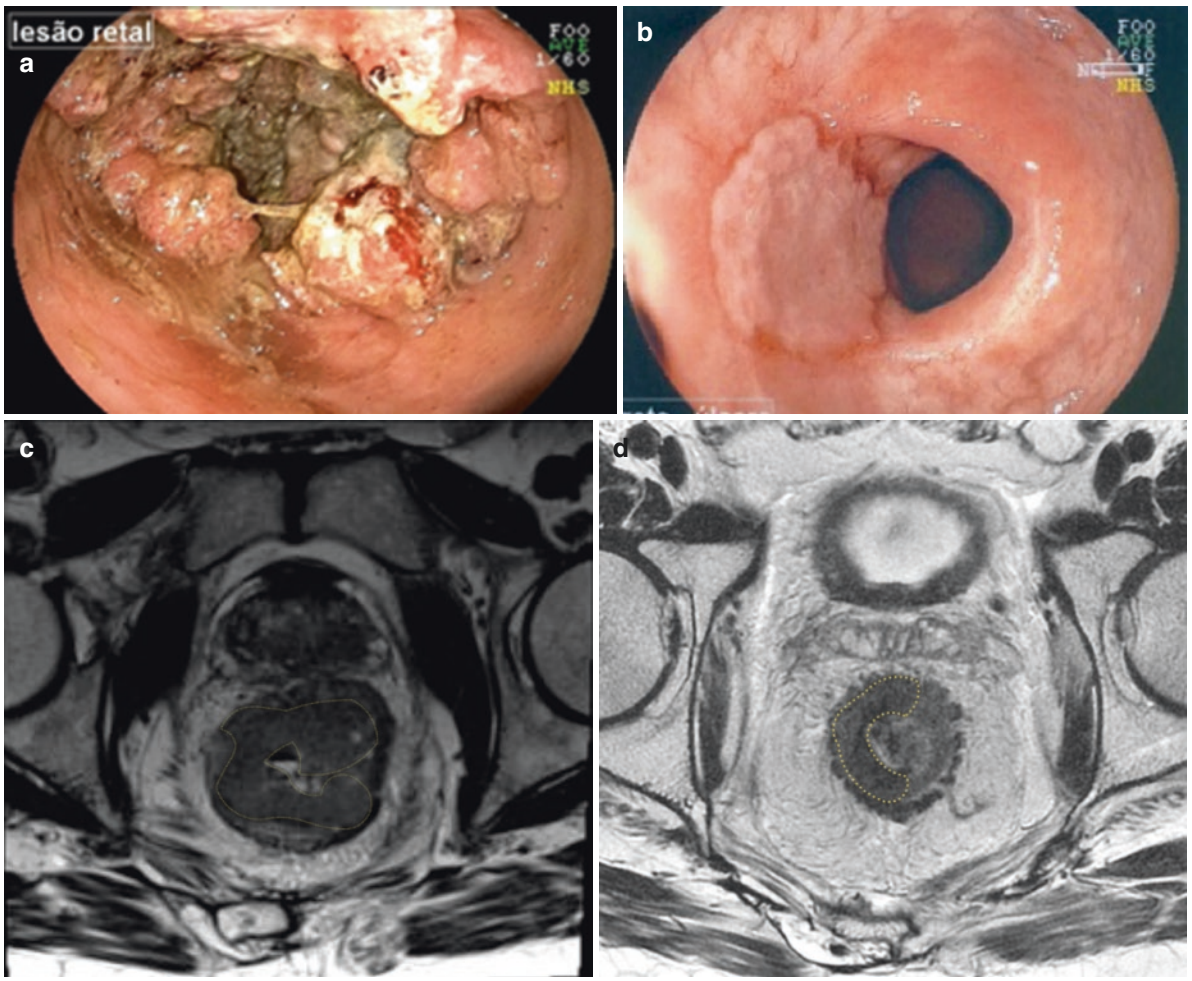

Fig. 28.2 Near-complete response followed by cCR. Endoscopic view of a rectal canvcer at baseline (**a**) and exhibiting near-complete/major (>70%) response by endoscopy at 6 weeks (**b**). Similar findings can be seen in baseline MR showing a mrT2/T3aN0 (**c**) and >70% response (mrTRG2) at 6 weeks (**d**). Achievement of a cCR is more likely, and patients should be reassessed in 6–8-week intervals. Further reassessment of response at 16 weeks showed cCR by endoscopy and MR

Endoscopic and Clinical Assessment

Historically, the first experiences of WW were reported prior to the development and standardization of radiological imaging in rectal cancer. Therefore, assessment of tumor response relied mostly on clinical (DRE) and endoscopic assessment [4].

DRE may seem like a simple and a rather straightforward tool for assessment of tumor response. However, DRE may be quite challenging for distinguishing between cCR and residual disease in many clinical scenarios. In this setting, it is recommended that the colorectal surgeons involved in organ-preserving programs be able to examine patients by DRE at baseline and during assessment of response. A DRE assessment of the baseline features of the primary tumor may aid the interpretation of response to treatment. Usually, cCR should result in a smooth and regular mucosal surface of the rectum. Even though slight induration of the rectal wall may often be palpated, ulcerations, nodules, stenosis, and masses should always raise the suspicion for residual cancer, and patients with these characteristics are thought not to be appropriate candidates for WW [2].

Endoscopic assessment may be equally challenging. Even though rigid proctoscopy may suffice for the identification of a cCR with strict criteria (see above), flexible endoscopy provides additional benefits in terms of improved visualization, more accurate documentation, training, and patient comfort. In addition, flexible instruments may provide the opportunity for retroflexion and more precise examination of the areas immediately adjacent to the dentate line. Finally, magnifying

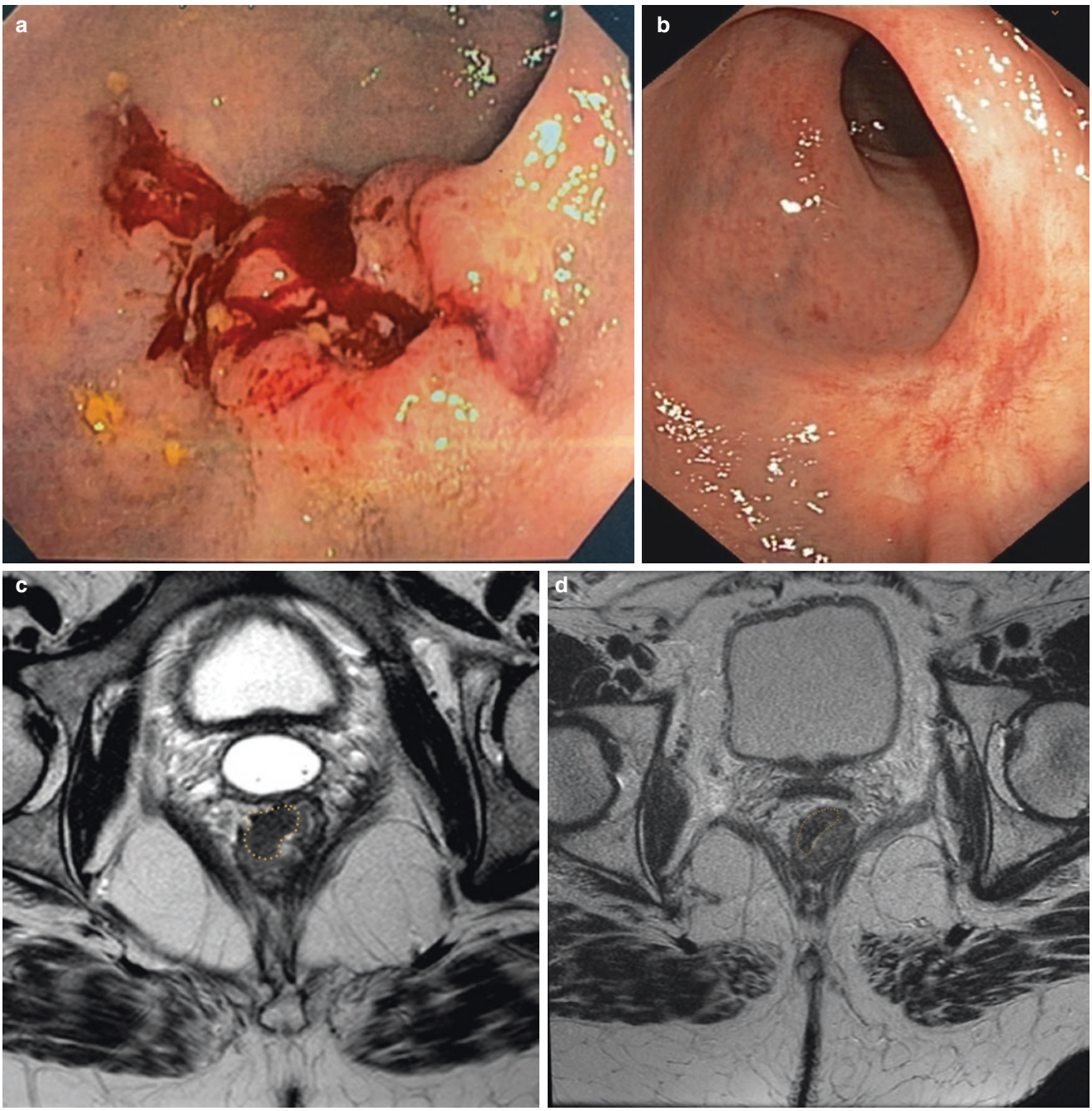

Fig. 28.3 Complete clinical response. Endoscopic view of a rectal cancer at baseline (**a**) and exhibiting strict criteria of cCR by endoscopy at 6 weeks (**b**). Similar findings can be seen in baseline MR showing a mrT2 (**c**, dotted yellow line) and mrTRG1 (**d**, dotted yellow line) at 6 weeks

endoscopic features including narrowband imaging may provide additional advantages during the assessment of tumor response after nCRT (Fig. 28.8).

Radiological Studies

Several radiological tools have been tested in clinical practice for the assessment of tumor response to nCRT. Endorectal ultrasound (ERUS) was originally used in baseline staging for rectal cancer and was also used for the assessment of tumor response to nCRT. This imaging modality provides good accuracy for the identification of complete response in the primary cancer (ypT status). However, patient discomfort and the difficulties in assessing mesorectal disease away from the rectal lumen contributed to the replacement of ERUS by alternative radiological imaging modalities [57, 58].

Magnetic resonance is currently the imaging modality of choice for baseline staging and assessment of response to

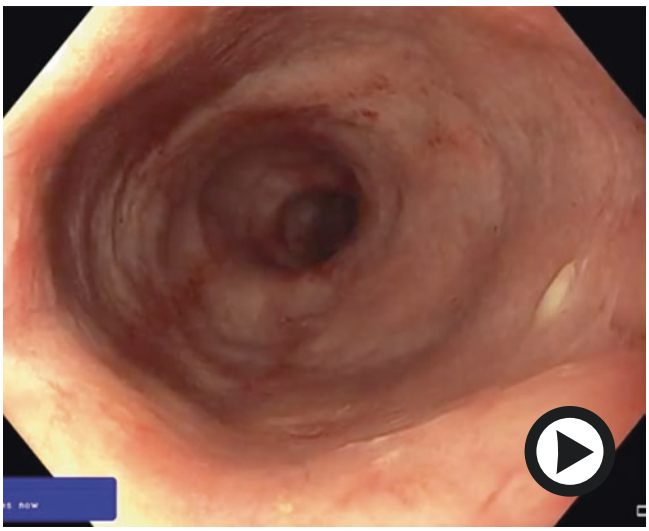

Fig. 28.4 Complete clinical response. Endoscopic view of a cCR showing clear whitening of the mucosa, telangiectasias in the submucosa, and no ulceration of the mucosa. (https://doi.org/10.1007/000-33g)

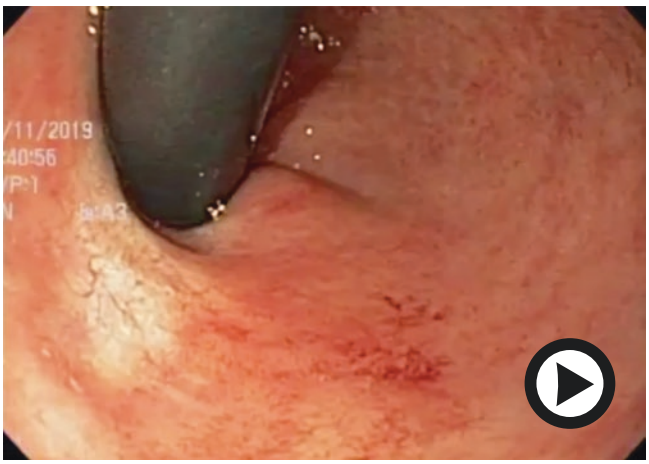

Fig. 28.5 Complete clinical response: retroflexion view. Endoscopic view of a cCR using the retroflexion maneuver to appropriately assess a tumor close to the anal verge. (https://doi.org/10.1007/000-33f)

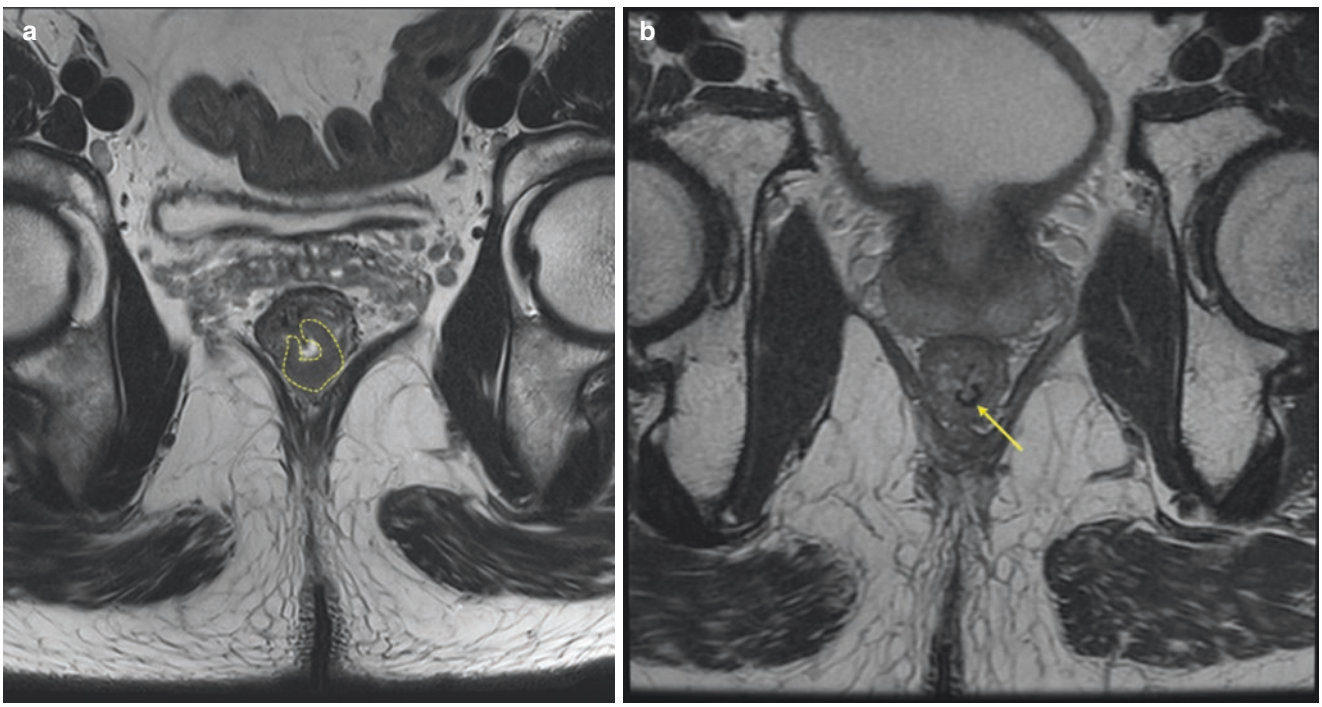

Fig. 28.6 MR complete response. Radiological assessment of tumor response to nCRT. Posttreatment axial T2-weighted images indicate the presence of a low-signal-intensity area (**a**) at the site harboring the original tumor at baseline (**b**)

neoadjuvant therapy in rectal cancer [43]. High-resolution protocols, synoptic reporting, and T2-weighted images are usually sufficient for the assessment of response and identification of patients who are appropriate candidates for a WW program. Typical findings consistent with a cCR include areas with low-signal intensity and variable shapes/distribution in the rectum, as previously described [59]. Currently, these low-signal intensity areas are graded by a classification system similar to pathological classification systems used for tumor regression grades (TRG) [60]. mrTRG classification attempts to estimate the histologic TRG, where mrTRG1 corresponds to maximal regression and mrTRG5 corresponds to no regression. Strict criteria of a cCR include the presence of mrTRG1 areas within the area of the original

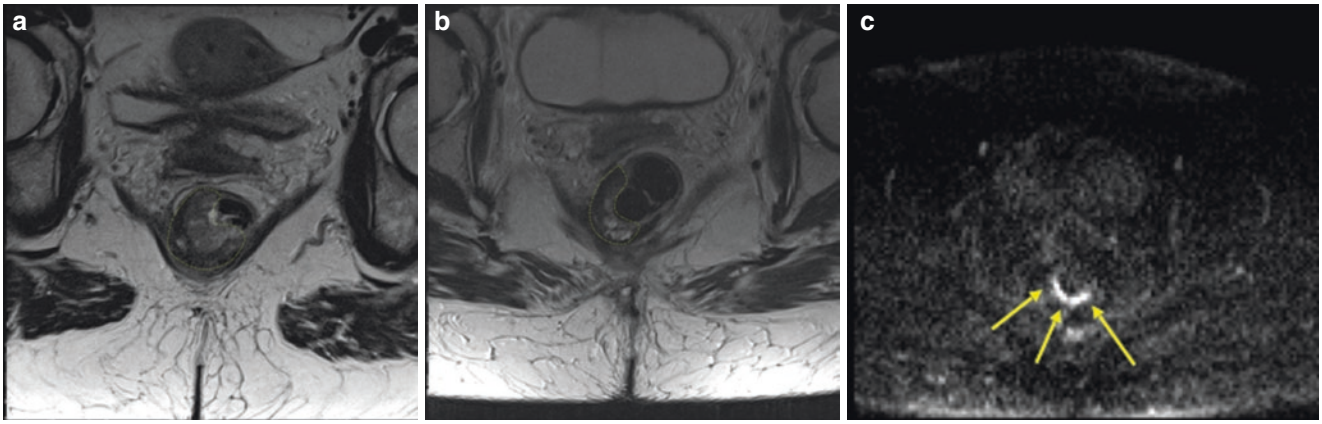

Fig. 28.7 MR and DWI incomplete response. Radiological assessment of tumor response to nCRT. Posttreatment axial T2-weighted images indicate the presence of a high-signal-intensity (**a**) area at the site harboring the original tumor at baseline (**b**). DWI sequences indicate the presence of restriction, likely representing residual cancer (**c**)

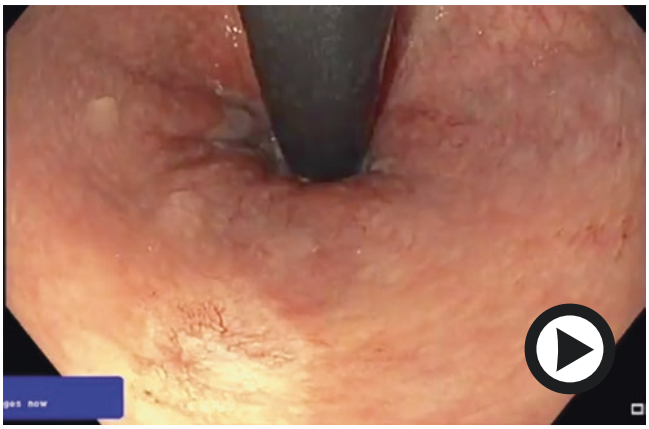

Fig. 28.8 Complete clinical response: narrowband imaging. Endoscopic view of a cCR using narrowband imaging showing clearly the presence of submucosal telangiectasias. (https://doi.org/10.1007/000-33h)

rectal cancer in the rectal wall and/or the mesorectum. MR also allows for functional imaging of rectal cancer using diffusion-weighted imaging (DWI) sequences. By detecting the restriction of water molecule movement within the area of previous cancer, DWI indicates areas of high-signal intensity [confirmed by apparent diffusion coefficient maps] highly suspicious for the presence of cancer cells. Data suggests that DWI may provide additional information and help radiologists in confirming the presence of cCR or residual disease [61, 62].

Metabolic imaging modalities including positron emission tomography (PET) alone or combined with computed tomography (PET/CT) have also been studied in the setting of tumor response assessment after neoadjuvant treatment for rectal cancer. Even though initial studies including both PET alone and PET/CT imaging were disappointing [63], more recent data supports the potential role of PET/CT in the selection of patients for WW [64, 65]. A decrease in metabolic activity as indicated by the difference in standard uptake values and in metabolic tumor volumes between baseline and posttreatment studies seems to be the best predictor of response by PET/CT (Fig. 28.9) [65, 66]. Future studies using PET/MR may provide additional information for the precise selection of these patients.

Surveillance/Follow-up Strategy

Even though multiple series have reported on the outcomes of patients with rectal cancer under WW using different surveillance protocols, most schedules and assessment modalities vary only in subtle details. Surveillance schedules need to address the risk of local tumor regrowth and the risk of distant metastasis. Even though the risk of local regrowth at 3 years may reach nearly 30%, the majority of local regrowths are detected within the first year. Therefore, most follow-up schedules have recommended more intensive and strict surveillance during this initial period of observation (Fig. 28.10) [8, 10, 11].

Local Reassessment After Achievement of a cCR

One of the premises of the WW strategy is appropriate surveillance. Therefore, this strategy should be considered only in patients committed to complying with a strict surveillance program. Once patients have achieved a cCR and formally entered a WW program, intensive surveillance for local regrowth is needed, especially during the initial 2 years. Tumor response is usually reassessed by clinical and endoscopic measures every 3 months. MRI has been progressively incorporated into surveillance schedules to complement clinical and endoscopic assessments and is now recommended every 6 months during the first 2 years. Recent

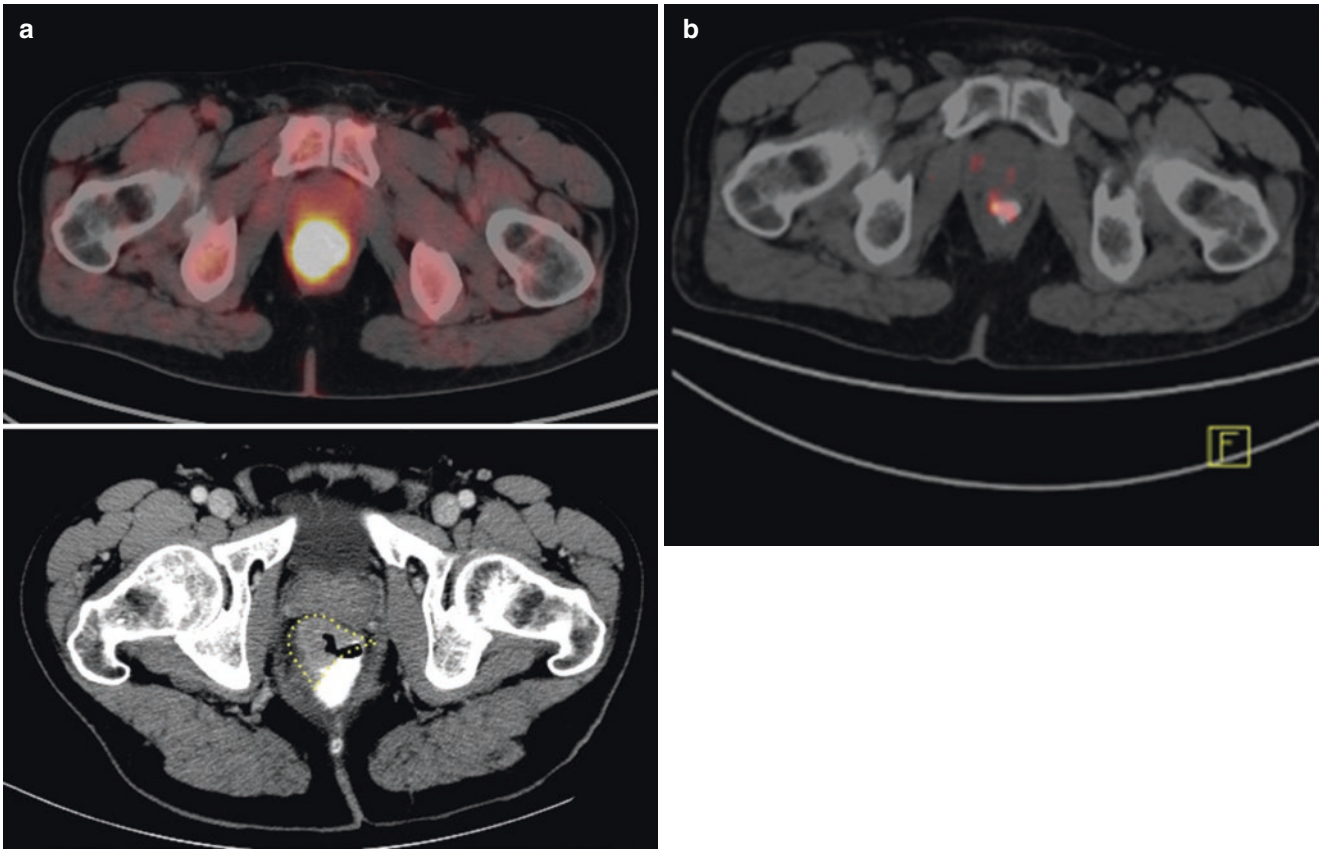

Fig. 28.9 PET/CT. Molecular imaging using fluorodeoxyglucose (FDG) PET/CT for the assessment of tumor response to nCRT. Baseline images show obvious FDG uptake in the primary tumor (**a**, PET and CT images fused with FDG uptake [top] and CT thickening of the anterior rectal wall [bottom]). Posttreatment scans show significant decrease in FDG uptake and metabolic tumor volume (**b**). This patient achieved a cCR and entered a successful WW program

data using conditional survival estimates indicate that in patients with a cCR sustained for 2 years, the risk for local regrowth is low (≤10%), suggesting that intensive follow-up schedules are less critical after 2 years [67].

Once patients have completed 2 years of follow-up, we typically reassess for continued tumor response every 6 months for the following 3 years. The need for additional surveillance beyond 5 years remains an unanswered question. Some series have reported the detection of local regrowths as late as 7 years after completion of nCRT [68]. Therefore, in the absence of long-term data, we recommend that patients who have undergone WW management should be monitored on a yearly basis indefinitely within a survivorship program.

Surveillance for Metastatic and Metachronous Disease

Patients with rectal cancer who achieve a cCR are still at risk for developing metastatic disease or metachronous colorectal cancer [10, 12, 68]. Even though the risk of metastatic disease among patients with cCR is significantly lower, surveillance strategies for metastatic disease usually follow the same recommendations as for any colorectal cancer, preferably with a CT of the chest, abdomen, and pelvis [69]. The need for a restaging CT is particularly important for patients with initial cCR who develop a local regrowth, as these patients are apparently at higher risk for metastatic disease [12]. Also, endoscopic surveillance of the colon (full colonoscopy evaluation) should follow current guidelines for patients with a high risk for developing colorectal cancer (personal history of colorectal cancer).

Local Regrowth

The actuarial rate of local regrowth at 2 years is around 25% and appears as an exponential curve, with most of the recurrences being detected during the first year of follow-up [7, 8, 10–12]. The vast majority of local regrowths have an endoluminal component and are therefore amenable to endoscopic and/or clinical detection during active surveillance (Fig. 28.11) [5, 7]. A small percentage of regrowths are

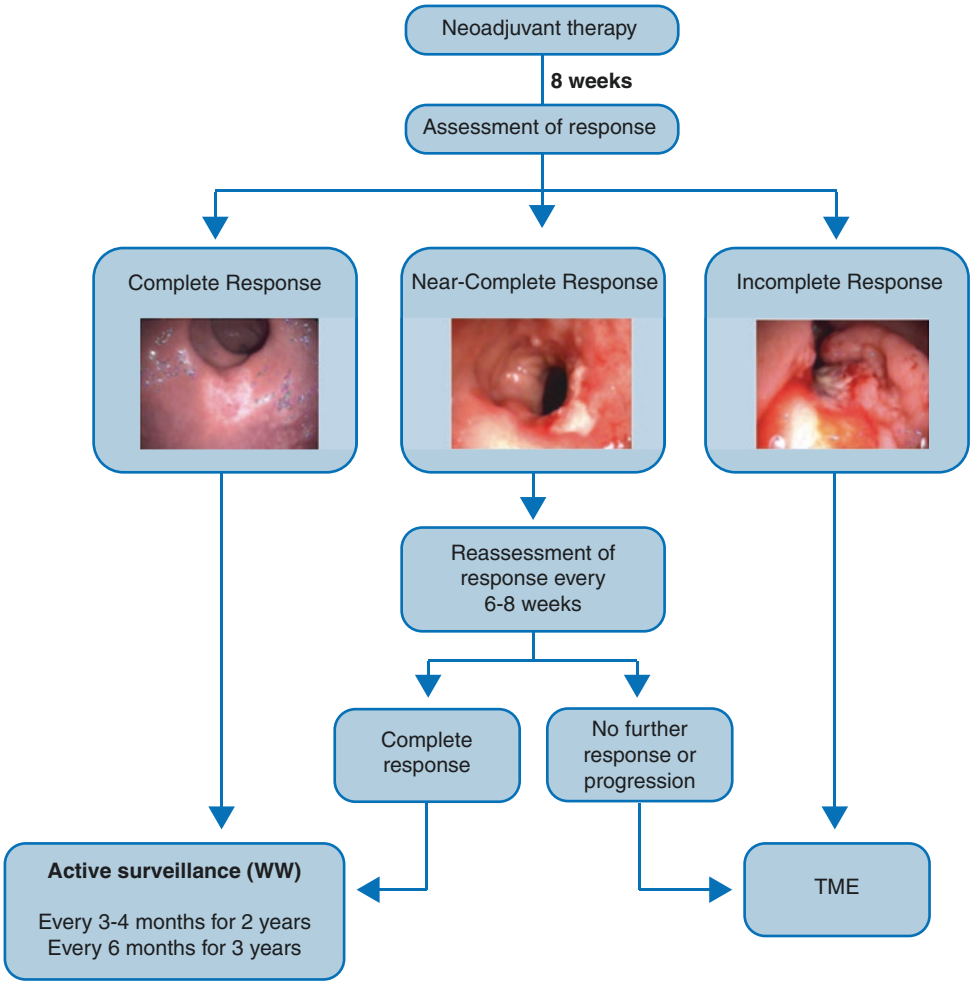

Fig. 28.10 Treatment algorithm for rectal cancer patients treated with neoadjuvant therapy interested in the WW approach for organ preservation

detected exclusively outside the rectal wall (mesorectal or lateral pelvic sidewall disease) (Fig. 28.12) [5, 7].

Risk factors for local regrowth have been investigated across many studies [11, 70, 71]. So far, the only risk factor for the development of local regrowth seems to be clinical T stage at baseline [11, 70]. Data derived from one study and a meta-analysis using individual participant data of patients undergoing contemporary MR staging suggests that for every increase in baseline clinical T stage (cT2, cT3, and cT4), there is a 10% increase in the risk for local regrowth (20%, 30%, and 40%, respectively) [11]. The influence of cT stage on local regrowth appears to be restricted to the first 2 years after cCR is attained. Based on conditional survival estimates, the risk of a local regrowth/recurrence after a cCR has been sustained for >2 years appears to be independent of baseline cT stage [67].

Systematic reviews of retrospective studies suggest that nearly 90% of local regrowths are amenable to R0 salvage resection [10]. In most cases, the salvage surgery is proctectomy [7, 12]. Patients who undergo salvage proctectomy have similar rates of R0 margins, postoperative morbidity, and oncological outcomes as patients who undergo proctectomy within 8–12 weeks after an incomplete response to nCRT [72]. Transanal local excision may also be a salvage option for tumor regrowth in patients with baseline early disease (cT2N0) entered in a WW protocol. However, transanal local excision is not routinely offered as the primary salvage surgical option for tumor regrowth in patients with baseline clinical stage II or stage III entered in a WW protocol.

Systemic Recurrences

Overall, patients with a cCR who are managed nonoperatively appear to have lower rates of distant metastases than patients with incomplete response to neoadjuvant treatment. In addition, most studies comparing patients with cCR to patients with pCR indicate no differences in the rates of distant metastases, suggesting no benefit of radical surgery in preventing M1 disease in these patients [10]. This lack of a difference is particularly notable in view of the fact that in most studies of WW, patients with cCR did not routinely receive adjuvant chemotherapy, whereas nearly 50% of

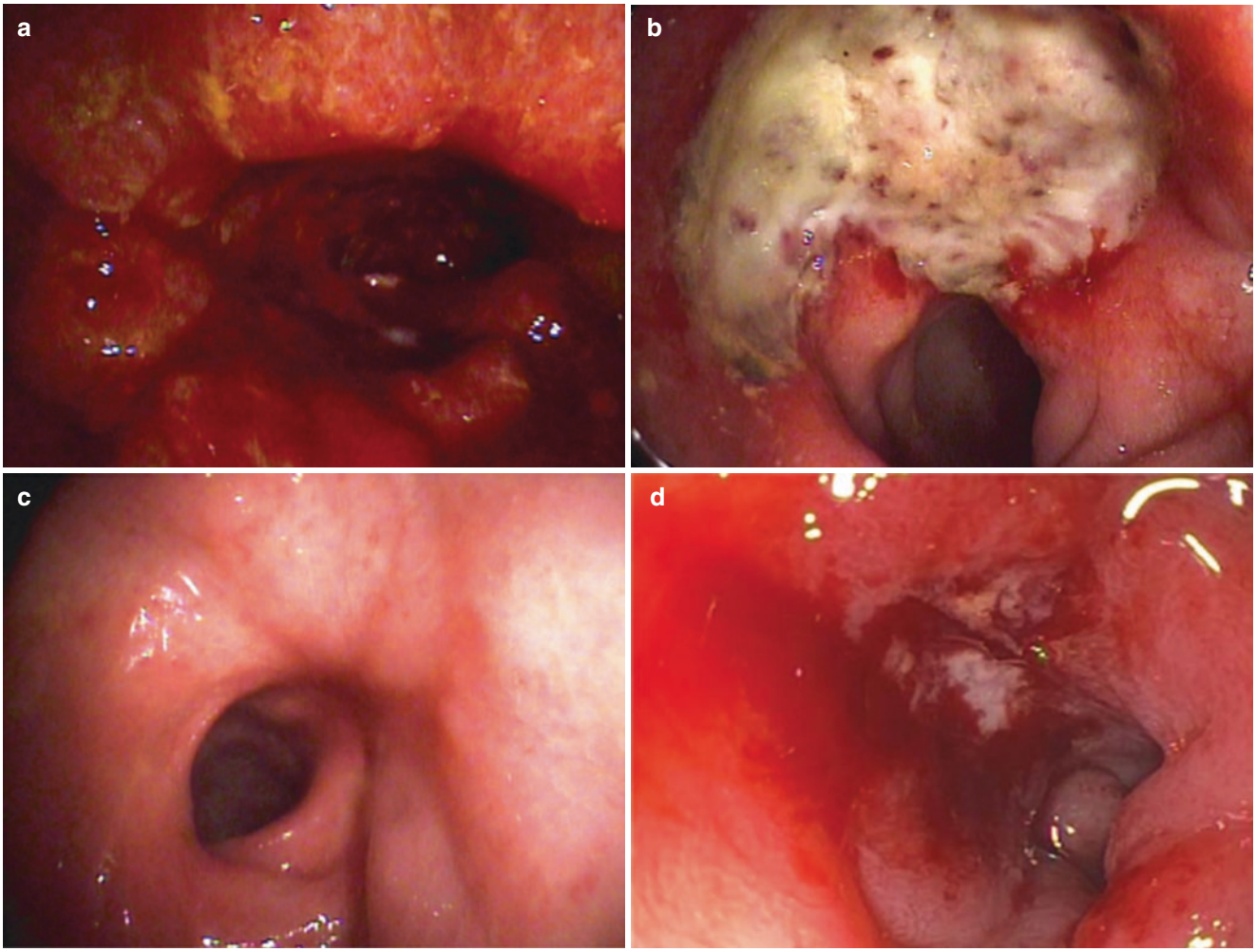

Fig. 28.11 Tumor regrowth in the bowel wall. Endoscopic view of a rectal tumor at baseline (**a**) in a patient with LARC treated with TNT (CRT followed by consolidation chemotherapy). The tumor had a partial response at the completion of CRT (**b**) and a cCR 4 weeks after completing 8 cycles of consolidation mFOLFOX-6 (**c**). Signs of mucosal regrowth were seen in follow-up 20 weeks after completion of TNT (**d**)

patients with pCR after radical surgery had received adjuvant systemic chemotherapy, mostly based on baseline staging characteristics [73].

However, patients with local regrowth after a cCR appear to be at increased risk for distant metastasis compared with patients with no regrowth after a cCR [12, 70]. It is possible that tumor regrowth may be related to a more aggressive tumor biology, which may explain the difference in the rates of metastasis. It remains unclear whether an up-front proctectomy would have prevented development of metastatic disease in patients who underwent WW instead.

Oncologic Outcomes

The current evidence on the safety and efficacy of the WW strategy in rectal cancer is based on retrospective institutional case series. Even though original reports of WW were based on the rationale of providing long-term organ preservation without oncological compromise, most of the currently available series include patients who were treated with WW accidentally, because they refused or were unfit for surgery. These studies are heterogenous regarding patient selection, imaging studies for baseline staging, neoadjuvant treatment regimens, time to assess tumor response after neoadjuvant therapy, and strategies and length of follow-up. More important the clinical and radiological criteria of tumor response were variable and not defined prospectively. In addition, the total number of patients treated during the study period was not consistently reported. In this setting, several limitations for the interpretation of the data may arise, including a strong potential for selection bias and a lack of a complete denominator. In the absence of this information, it becomes difficult to provide an accurate estimate of the proportion of patients that may potentially benefit from organ preservation. The combined experience of these series, sum-

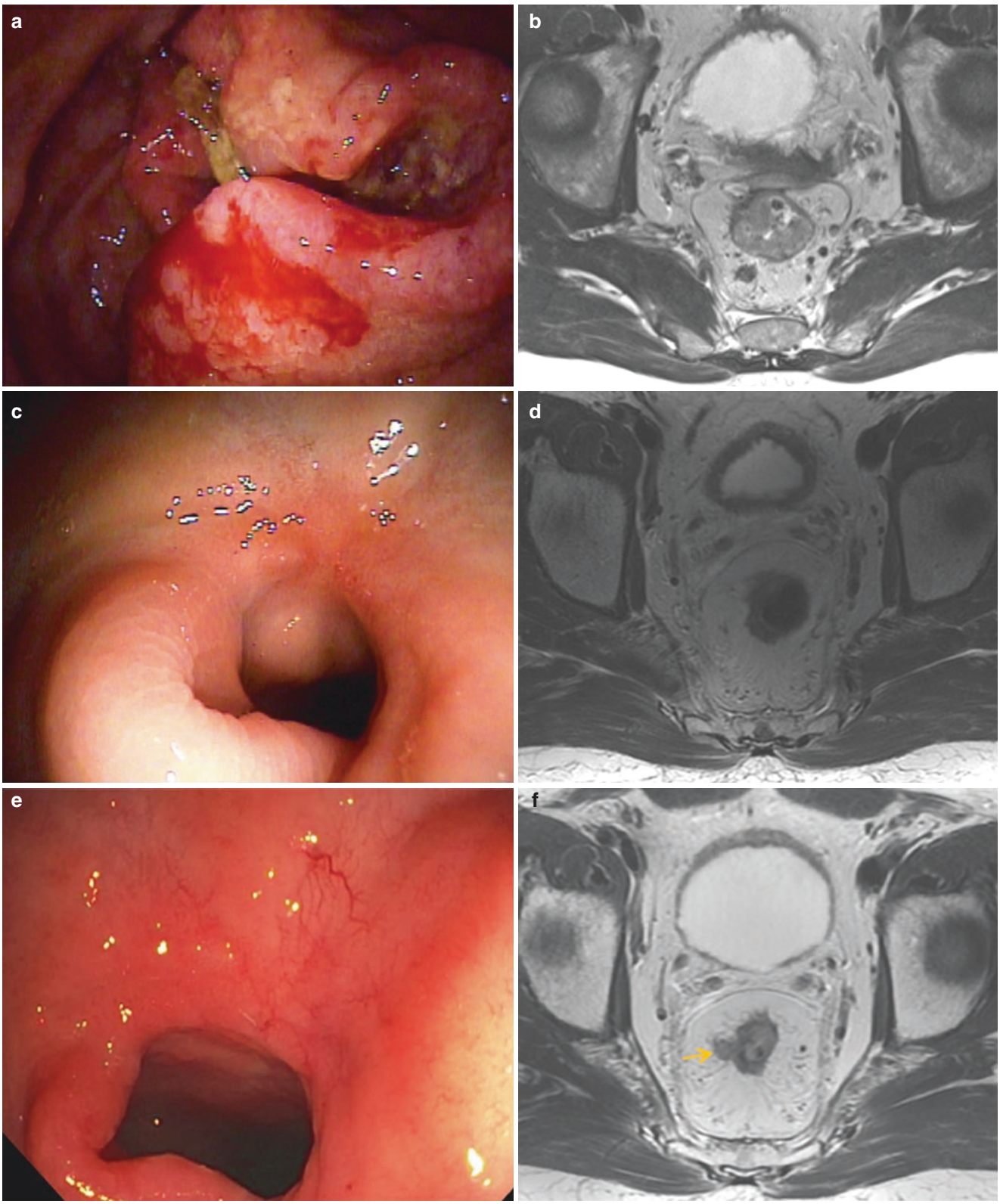

Fig. 28.12 Tumor regrowth in the mesorectum. Paired endoscopic (**a**, **c**, **e**) and axial T2 MRI (**b**, **d**, **f**) images of a patient with rectal cancer at baseline (**a**, **b**), 14 weeks after completion of total neoadjuvant therapy (**c**, **d**), and 20 months after completion of total neoadjuvant therapy (**e**, **f**). Arrow points to mesorectal regrowth. Pathology confirmed the diagnosis of adenocarcinoma

marized as systematic reviews and a large pooled analysis, suggests that between 3% and 30% of patients entered in a WW protocol will develop regrowth of the primary tumor, in most patients within the first 2 years of follow-up [8–11, 68]. In one pooled analysis, the calculated 2-year rate of regrowth was 15.7% (95% CI 11.8–20.1) [8]. Most regrowth occurs locally at the site of the primary tumor in the bowel wall, with or without involvement of the regional lymph nodes. Isolated regrowth in the mesorectum without involvement of the rectal wall is unusual. A curative (R0) surgical resection after regrowth was achieved in 80–100% of patients (average 95.4%; 95% CI, 89.6–99.3) [8, 68]. The reported rate of distant metastasis ranged from 0% to 16.7% (average 6.8%) of patients and was found to be higher in patients with local tumor regrowth, compared to patients without it [8, 10, 52]. To estimate the oncologic benefits of the WW approach, some studies have compared the survival of patients with a clinical complete response entered in the WW protocol with patients with tumors of similar clinical stage treated with neoadjuvant therapy and proctectomy who had a pathological complete response. Patients treated with proctectomy had a better disease-free survival compared to patients treated with WW (pooled HR 0.47, 95% CI 0.28–0.78); however, there was no difference in overall survival between groups [8, 9]. Also, differences in DFS here are mainly driven by the risk of local regrowth where the possibility of salvage resection is between 80% and 100% [8–11, 68].

The ideal study to prove the safety and efficacy of WW will be a randomized trial comparing WW and proctectomy in patients with a clinical complete response after neoadjuvant therapy. However, it is unlikely that patients with a clinical complete response will agree to a randomization between WW versus proctectomy. The organ preservation in rectal adenocarcinoma (OPRA) trial is prospectively investigating the impact of WW on disease-free survival for patients with clinical stage II and III rectal adenocarcinoma treated with total neoadjuvant therapy [52].

Functional Outcomes

Very few studies have specifically assessed functional outcomes in patients who underwent WW management after achieving a cCR. There seem to be significant differences in the quality of life and anorectal, sexual, and urinary functions between proctectomy patients and WW patients [74]. Patients with a sustained cCR after 2 years of WW had better quality of life and general health (SF36 and EORTC-QLQ-C30), fewer defecation problems (Vaizey and low anterior resection syndrome scores), fewer urinary problems (International Prostate Syndrome Score), and better sexual function (EORTC-QLQ-C30) compared to a matched group of patients treated with proctectomy. However, one third of the WW patients still had considerable symptoms associated with low anterior resection syndrome, suggesting a potential effect of nCRT on functional outcomes despite the avoidance of proctectomy [74]. WW patients also had superior functional outcomes compared with patients who had undergone local excision after nCRT, based on fecal incontinence scores and anorectal manometry [75].

Prediction of Tumor Response

An accurate tool for the prediction of a sustained tumor response to neoadjuvant therapy will help improve the selection of patients for WW and avoid overtreatment of patients unlikely to respond to chemoradiation who have early clinical stage tumors that would otherwise proceed directly to proctectomy. Individual gene mutations and genomic instability have been associated with tumor response to nCRT [76, 77]. A large institutional series suggests that tumors of the microsatellite instability (MSI) phenotype, found in ≤5% of all rectal cancers, are more sensitive to nCRT compared to microsatellite stable tumors [78]. However, these results were not confirmed in a retrospective review of the National Cancer Database [79]. Tumors with K-ras or K-ras/p53 mutations appear to be more resistant to nCRT [80, 81]. Although they may help identify a subset of patients less likely to achieve a cCR, these genetic alterations provide no WW-relevant information for the majority of rectal cancer patients.

Prediction of tumor response based on differential gene expression profiles has been largely unsuccessful [82, 83]. Significant intertumoral and intratumoral heterogeneity may explain gene signatures with a very low number of overlapping genes and inaccurate separation between poor and good responders [84][8]. However, a prediction score based on DNA repair genes has been recently suggested for this particular purpose [85]. In that study, low scores were associated with poor response to nCRT regardless of the DNA expression platform used. A low score (observed in nearly 40% of the patients tested) resulted in poor response to nCRT in 70–90% of the cases. Using this strategy in consecutive cT2N0 patients is expected to result in avoidance of unnecessary nCRT in 36% of patients, restriction of nCRT to 60% of patients, and good response and the possibility of organ preservation in nearly 75% of the cases [85].

Another interesting strategy for the prediction of tumor response is the use of patient-derived rectal cancer organoid cultures. These “tumoroids” appear to retain molecular features of the primary tumors from which they were derived. In addition, their ex vivo responses to chemotherapy and radiation treatment correlate with the clinical responses

observed in individual patients' tumors. Therefore, future studies attempting to predict complete tumor response to different neoadjuvant treatment strategies using this ex vivo platform may help lead to the development of an algorithm for accurate selection of ideal candidates for WW [86].

References

1. Amin MB, et al., editors. AJCC cancer staging manual. 8th ed: Springer, New York; 2017.
2. Habr-Gama A, Perez RO, Wynn G, Marks J, Kessler H, Gama-Rodrigues J. Complete clinical response after neoadjuvant chemoradiation therapy for distal rectal cancer: characterization of clinical and endoscopic findings for standardization. Dis Colon Rectum. 2010;53:1692–8.
3. Garcia-Aguilar J, Shi Q, Thomas CR Jr, et al. A phase II trial of neoadjuvant chemoradiation and local excision for T2N0 rectal cancer: preliminary results of the ACOSOG Z6041 trial. Ann Surg Oncol. 2012;19:384–91.
4. Habr-Gama A, de Souza PM, Ribeiro U Jr, et al. Low rectal cancer: impact of radiation and chemotherapy on surgical treatment. Dis Colon Rectum. 1998;41:1087–96.
5. Habr-Gama A, Perez RO, Proscurshim I, et al. Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. J Gastrointest Surg. 2006;10:1319–28; discussion 1328–1319.
6. Heald RJ, Beets G, Carvalho C. Report from a consensus meeting: response to chemoradiotherapy in rectal cancer - predictor of cure and a crucial new choice for the patient: on behalf of the Champalimaud 2014 Faculty for 'Rectal cancer: when NOT to operate'. Color Dis. 2014;16:334–7.
7. Habr-Gama A, Gama-Rodrigues J, Sao Juliao GP, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys. 2014;88:822–8.
8. Dossa F, Chesney TR, Acuna SA, Baxter NN. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2017;2(7):501–13.
9. Kong JC, Guerra GR, Warrier SK, Ramsay RG, Heriot AG. Outcome and salvage surgery following "Watch and Wait" for rectal cancer after neoadjuvant therapy: a systematic review. Dis Colon Rectum. 2017;60:335–45.
10. Dattani M, Heald RJ, Goussous G, et al. Oncological and survival outcomes in watch and wait patients with a clinical complete response after neoadjuvant chemoradiotherapy for rectal cancer: a systematic review and pooled analysis. Ann Surg. 2018;268:955–67.
11. Chadi SA, Malcomson L, Ensor J, et al. Factors affecting local regrowth after watch and wait for patients with a clinical complete response following chemoradiotherapy in rectal cancer (InterCoRe consortium): an individual participant data meta-analysis. Lancet Gastroenterol Hepatol. 2018;3:825–36.
12. Smith JJ, Strombom P, Chow OS, et al. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. JAMA Oncol. 2019;5:e185896.
13. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg. 2004;240:711–7; discussion 717–718.
14. Dewdney A, Cunningham D, Tabernero J, et al. Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). J Clin Oncol. 2012;30:1620–7.
15. Garcia-Aguilar J, Chow OS, Smith DD, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. Lancet Oncol. 2015;16:957–66.
16. Habr-Gama A, Sabbaga J, Gama-Rodrigues J, et al. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? Dis Colon Rectum. 2013;56:1109–17.
17. Habr-Gama A, Perez RO, Sabbaga J, Nadalin W, Sao Juliao GP, Gama-Rodrigues J. Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period. Dis Colon Rectum. 2009;52:1927–34.
18. Cercek A, Roxburgh CSD, Strombom P, et al. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. JAMA Oncol. 2018;4(6):e180071.
19. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg. 2006;93:1215–23.
20. Myerson RJ, Tan B, Hunt S, et al. Five fractions of radiation therapy followed by 4 cycles of FOLFOX chemotherapy as preoperative treatment for rectal cancer. Int J Radiat Oncol Biol Phys. 2014;88:829–36.
21. Appelt AL, Ploen J, Harling H, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. Lancet Oncol. 2015;16:919–27.
22. Sun Myint A, Smith FM, Gollins S, et al. Dose escalation using contact X-ray brachytherapy after external beam radiotherapy as nonsurgical treatment option for rectal cancer: outcomes from a single-center experience. Int J Radiat Oncol Biol Phys. 2018;100:565–73.
23. Wrenn SM, Cepeda-Benito A, Ramos-Valadez DI, Cataldo PA. Patient perceptions and quality of life after colon and rectal surgery: what do patients really want? Dis Colon Rectum. 2018;61:971–8.
24. Nigro ND, Vaitkevicius VK, Considine B Jr. Combined therapy for cancer of the anal canal: a preliminary report. Dis Colon Rectum. 1974;17:354–6.
25. Denost Q, Laurent C, Capdepont M, Zerbib F, Rullier E. Risk factors for fecal incontinence after intersphincteric resection for rectal cancer. Dis Colon Rectum. 2011;54:963–8.
26. Celerier B, Denost Q, Van Geluwe B, Pontallier A, Rullier E. The risk of definitive stoma formation at 10 years after low and ultralow anterior resection for rectal cancer. Colorectal Dis. 2016;18:59–66.
27. Didailler R, Denost Q, Loughlin P, et al. Antegrade enema after total mesorectal excision for rectal cancer: the last chance to avoid definitive colostomy for refractory low anterior resection syndrome and fecal incontinence. Dis Colon Rectum. 2018;61:667–72.
28. Celentano V, Cohen R, Warusavitarne J, Faiz O, Chand M. Sexual dysfunction following rectal cancer surgery. Int J Color Dis. 2017;32:1523–30.
29. Lange MM, Maas CP, Marijnen CA, et al. Urinary dysfunction after rectal cancer treatment is mainly caused by surgery. Br J Surg. 2008;95:1020–8.
30. Diers J, Wagner J, Baum P, Lichthardt S, Kastner C, Matthes N, Matthes H, Germer CT, Löb S, Wiegering A. Nationwide in-hospital mortality rate following rectal resection for rectal cancer according to annual hospital volume in Germany. BJS Open. 2020;4(2):310–9.

31. Garg PK, Goel A, Sharma S, Chishi N, Gaur MK. Protective diversion stoma in low anterior resection for rectal cancer: a meta-analysis of randomized controlled trials. Visc Med. 2019;35:156–60.
32. Fish DR, Mancuso CA, Garcia-Aguilar JE, Lee SW, Nash GM, Sonoda T, Charlson ME, Temple LK. Readmission after ileostomy creation: retrospective review of a common and significant event. Ann Surg. 2017;265(2):379–87.
33. Peeters KC, van de Velde CJ, Leer JW, Martijn H, Junggeburt JM, Kranenbarg EK, Steup WH, Wiggers T, Rutten HJ, Marijnen CA. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients--a Dutch colorectal cancer group study. J Clin Oncol. 2005;23(25):6199–206.
34. Ito M, Kobayashi A, Fujita S, Mizusawa J, Kanemitsu Y, Kinugasa Y, Komori K, Ohue M, Ota M, Akazai Y, Shiozawa M, Yamaguchi T, Akasu T, Moriya Y, Colorectal Cancer Study Group of Japan Clinical Oncology Group. Urinary dysfunction after rectal cancer surgery: Results from a randomized trial comparing mesorectal excision with and without lateral lymph node dissection for clinical stage II or III lower rectal cancer (Japan Clinical Oncology Group Study, JCOG0212). Eur J Surg Oncol. 2018;44(4):463–8.
35. Sörensson M, Asplund D, Matthiessen P, Rosenberg J, Hallgren T, Rosander C, González E, Bock D, Angenete E. Self-reported sexual dysfunction in patients with rectal cancer. Colorectal Dis. 2019; https://doi.org/10.1111/codi.14907.
36. Chen L, Glimelius I, Neovius M, et al. Risk of disability pension in patients following rectal cancer treatment and surgery. Br J Surg. 2015;102:1426–32.
37. Binkley GE. Radiation therapy in the treatment of rectal cancer. Ann Surg. 1929;90(6):1000–14.
38. Habr-Gama A, Sao Juliao GP, Vailati BB, et al. Organ preservation in cT2N0 rectal cancer after neoadjuvant chemoradiation therapy: the impact of radiation therapy dose-escalation and consolidation chemotherapy. Ann Surg. 2019;269(1):102–7.
39. Glynne-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28:iv22–40.
40. Taylor FG, Quirke P, Heald RJ, et al. Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone: a prospective, multicenter, European study. Ann Surg. 2011;253:711–9.
41. Habr-Gama A, Gama-Rodrigues J, Perez RO. Is tailoring treatment of rectal cancer the only true benefit of long-course neoadjuvant chemoradiation? Dis Colon Rectum. 2013;56:264–6.
42. Rullier E, Rouanet P, Tuech JJ, et al. Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial. Lancet. 2017;390:469–79.
43. Ortega CD, Perez RO. Role of magnetic resonance imaging in organ-preserving strategies for the management of patients with rectal cancer. Insights Imaging. 2019;10:59.
44. Wada Y, Kashida H, Kudo SE, Misawa M, Ikehara N, Hamatani S. Diagnostic accuracy of pit pattern and vascular pattern analyses in colorectal lesions. Dig Endosc. 2010;22:192–9.
45. Das P, Skibber JM, Rodriguez-Bigas MA, et al. Predictors of tumor response and downstaging in patients who receive preoperative chemoradiation for rectal cancer. Cancer. 2007;109:1750–5.
46. Garcia-Aguilar J, Smith DD, Avila K, et al. Optimal timing of surgery after chemoradiation for advanced rectal cancer: preliminary results of a multicenter, nonrandomized phase II prospective trial. Ann Surg. 2011;254:97–102.
47. Kalady MF, de Campos-Lobato LF, Stocchi L, et al. Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. Ann Surg. 2009;250:582–9.
48. Sloothaak DA, Geijsen DE, van Leersum NJ, et al. Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. Br J Surg. 2013;100:933–9.
49. Perez RO, Habr-Gama A, Sao Juliao GP, et al. Optimal timing for assessment of tumor response to neoadjuvant chemoradiation in patients with rectal cancer: do all patients benefit from waiting longer than 6 weeks? Int J Radiat Oncol Biol Phys. 2012;84:1159–65.
50. Van den Begin R, Kleijnen JP, Engels B, et al. Tumor volume regression during preoperative chemoradiotherapy for rectal cancer: a prospective observational study with weekly MRI. Acta Oncol. 2018;57:723–7.
51. Perez RO, Habr-Gama A, Sao Juliao GP, et al. Predicting complete response to neoadjuvant CRT for distal rectal cancer using sequential PET/CT imaging. Tech Coloproctol. 2014;18:699–708.
52. Smith JJ, Chow OS, Gollub MJ, et al. Organ Preservation in Rectal Adenocarcinoma: a phase II randomized controlled trial evaluating 3-year disease-free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy, and total mesorectal excision or nonoperative management. BMC Cancer. 2015;15:767.
53. Hayden DM, Jakate S, Pinzon MC, Giusto D, Francescatti AB, Brand MI, Saclarides TJ. Tumor scatter after neoadjuvant therapy for rectal cancer: are we dealing with an invisible margin? Dis Colon Rectum. 2012;55(12):1206–12.
54. Duldulao MP, Lee W, Streja L, Chu P, Li W, Chen Z, Kim J, Garcia-Aguilar J. Distribution of residual cancer cells in the bowel wall after neoadjuvant chemoradiation in patients with rectal cancer. Dis Colon Rectum. 2013;56(2):142–9.
55. Perez RO, Habr-Gama A, Pereira GV, et al. Role of biopsies in patients with residual rectal cancer following neoadjuvant chemoradiation after downsizing: can they rule out persisting cancer? Color Dis. 2012;14:714–20.
56. Maas M, Lambregts DM, Nelemans PJ, et al. Assessment of clinical complete response after chemoradiation for rectal cancer with digital rectal examination, endoscopy, and MRI: selection for organ-saving treatment. Ann Surg Oncol. 2015;22:3873–80.
57. Murad-Regadas SM, Regadas FS, Rodrigues LV, et al. Role of three-dimensional anorectal ultrasonography in the assessment of rectal cancer after neoadjuvant radiochemotherapy: preliminary results. Surg Endosc. 2009;23:1286–91.
58. Murad-Regadas SM, Regadas FS, Rodrigues LV, et al. Criteria for three-dimensional anorectal ultrasound assessment of response to chemoradiotherapy in rectal cancer patients. Color Dis. 2011;13:1344–50.
59. Lambregts DM, Maas M, Bakers FC, et al. Long-term follow-up features on rectal MRI during a wait-and-see approach after a clinical complete response in patients with rectal cancer treated with chemoradiotherapy. Dis Colon Rectum. 2011;54:1521–8.
60. Patel UB, Taylor F, Blomqvist L, et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. J Clin Oncol. 2011;29:3753–60.
61. Lambregts DM, van Heeswijk MM, Delli Pizzi A, et al. Diffusion-weighted MRI to assess response to chemoradiotherapy in rectal cancer: main interpretation pitfalls and their use for teaching. Eur Radiol. 2017;27(10):4445–54.
62. Lambregts DM, Vandecaveye V, Barbaro B, et al. Diffusion-weighted MRI for selection of complete responders after chemoradiation for locally advanced rectal cancer: a multicenter study. Ann Surg Oncol. 2011;18:2224–31.
63. Guillem JG, Ruby JA, Leibold T, Akhurst TJ, Yeung HW, Gollub MJ, Ginsberg MS, Shia J, Suriawinata AA, Riedel ER, Mazumdar M, Saltz LB, Minsky BD, Nash GM, Paty PB, Temple LK, Weiser MR, Larson SM. Neither FDG-PET nor CT can distinguish between a pathological complete response and an incomplete response after neoadjuvant chemoradiation in locally advanced rectal cancer: a prospective study. Ann Surg. 2013;258(2):289–95.
64. Perez RO, Habr-Gama A, Gama-Rodrigues J, et al. Accuracy of positron emission tomography/computed tomography and clinical

assessment in the detection of complete rectal tumor regression after neoadjuvant chemoradiation: long-term results of a prospective trial (National Clinical Trial 00254683). Cancer. 2012;118:3501–11.
65. Rymer B, Curtis NJ, Siddiqui MR, Chand M. FDG PET/CT can assess the response of locally advanced rectal cancer to neoadjuvant chemoradiotherapy: evidence from meta-analysis and systematic review. Clin Nucl Med. 2016;41:371–5.
66. Dos Anjos DA, Perez RO, Habr-Gama A, et al. Semiquantitative volumetry by sequential PET/CT may improve prediction of complete response to neoadjuvant chemoradiation in patients with distal rectal cancer. Dis Colon Rectum. 2016;59:805–12.
67. Sao Juliao GP, Karagkounis G, Fernandez LM, et al. Conditional survival in patients with rectal cancer and complete clinical response managed by watch and wait after chemoradiation: recurrence risk over time. Ann Surg. 2020;272(1):138–44.
68. van der Valk MJM, Hilling DE, Bastiaannet E, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet. 2018;391:2537–45.
69. Benson AB, Venook AP, Al-Hawary MM, Cederquist L, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Engstrom PF, Grem JL, Grothey A, Hochster HS, Hoffe S, Hunt S, Kamel A, Kirilcuk N, Krishnamurthi S, Messersmith WA, Meyerhardt J, Mulcahy MF, Murphy JD, Nurkin S, Saltz L, Sharma S, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Wuthrick E, Gregory KM, Gurski L, Freedman-Cass DA. Rectal cancer, Version 2.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2018;16(7):874–901.
70. Habr-Gama A, São Julião GP, Gama-Rodrigues J, et al. Baseline T classification predicts early tumor regrowth after nonoperative management in distal rectal cancer after extended neoadjuvant chemoradiation and initial complete clinical response. Dis Colon Rectum. 2017;60:586–94.
71. Habr-Gama A, Sao Juliao GP, Vailati BB, et al. Organ preservation among patients with clinically node-positive rectal cancer: is it really more dangerous? Dis Colon Rectum. 2019;62(6):675–83.
72. Nasir I, Fernandez L, Vieira P, et al. Salvage surgery for local regrowths in Watch & Wait - are we harming our patients by deferring the surgery? Eur J Surg Oncol. 2019;45:1559–66.
73. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol. 2010;11:835–44.
74. Hupkens BJP, Martens MH, Stoot JH, et al. Quality of life in rectal cancer patients after chemoradiation: watch-and-wait policy versus standard resection - a matched-controlled study. Dis Colon Rectum. 2017;60:1032–40.
75. Habr-Gama A, Lynn PB, Jorge JM, et al. Impact of organ-preserving strategies on anorectal function in patients with distal rectal cancer following neoadjuvant chemoradiation. Dis Colon Rectum. 2016;59:264–9.
76. Chen Z, Liu Z, Li W, Qu K, Deng X, Varma MG, Fichera A, Pigazzi A, Garcia-Aguilar J. Chromosomal copy number alterations are associated with tumor response to chemoradiation in locally advanced rectal cancer. Genes Chromosomes Cancer. 2011;50(9):689–99.
77. Garcia-Aguilar J, Chen Z, Smith DD, Li W, Madoff RD, Cataldo P, Marcet J, Pastor C. Identification of a biomarker profile associated with resistance to neoadjuvant chemoradiation therapy in rectal cancer. Ann Surg. 2011;254(3):486–92; discussion 492–3.
78. de Rosa N, Rodriguez-Bigas MA, Chang GJ, et al. DNA mismatch repair deficiency in rectal cancer: benchmarking its impact on prognosis, neoadjuvant response prediction, and clinical cancer genetics. J Clin Oncol. 2016;34:3039–46.
79. Hasan S, Renz P, Wegner RE, et al. Microsatellite instability (MSI) as an independent predictor of pathologic complete response (PCR) in locally advanced rectal cancer: a National Cancer Database (NCDB) analysis. Ann Surg. 2020;271(4):716–23.
80. Duldulao MP, Lee W, Nelson RA, et al. Mutations in specific codons of the KRAS oncogene are associated with variable resistance to neoadjuvant chemoradiation therapy in patients with rectal adenocarcinoma. Ann Surg Oncol. 2013;20:2166–71.
81. Chow OS, Kuk D, Keskin M, et al. KRAS and combined KRAS/TP53 mutations in locally advanced rectal cancer are independently associated with decreased response to neoadjuvant therapy. Ann Surg Oncol. 2016;23:2548–55.
82. Perez RO, Habr-Gama A, Sao Juliao GP, et al. Should we give up the search for a clinically useful gene signature for the prediction of response of rectal cancer to neoadjuvant chemoradiation? Dis Colon Rectum. 2016;59:895–7.
83. Lopes-Ramos C, Koyama FC, Habr-Gama A, et al. Comprehensive evaluation of the effectiveness of gene expression signatures to predict complete response to neoadjuvant chemoradiotherapy and guide surgical intervention in rectal cancer. Cancer Genet. 2015;208:319–26.
84. Bettoni F, Masotti C, Habr-Gama A, et al. Intratumoral genetic heterogeneity in rectal cancer: are single biopsies representative of the entirety of the tumor? Ann Surg. 2017;265:e4–6.
85. Jimenez L, Perez RO, Sao Juliao GP, et al. Prediction of poor response to neoadjuvant chemoradiation in patients with rectal cancer using a DNA repair deregulation score: picking the losers instead of the winners. Dis Colon Rectum. 2020;63:300–9.
86. Ganesh K, Wu C, O'Rourke KP, et al. A rectal cancer organoid platform to study individual responses to chemoradiation. Nat Med. 2019;25:1607–14.

Proctectomy for Rectal Cancer

29

John Migaly and Eric G. Weiss

Key Concepts

- Removal of the rectum and mesorectum should routinely be performed using sharp dissection in the plane surrounding the mesorectal fascia to ensure removal of all mesorectum at risk for nodal spread.
- The quality of the mesorectum should be graded and the non-peritonealized radial margin of resection inked so that the pathologist can measure circumferential margin status.
- Multidisciplinary decision-making regarding the use of neoadjuvant and/or adjuvant therapy improves outcomes in patients with rectal cancer.
- Functional derangements are common following restorative proctectomy. Minimizing these derangements should be kept in mind when choosing type of neorectal reservoir and/or whether to perform anastomosis. Patients suffering from anterior resection syndrome may benefit from ongoing support and counseling.
- Adherence to oncologic principles should be maintained when performing proctectomy using minimally invasive surgical techniques.
- Locally advanced rectal cancer extending into other organs requires expertise at dissection outside of the usual tissue planes. With proper planning and combined surgery with other specialties, patients may enjoy good long-term outcomes.
- Pelvic failure rates have improved significantly over the past several decades as a result of increased attention to detail during proctectomy and the increased use of neoadjuvant therapy.

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Background

As recently as four decades ago, pelvic recurrence following resection of locally advanced rectal cancer was estimated to be about 30%, with over 80% of those recurrences becoming clinically evident within the first 2 years following surgery. During this same time period, the overall recurrence rate was noted to be approximately 40% for generalist surgeons and between 10% and 20% for specialist surgeons, bringing attention to the concept that operative technique may have a profound impact on prognosis [1]. Since that time, there has been a focus on the quality of proctectomy for rectal cancer and the use and timing of adjuvant radiotherapy and chemotherapy that has improved outcomes for patients.

Bill Heald et al. demonstrated that attention to anatomic detail during proctectomy was associated with good outcomes and were successful in promoting this concept throughout the surgical community. Heald emphasized that appropriate resection of the mesorectum in rectal cancer surgery was the key to minimize pelvic recurrence. The embryologic planes are defined by the fascia propria of the mesorectum and the structures contained within this fascia: perirectal fat, blood vessels, and the lymph nodes and channels. Heald encouraged surgeons to strive for extirpation of the contents of this space along embryologic fusion planes, as a means to reduce local recurrence of rectal cancer [2].

At the same time, Phil Quirke, a pathologist colleague of Heald, described optimal gross and histologic evaluation of proctectomy specimens, specifically the measurement of circumferential radial margin (CRM) and grade of mesorectal excision. As opposed to prior custom, where only the proximal and distal margins of resection were thought to be of importance, it became clear that assessment of CRM was critical, as the most common cause of pelvic failure was not the axial extent of the tumor but rather the radial spread of the tumor. This should not have been surprising, as one would assume that all margins of resection are equally important. Pathologic data dating back three decades demon-

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strates that rectal cancer with less than a 1 mm circumferential resection margin (<1 mm considered a positive resection margin) has a greater than 50% local recurrence rate, while those with a greater than 1 mm margin had a 17% local recurrence rate [3, 4]. Achieving negative CRM can be challenging, because of the bony confines of the pelvis, along with key vasculature and urogenital structures at the margins of resection.

The work of Heald and Quirke heralded the era of "specimen-oriented surgery," as they promoted the concept of "total mesorectal excision" (TME). The complete excision of the contents of the mesorectal envelope at risk for mesorectal metastases is the driving principle of proctectomy. It is the sharp dissection along these planes and the intact removal of the mesorectum and the contents therein that minimizes the risk of local recurrence. In head-to-head comparisons of "traditional" low anterior resection or abdominal perennial resection versus utilization of the technique of TME, TME technique yields significant reduction in the local recurrence rates.

The now routine utilization of radiation and chemotherapy in the neoadjuvant setting for the treatment of locally advanced rectal cancer represents the second most significant leap forward in improving cancer related outcomes after proctectomy. Anna Martling and her colleagues provided additional data to legitimize the idea that radiotherapy in combination with TME, further reduces the risk of recurrence of rectal adenocarcinomas in comparison to TME alone [5–7].

Anatomy of the Rectum and Mesorectum

A nerve sparing proctectomy that utilizes the technique of TME is facilitated by a working knowledge of the embryologic origins of the structures within the pelvis; this yields greater understanding of the dissection planes and patterns of lymphatic and non-lymphatic spread of rectal tumors.

The hindgut develops into the rectum and the upper portion of the anal canal. The last portion of the hindgut becomes the cloaca with the allantois. The urogenital septum forms between the cloaca and allantois and form the perineal body which separates the urogenital structures from the terminal gastrointestinal tract. These planes form the basis of the planes utilized for TME.

The blood supply to the rectum can be considered to be segmental; however, in truth, the rectum has a rich interconnected submucosal vascular plexus which makes the rectum very difficult to truly devascularize during proctectomy. The hindgut receives its blood supply from the dorsal mesentery which eventually becomes the mesorectum. The upper rectum receives its blood supply from the inferior mesenteric artery (IMA) which comes directly off of the abdominal aorta. The IMA splits into left colic artery and superior rectal (hemorrhoidal) artery 2–3 cm from its origin at the aorta. The left colic artery courses superiorly toward the splenic flexure and the superior rectal artery courses inferiorly toward the rectum at the root of the mesentery.

It should be noted that there is not universally agreed upon nomenclature regarding the IMA and its branches, as some surgeons assert that the IMA becomes the superior rectal artery when it "crosses the common iliac artery," after it has given off some of the sigmoidal arteries. This latter designation is potentially problematic, as it ignores the principle of naming arteries based on their branch points, and because it is difficult to ascertain exactly where an artery "crosses" another anatomically in space, especially after mobilization of the mesosigmoid. This distinction is important during proctectomy for rectal cancer, as a precise definition of arterial anatomy is key to understanding potential differences in outcome following "high" versus "low" ligation of the IMA/superior rectal artery. One surgeon's "high" ligation of the IMA might be considered "low" ligation (of the superior rectal artery) by another.

The superior rectal artery supplies blood to the upper third of the rectum, while the middle rectal artery supplies the blood to the mid rectum. Despite being a structure included in all anatomic and surgical texts, the middle rectal artery is identifiable in about 10–20% of patients at the time of surgery. The inferior rectal artery supplies the lowest third of the rectum and arises from the terminal branches of the internal iliac artery. The venous drainage of the rectum somewhat mirrors the arterial blood supply, with the venous supply of the upper rectum draining into the portal circulation via the inferior mesenteric vein and the remainder of the rectum draining into the systemic system via the iliac veins.

The mesorectum itself contains lymph nodes, blood supply, perirectal fat, and connective tissue associated with the rectum. The mesorectum is surrounded by an envelope of tissue referred to as the fascia propria of the rectum. Along the "sacral hollow," there are the iliac vessels, the hypogastric nerves, and the presacral veins which are covered by a thin lining anteriorly of what is referred to as the presacral fascia. Between the presacral fascia and the fascia propria of the rectum is an avascular, loose areolar plane which is the plane of dissection for an oncologic proctectomy for tumors that do not broach the mesorectal fascia. This is what Bill Heald refers to as the "holy plane" of dissection (Fig. 29.1). The degree of precision by the surgeon while dissecting in this plane determines whether or not the patient has a complete oncologic resection and a complete mesorectum on pathology review. Violating the fascia propria of the rectum can result in retained mesorectum after extirpation, which increases the likelihood of recurrence, and violating the presacral fascia can result in nerve injury leading to subsequent sexual and/or bladder dysfunction. Violating the presacral

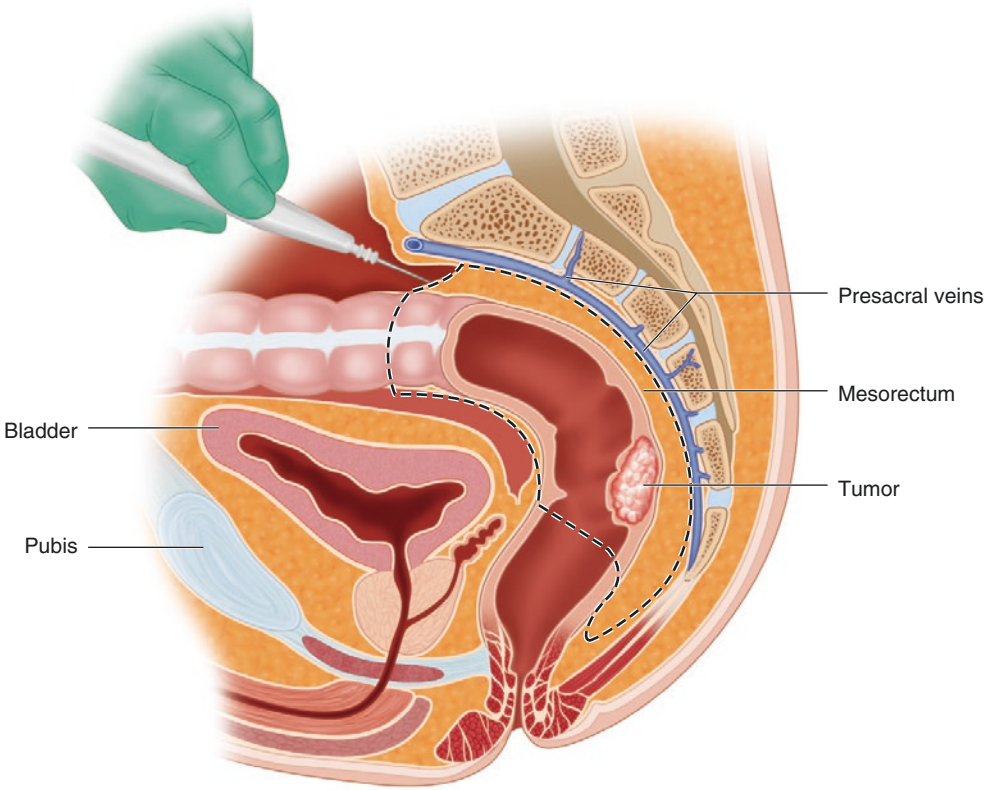

Fig. 29.1 The "holy plane" described by Heald is demonstrated

fascia can also result in bleeding from the iliac vessels or the presacral venous plexus. Bleeding from the presacral venous plexus can be quite problematic, as the venous pressure in the pelvic plexus can be comparable or even higher than the pressure in the inferior vena cava. The dissection for an oncologic proctectomy or TME when performed correctly should be sharp and bloodless.

Anteriorly, at about the middle third of the rectum, the rectum is separated from the prostate/seminal vesicles and autonomic nerve plexus by a thin septum known as Denonvilliers' fascia. Remaining outside or posterior to Denonvilliers' fascia during dissection decreases the likelihood that the periprostatic or perivaginal autonomic nerves being injured (Fig. 29.2). There is usually very little or no mesorectal tissue between the rectum and the prostate or vagina anteriorly at the lowest third of the rectum.

Posteriorly, at approximately the level of S4, the presacral fascia and the fascia propria of the rectum connect and thicken to form Waldeyer's fascia, which needs to be divided during a proctectomy to fully mobilize the rectum posteriorly to the levator muscle complex [8].

The sympathetic innervation of the urogenital organs originates from the superior hypogastric plexus and the parasympathetic innervation arises from the pelvic splanchnic nerves. The superior hypogastric plexus travels caudally from about the level of the inferior mesenteric artery toward the bifurcation of the aorta along the anterior surface of the aorta. At the level of the sacral promontory, the hypogastric plexus splits into two discrete nerves: the left and right hypogastric nerves. The hypogastric nerves travel along the pelvic side wall, lateral and posterior to the pelvic plexus. They are joined by the pelvic splanchnic nerves, also known as the pelvic autonomic nerves, the *nervi erigentes*. When these sympathetic and parasympathetic nerves intermingle, they are known as the inferior hypogastric plexus. The inferior hypogastric plexus can be tethered to the mesorectum inferolaterally and must be separated carefully during dissection. Injuries to these nerves can result in urogenital abnormalities such as urinary retention, retrograde ejaculation in the case of sympathetic nerve injury, and loss of erection in the case of parasympathetic nerve injury [9].

Priorities in Proctectomy for Rectal Cancer

The innumerable permutations of neoadjuvant therapy for locally advanced rectal cancer, ranging from short-course radiation only to total neoadjuvant therapy, do not obviate the need for a skilled surgeon with impeccable operative technique. The effects of neoadjuvant therapy and optimal surgery are additive, not compensatory. There are an ever-expanding number of technologies available to the surgeon, which adds additional complexity to the options; however, priorities in rectal cancer surgery should stay constant:

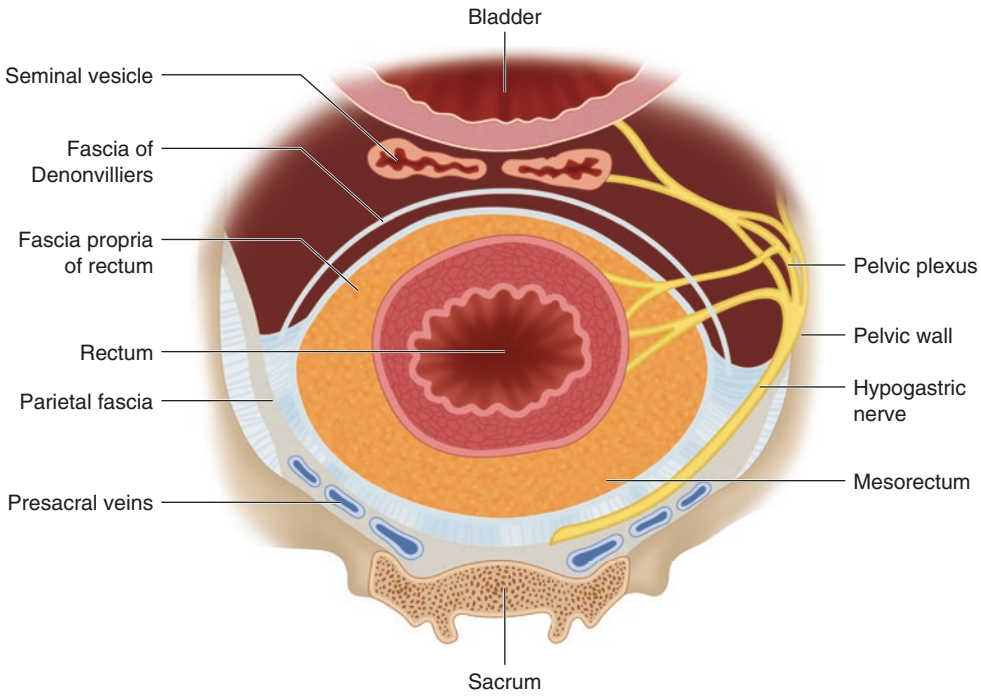

Fig. 29.2 Axial view of the rectum demonstrating the relevant anatomical structures to perform nerve sparing total mesorectal resection

1. An appropriate mesorectal excision using sharp dissection should be performed to provide the optimal oncologic resection.
2. Nerve sparing proctectomy should be performed.
3. Continent reconstruction should be performed whenever possible, but not at the expense of positive resection margin or poor functional outcome.

Preoperative Preparation

Typically, patients undergoing elective proctectomy will undergo cathartic bowel preparation and oral antibiotics (neomycin/erythromycin or neomycin/metronidazole). Rectal washout in the operating room or enemas immediately preoperatively can be helpful to clean remaining stool from the rectum, but should not be used in lieu of oral mechanical bowel preparation (MBP) in combination with oral antibiotics (OA).

Despite the decades-long debate that follows Nichols' work in colon antisepsis and the multiple paradigm shifts that ensued, currently there is high-quality registry data that support the use of MBP in combination with OA [10–14]. In a study of 9940 patients in the Veteran's Affairs Surgical Quality Improvement Program, it was found that patients undergoing colectomy with both MBP and OA had half the rate of surgical site infection (SSI) as those patients who underwent MBP alone and also half the rate of SSI when compared to those patient who underwent no bowel preparation [15]. In a series of 4999 patients using the National Surgical Quality Improvement Program (NSQIP) registry, patients who received MBP with OA had significant lower SSI, anastomotic leak, and procedure-related readmission when compared with those who had no bowel preparation, MBP alone or OA only [16]. An additional NSQIP study of 8442 patients found that combined MBP with OA was independently associated with a reduced rate of anastomotic leak and postoperative ileus [17].

The most recent version of the American Society of Colon and Rectal Surgeons Clinical Practice Guidelines Committee's published practice parameters recommends the combined use of both "MBP" with OA for the use of bowel preparation before elective colon and rectal surgery [18]. Margolin et al. published the largest series to date looking at 27,804 undergoing elective colorectal resections and recapitulated prior findings of the benefits of combined MBP and OA on SSI, deep organ space infection, and anastomotic leak but also showed no increased risk of *Clostridium difficile* infection in these patients [19].

Studies examining the benefits of rectal enemas versus traditional MBP are predominantly small limited series that are poorly designed; therefore we do not advise substituting rectal enemas for MBP with OA [20–23]. Furthermore, if restorative proctectomy with proximal fecal diversion is contemplated, enemas will not adequately clear the stool from the intervening colon (between the loop stoma and the anastomosis). If anastomotic leak occurs, this residual stool may slowly extrude from the leak site.

Potential stoma sites should be marked preoperatively and the patient educated regarding stoma care by an enterostomal therapist (ETRN)/certified wound ostomy continence nurse (CWOCN).

Operative Approaches

Open Low Anterior Resection

The patient is placed in the low lithotomy or split-leg position. Lithotomy is necessary for cases in which handsewn coloanal anastomosis is contemplated; split leg is preferred when stapled anastomosis will be performed. In open cases, ureteral stents are not usually helpful unless it is a reoperative pelvic procedure (e.g., recurrence) or a patient with markedly elevated body mass index (BMI). A digital rectal examination should be performed to both localize the tumor and assess diameter and compliance of the anus, which will assist in selection of stapler size for stapled end to end anastomoses. If the tumor cannot be palpated, it may be helpful to perform proctoscopy at this time to localize the tumor. Proctoscopy should also be used liberally throughout the rectal dissection to ensure that tumor location is precisely identified. Palpation of the tumor through the rectal wall during proctectomy may be inaccurate, especially in cases where the tumor is small or the patient has undergone neoadjuvant therapy. Flexible video endoscopy with carbon dioxide insufflation is preferred, as the entire operating team can view the images and the use of carbon dioxide will limit bowel distention.

A midline incision is typically performed so as to accommodate temporary intestinal stoma sites. It can be extended as cephalad as necessary to allow for safe mobilization of the splenic flexure. In rare cases of patients with a redundant sigmoid colon identified on preoperative imaging and low BMI, a Pfannenstiel incision can be utilized.

Dissection typically begins with sigmoid colon in a lateral to medial technique along the white line of Toldt. The sigmoid colon is mobilized off of the retroperitoneum in a cephalad direction toward the descending colon. The left-sided gonadal vessels can be located during the sigmoid colon mobilization at the level of the pelvic inlet, and the vessels can be traced to their entrance into the inguinal canal. The left ureter can be located medial to the left gonadal vessels at the level of the bifurcation of the left common iliac artery. It is sometimes helpful to place a vessel loop around the left ureter to aid with subsequent confirmations of the location and course of the left ureter. Mobilization of the left colon continues to include the mobilization of the splenic flexure. The loose attachments to the spleen are sharply taken, and the colon is mobilized off of Gerota's fascia. Attention is then turned toward entering the lesser sac at the level of the mid-transverse colon; the transverse colon is retracted and the omentum is retracted away from it. The omentum is usually split into two leaflets, both of which must be divided in order to enter the lesser sac. The correct plane is identified when the surgeon can see the anterior surface of the body and tail of the pancreas and the posterior wall of the stomach. Once this is assured, the transverse colon can be liberated from its omental attachments by sequentially dividing the omentum from the transverse colon toward the flexure. The splenic flexure must be completely mobilized to allow for maximal mobility.

The inferior mesenteric vein is identified at its root at the level of the ligament of Treitz. A high ligation of the IMV is performed, after meticulously assuring that there are no arterial branches in the tissue to be divided. A high ligation of the IMV will sometime supply as much as an additional 15 cm of reach of the left colon into pelvis. Any remaining mesenteric attachments of the left colon are taken off the tail and body of the pancreas flush with its lower border.

Once this is done, the patient is placed in slight Trendelenburg, and the small bowel is placed behind moist lap sponges in the right upper quadrant to facilitate pelvic dissection. The rectosigmoid junction is retracted upward and out of the abdomen. The sacral promontory is identified along with the superior rectal artery immediately above it at the root of the rectosigmoid mesentery. There should be a bare area in the sulcus between these two structures. The cautery is used to score the investing layer of the mesentery at this location beginning 1–2 cm superior to the sacral promontory, just posterior to the arc of the superior rectal artery, and then extending the division of the peritoneum to the root of the IMA. Dissection in this space allows for entry into the areolar plane between the presacral fascia and the fascia propria of the rectum beginning at the sacral promontory. The hypogastric nerve plexus is swept posteriorly and preserved. Once this space is opened up, the surgeon passes the hand below the superior rectal artery and through to the other side of the mesentery. Then the dissection is carried cephalad in this avascular plane along the anterior surface of the aorta until the inferior mesenteric artery is identified. The artery is skeletonized, taking care to assure that the nerve fibers of the superior hypogastric plexus are brushed downward and preserved.

The surgeon then decides whether to divide the IMA at the aorta or whether to divide the superior rectal artery at its origin (about 2 cm from the aorta) while preserving the left colic artery. This is a decision based on mobility and quality of the colon conduit, as there have been no demonstrable differences in oncologic outcomes when comparing the techniques. The advantage of dividing the IMA at the aorta is greater mobility; the downside is that arterial supply to the conduit is solely from the left branch of the middle colic artery which must be meticulously preserved during mobilization of the splenic flexure and division of the IMV. The advantage of dividing the superior rectal artery at its origin is that the conduit has dual blood supply from both the middle colic artery and IMA (via the left colic artery, which rotates on its axis inferiorly provided that the splenic flexure was completely mobilized and the IMV divided); the downside is loss of some mobility of the conduit. In patients with distal rectal tumors, it is typical that division of the IMA at the

aorta is necessary. In patients with proximal rectal tumors and a redundant sigmoid colon, it is often possible to preserve the left colic artery. In order to assure adequate length of the left colon conduit, the tip of the mobilized conduit should be able to reach the base of the penis in a male and the mons pubis in a female.

The colon is then divided at approximately the descending sigmoid junction, and the intervening mesentery is divided. Division of the colon should be undertaken by a method consistent with the planned anastomotic technique. If a straight stapled end-to-end anastomosis is contemplated, the colon can be divided sharply, purse-string suture placed, and anvil of the stapler inserted. The distal side of the colon on the specimen can be oversewn with suture. There is no need to utilize a mechanical stapler to divide the colon at this juncture, as both sides of the staple line will ultimately be removed from the patient, and using a stapler will thus be a needless expense. However, if a colonic J-pouch or Baker anastomosis is contemplated, and then it is appropriate to divide the colon with a linear cutting stapler. If a handsewn coloanal anastomosis is planned, the colon can be divided sharply and closed with suture or stapled to minimize any chance of spillage when the conduit is passed to the anus. The left colon conduit is then placed behind moist lap sponges along the small bowel in the upper abdomen.

Attention is then turned toward the rectal dissection. The operating surgeon, most commonly using a St. Marks retractor, retracts the rectum anteriorly and toward the pubic symphysis to accentuate the plane between the presacral fascia and the fascia propria of the rectum; this plane is referred to as "the holy plane." Posteriorly the left and right hypogastric nerves are identified and kept out of harm's way. The dissection should be done entirely utilizing sharp dissection with the electrocautery or scissors (Fig. 29.3). This dissection should be bloodless if the appropriate planes are maintained. The loose areolar fibers are divided posteriorly in small brush like strokes as the assistant periodically repositions the St. Marks retractor deeper and deeper as the posterior dissection proceeds. As the dissection proceeds posteriorly toward the tip of the coccyx, this loose areolar tissue coalesces and thickens to form Waldeyer's fascia. Waldeyer's fascia is subsequently divided until the superior portion of the levators is encountered. The lateral stalks are taken in the same fashion down to the pelvic floor. Alternatively, a bipolar vessel sealing device can be utilized to divide the lateral stalks at the pelvic sidewall, which may minimize bleeding from the middle rectal arteries. As always, the benefit must be balanced with the cost of the device. Anteriorly the plane between the rectum and the seminal vesicles/prostate or vagina must be carefully dissected so as to ensure complete removal of the tumor and also to avoid injury to the prostate/vagina and nerves that lie adjacent to Denonvilliers' fascia. For mid and distal rectal cancers, the rectum must be freed up anteriorly down to the pelvic floor so that a stapler can be used to transect the rectum flush with the levators. Prior to transection of the rectum, it is imperative that tumor location is confirmed. Flexible video proctoscopy allows for the abdominal surgeon to identify the exact level of the tumor just prior to rectal division. Rectal transection at this level can be challenging. Options include utilizing a low-profile transverse stapling device or a laparoscopic linear cutting stapler.

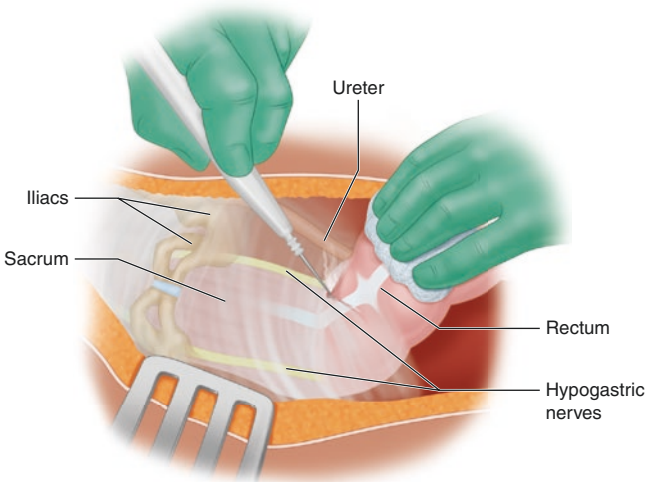

Fig. 29.3 The loose areolar tissue is sharply divided with electrocautery

For proximal rectal cancer, there is no oncologic benefit to removal of mesorectum more than 5 cm distal to the tumor; thus a "tumor specific mesorectal excision" may be performed. This will allow preservation of the distal rectum, which is associated with improved functional outcomes and lower anastomotic leak rates as compared to removal of nearly the entire rectum and distal colorectal or coloanal anastomosis. It is, however, critical to divide the mesorectum at the appropriate level perpendicular to the longitudinal axis of the rectum and avoid "coning in" on the mesorectum. Unfortunately, the moniker "TME" is used to describe this technique as well, which causes some confusion. Overall, it is better to think of "TME" as a technique of dissecting in the avascular plane surrounding the mesorectum, rather than as an operation. "Proctectomy" is the more appropriate term for the operation.

For very distal cancers that do not invade the anal sphincter muscles or pelvic floor, it may be appropriate to divide the rectum via a transanal approach. This can be done prior to, after, or synchronously with the abdominal mobilization. Placement of a self-retaining retractor and utilization of any of a number of operating anoscopes may facilitate exposure. The rectum is typically divided using electrocautery in full-thickness fashion at an appropriate distance from the tumor. The dissection proceeds proximally in the appropriate plane outside of the mesorectum, with the goal of connecting

with the mobilization performed by the abdominal operator. It is frequently helpful to have the abdominal operator help guide the dissection by placing a hand in the pelvis in the previously dissected spaces which can then be identified by palpation from the perineum.

In an effort to restore intestinal continuity despite the presence of a tumor in the most distal rectum, some surgeons have advocated performing "intersphincteric resection" with removal of some or all of the internal anal sphincter muscle and construction of coloanal anastomosis. Others have extended the resection to include a portion of the external anal sphincter muscle when indicated by tumor anatomy. Interpreting data regarding oncologic and functional outcomes has been challenging, as there is no precise definition of "intersphincteric resection" with regard to how much of the sphincter is removed, and there is a paucity of prospective randomized trials. Results from case series (mostly from Japan and South Korea) have been mixed, although it appears that ypT3 disease and partial external anal sphincter resection during restorative proctectomy are associated with suboptimal outcomes [24–28].

Once the rectum is passed off of the table, the surgeon should observe a layer of glistening tissue overlying the mesorectum which represents an intact fascia propria of the rectum without any noticeable divots in the mesorectum (Fig. 29.4). The non-peritonealized radial margin should be marked with ink, optimally by the surgeon prior to sending it to the pathology laboratory. Typically, low colorectal and coloanal anastomoses should be constructed in conjunction with a proximal diverting loop ileostomy, placed approximately 25–30 cm proximal to the ileocecal valve. In rare cases, patients will have a redundant proximal colon that will allow for diverting loop distal transverse colostomy, which may be preferable as colostomy is associated with less risk of dehydration than ileostomy.

Straight Stapled Anastomosis

For continent reconstruction, there are several options that will be described. A straight stapled colorectal/coloanal anastomosis is the most common anastomosis described; it is performed using an end-to-end stapler and the anvil placed via a purse-string suture in the distal end of left colon conduit. The stapler is then passed transanally, and the pin of the stapler is brought out through the rectum as close as possible to the rectal transection staple line to avoid an ischemic ridge of tissue adjacent to a newly created anastomosis.

Following anastomotic construction, endoscopic inspection and pneumatic leak test should be performed. This is ideally accomplished using flexible video endoscopy with carbon dioxide insufflation. The proximal colon is occluded,

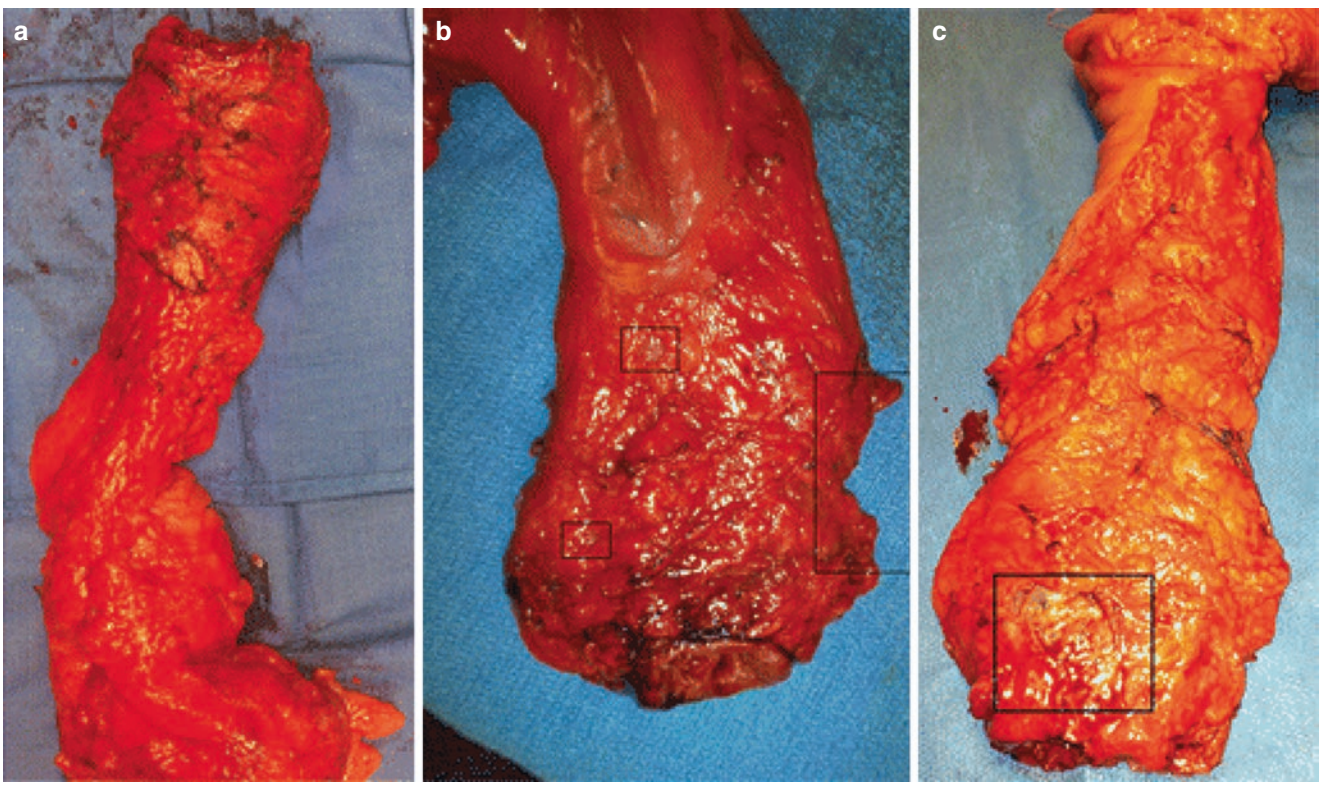

Fig. 29.4 TME specimens. (**a**) Complete TME specimen. (**b**) Nearly complete TME specimen. (**c**) Incomplete TME specimen. The *black outlines* indicate areas of mesorectal fascia violation. (Reused with permission from Fleshman [88]. Copyright © 2016 Springer Nature)

the pelvis is filled with saline, and gas is instilled via the colonoscope. Bubbling indicates a defect in the anastomosis, which should be repaired. The mucosa should be pink and healthy both proximally and distally, indicative of adequate arterial flow. Any areas of pulsatile hemorrhage can be addressed, typically using endoscopic clips.

Handsewn Coloanal Anastomosis

A handsewn coloanal anastomosis can be used in one of two situations: when an ultralow anastomosis is required or when there is a stapler misfire, wherein a handsewn technique can be used to salvage a technical mishap. It is often helpful to have orienting sutures on the colonic conduit to avoid twisting as it is passed by the abdominal operator to the perineal operator. Typically the anastomosis is created using single-layer absorbable suture, placed in interrupted and/or running fashion. Initial placement of sutures in the four quadrants of the anastomosis may facilitate exposure and orientation for the remaining sutures.

Colonic J-Pouch Anastomosis

The reservoir function of a straight coloanal anastomosis may not be ideal for many patients, and thus in select patients, there is the option of performing colonic J-pouch reconstruction. In brief, the distal conduit is folded into a "J-type" configuration that is approximately 7 cm in length and the antimesenteric bowel surface of the apex of the "J" is opened so that an 75–80 mm linear stapler can be passed into each limb of the colon and then fired, thus creating an approximately 7–8 cm common channel. If a double-stapled anastomosis is possible, the anvil of the stapler is subsequently sewn into the apex of the J-pouch, and an end-to-end anastomosis is performed as previously described (Fig. 29.5). If a handsewn coloanal anastomosis is performed, sutures are placed at the apex of the J-pouch, and it is delivered via the anus, the apex opened, and a handsewn anastomosis created as described above. J-pouch reconstruction is only possible if the folded colonic conduit will both reach to the anus and fit in the pelvis. Patients with visceral obesity and a narrow pelvis are often not suit-

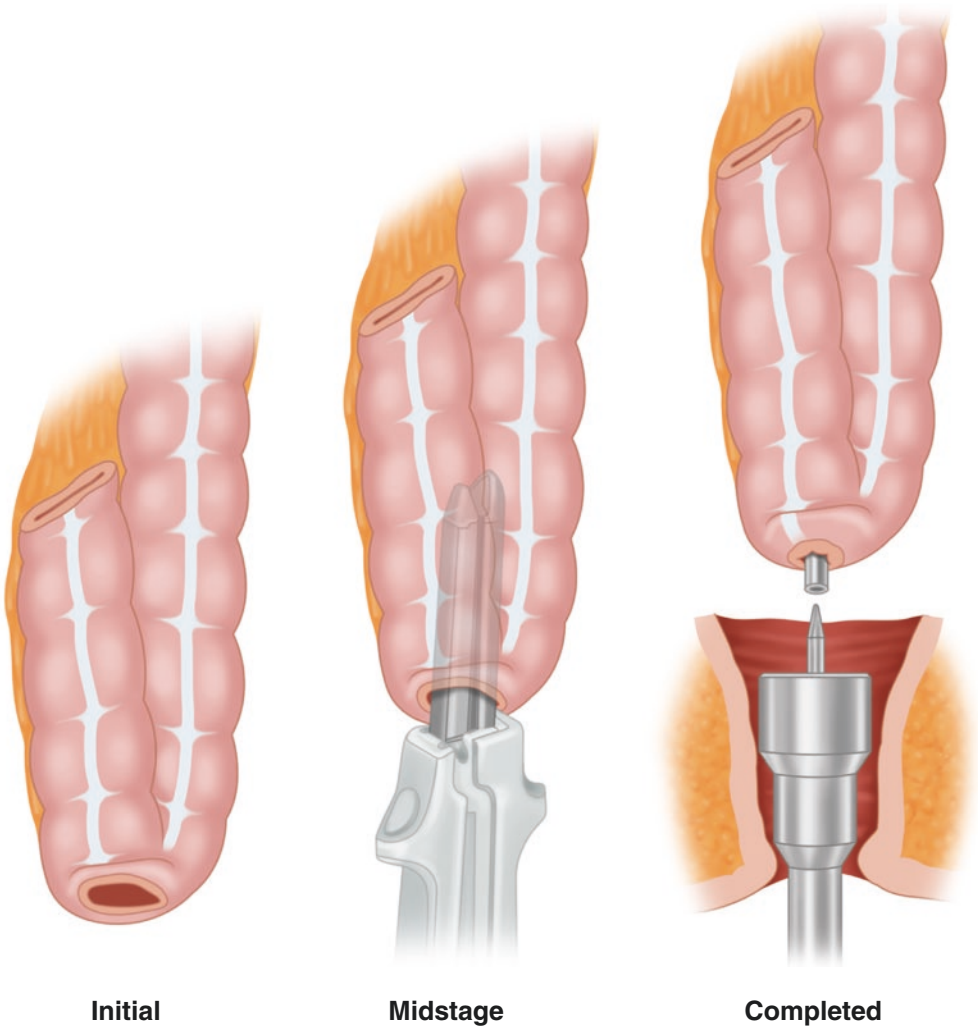

Fig. 29.5 The colon is folded onto itself and a J-pouch is created

able for this reconstruction. These parameters should be carefully assessed prior to construction of the pouch.

End-to-Side Anastomoses

In many cases, particularly in the narrow pelvis of males, or in obese patients, a colonic J-pouch is too bulky to be placed into pelvis. Another option for reconstruction is an end-to-side anastomosis which is a variant of a "Baker" reconstruction. A 3 cm side segment seems to be the most reasonable configuration. Several studies and reviews have found the Baker anastomosis is associated with function similar to that of a colonic J-Pouch [29].

Transverse Coloplasty

Transverse coloplasty is a technique to create a neorectum that avoided the need to pass the double thickness of colon with its mesentery into the pelvis, as is required for J-pouch anastomosis. An 8–10 cm incision is made along the longitudinal axis of the colon terminating about 5 cm proximal to the distal end. The incision is then closed transversely, creating a small pouch. Coloplasty was performed more frequently in the past, although recently its use has declined, as several studies have shown higher likelihood of leak and no difference in function when compared to other neorectal configurations [30–32].

Laparoscopic Low Anterior Resection

There are a variety of techniques that have been described to successfully accomplish laparoscopic low anterior resection (see Chap. 36). What follows is a description of the authors' preferred method. The patient is placed in the low lithotomy or split-leg position with both arms tucked. The knees should be no higher than the shoulders so that there is no potential for interference with the instruments during splenic flexure mobilization. The perineal area and buttocks should overhang the edge of the bed so that access to the perineum and anus are not obstructed and so the stapler can be easily angulated upward or downward. The chest is secured to the bed to allow for the extreme Trendelenburg and airplaning required.

After achieving pneumoperitoneum with a Veress needle in the left upper quadrant, the Veress needle is replaced with a 5 mm port. Diagnostic laparoscopy is then performed to assure that there is no evidence of peritoneal carcinomatosis, liver metastasis, or other factors that may alter the operative plan. After this, the following ports are placed under direct laparoscopic visualization: a supraumbilical 12 mm trocar, a 5 mm left iliac fossa trocar, a 5 mm right upper-quadrant trocar, and a 12 mm right iliac fossa trocar. The 5 mm camera is usually upsized to a 10 mm, 30° laparoscope. The 10 mm laparoscope typically provides a better-quality image and requires fewer camera exchanges (Fig. 29.6).

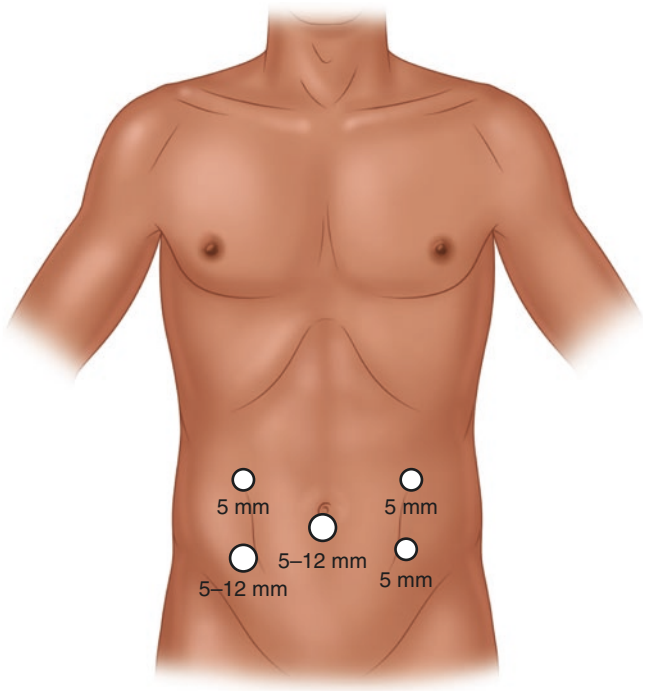

Fig. 29.6 Port placement for a laparoscopic low anterior resection

The sigmoid colon is placed on tension such that the IMA is clearly identified at its origin. We typically approach the mesentery from medial to lateral. The electrocautery is used to incise the investing layer at the root of the rectosigmoid mesentery. The mesentery is scored at a point just above the sacral promontory but beneath the superior rectal artery, and the incision is taken toward the root of the IMA. The loose areolar plane between the underside of the sigmoid mesentery and the retroperitoneum is identified, and the dissection is taken laterally with the goal of identifying the left ureter and the left gonadal vein. The origin of the IMA is skeletonized, and the ureter is once again identified before typically performing a high ligation of the IMA (see above). The inferior mesenteric vein (IMV) is then ligated proximal to any branch points. The high ligation of the IMA and the IMV is necessary not only from and oncologic perspective but also to assure that the left colon conduit can reach easily into the pelvis for a tension-free anastomosis. (See discussion above.)

The dissection is then continued underneath the sigmoid and the left colon mesentery until the left abdominal side wall is encountered. The left colon is then rotated and flipped medially, and the white line of Toldt (now purple in color) is easily taken with scissors or energy device.

The next task is to perform a complete laparoscopic mobilization of the splenic flexure. The lesser sac is entered, and

the splenic flexure is mobilized from the transverse colon side and from the left gutter. Attention is then turned toward the rectal dissection.

The assistant retracts the rectosigmoid junction of the colon toward the abdominal wall and slightly leftward. The operating surgeon retracts the rectum upward and toward the pubic symphysis to accentuate the plane between the presacral fascia and the fascia propria of the rectum; this plane is referred to as "the holy plane." Posteriorly the left and right hypogastric nerves are identified and kept out of harm's way. The loose areolar fibers are divided posteriorly identically in the fashion of a total mesorectal excision, past the tip of the coccyx, dividing Waldeyer's fascia until the superior portion of the levators are encountered. The lateral stalks are taken in the same fashion down to the pelvic floor. Anteriorly, the plane between the rectum and the seminal vesicles/prostate or vagina must be carefully dissected so as not to injure the prostate/vagina or nerves that lie adjacent to Denonvilliers' fascia. The rectum must be freed up anteriorly down to the pelvic floor so that a stapler can be used to transect the rectum flush with the levators. The rectum is pulled upward out of the pelvis and leftward, and then a laparoscopic bowel stapler is brought through the right iliac fossa 12 mm trocar and articulated so that the angle between the staple line and rectum is as close to 90° as possible. It is unlikely the pelvis will be wide enough to accommodate a 60 mm stapler; therefore, a 45 mm or 30 mm long stapler is usually the stapler of choice. The stapler is advanced across the rectum as far as possible and the stapler is fired. It is rare that the rectum can be completely transected with one stapler fire. However, minimizing the number of fires will minimize the number of crossing staple lines and subsequently the likelihood of a staple line leak. Once the rectum is transected, the specimen is exteriorized through any one of a number of incisions: periumbilical, left lower quadrant, Pfannenstiel, or from the site that will be used for the ileostomy/colostomy. After extracting the specimen, the colon is divided proximally at the sigmoid/descending colon junction. Usually if the exteriorized left colon can reach the pubic symphysis, there is sufficient length for a low colorectal anastomosis.

A purse-string suture is placed at the open end of the colon conduit and stapler anvil inserted. The colon is reduced back into the abdomen and the abdomen is reinsufflated. The colon is grasped, and care is taken to assure that the colon and mesentery are not twisted. An anvil grasper is used to draw the anvil into the pelvis. The assistant then passes the stapler transanally and engages it with the anvil under direct laparoscopic visualization. In female patients, as the stapler is closed, care must be taken to assure the posterior wall of the vagina is not incorporated into the staple line. After the stapler is closed, a vaginal exam is helpful in assuring that the posterior wall of the vagina moves freely and is not in any way tethered. The stapler is then fired and the anastomotic donuts are examined for completeness. Endoscopic inspection of the anastomosis and pneumatic leak test should be performed as described above. Construction of temporary proximal fecal diversion (loop ileostomy or colostomy) should be strongly considered, as described above.

Robotic Low Anterior Resection

The robotic surgery platform has rapidly become many surgeons' preferred approach for minimally invasive proctectomy. The ergonomics, magnification, 3D visualization, and wristed instrumentation make robotic surgery an attractive alternative to traditional laparoscopy. Most surgeons have evolved to a single-dock technique for LAR, particularly in light of the versatility of the da Vinci® Xi™ system. While there are innumerable port site configurations, below is a fairly simple single-dock port setup.

Pneumoinsufflation is established by placement of a right upper-quadrant optical trocar which then subsequently serves as the "assistant port." The bed is then placed in about 30° Trendelenburg and approximately 8° right side down. A diagonal line is drawn from the right anterior superior iliac spine (ASIS) through the umbilicus and to the left subcostal margin. The first robot port is placed along this line midway between left ASIS and the umbilicus. The next port is placed to the left of the prior port (along the same diagonal line) approximately 8 cm away with the final two ports, each being placed 8 cm to the left of the prior port along the same line. The first robot port will be the stapling port and the second will serve as the camera port. The robot will be brought in from the patient's left side.

The dissection in a robotic LAR is fairly identical to the technique for standard laparoscopy described earlier. After transection of the rectum, the specimen can be exteriorized after the robot is undocked. The remainder of the case, including anastomosis can be completed using standard laparoscopy.

Transanal Total Mesorectal Excision

Transanal total mesorectal excision (taTME) is a more novel technique that attempts to facilitate the most troublesome part of a minimally invasive proctectomy, namely, the final 3–6 cm of distal rectal dissection and distal rectal transection. The taTME is described as a two-team simultaneous approach, wherein one team works laparoscopically from the abdomen to mobilize the colon and splenic flexure, ligate the IMA and IMV, and mobilize the upper half of the rectum.

The other team works via a transanal approach by first starting with a circumferential full-thickness transection beginning in the intersphincteric plane and proceeding in a

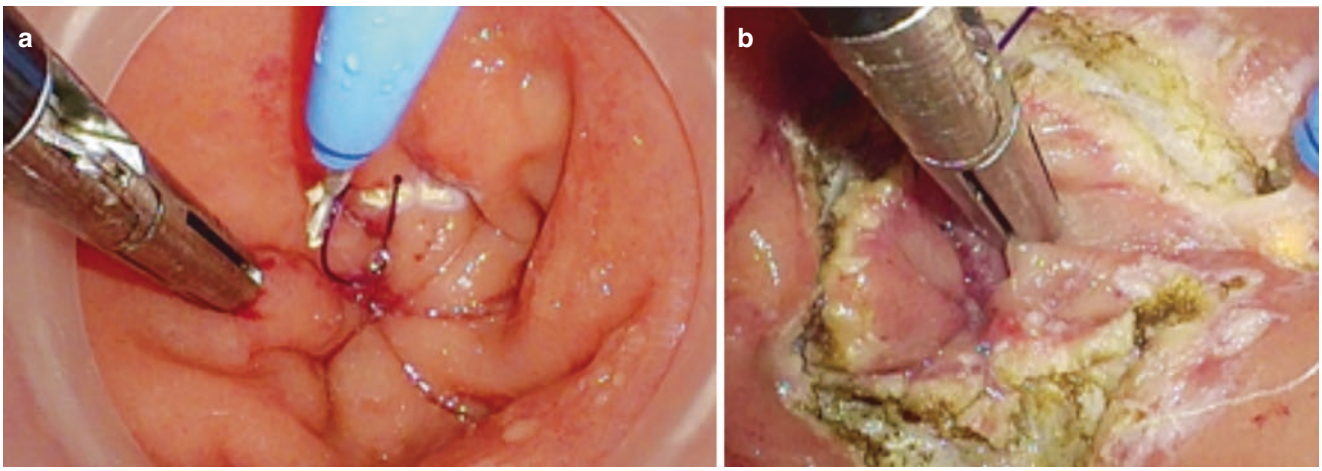

Fig. 29.7 Transanal anal view of taTME. (**a**) Rectal purse-string closure. (**b**) Full-thickness circumferential transection. (Reused with permission [33]. Copyright © 2007 Elsevier)

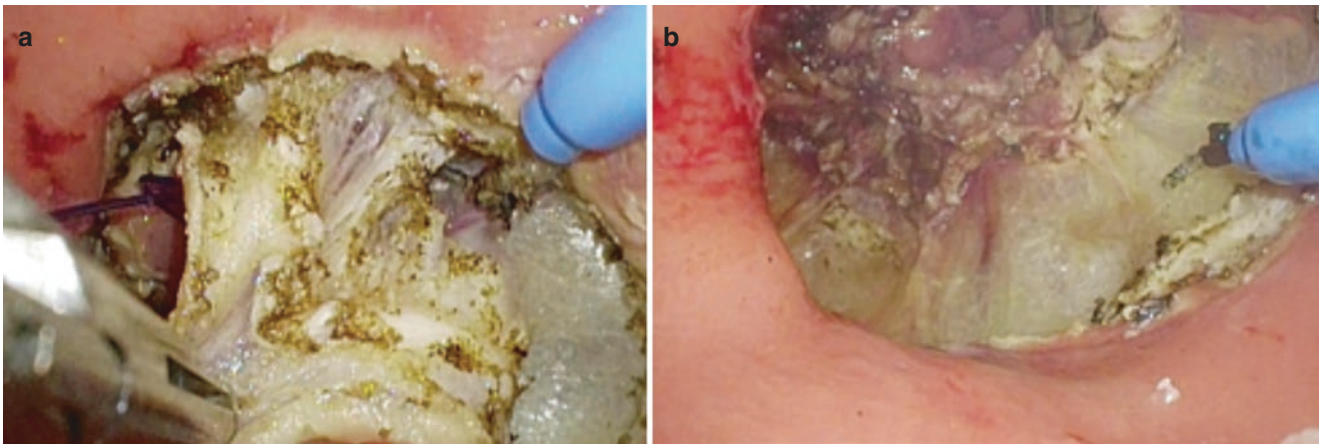

Fig. 29.8 Down-to-up dissection of taTME. (**a**) Anterior plane. (**b**) Posterior plane. (Reused with permission [33]. Copyright © 2007 Elsevier)

cephalad direction up to the top of the anorectal ring (Fig. 29.7). Once this achieved, a rectal pneumoinsufflation device is placed in the rectum, and the rectum is insufflated with CO_2. The team then proceeds to perform the distal half of the proctectomy from an anal approach via what is essentially transanal, single-port laparoscopy in a "down-to-up" approach (Fig. 29.8) [33]. When the two teams meet, the fully mobilized rectum is then pulled out of the transanal site and transected. A handsewn or stapled low colorectal/coloanal anastomosis is then performed, typically with diverting loop ileostomy/colostomy.

Proponents of taTME claim that the technique allows for a better distal margin and greater lymph node harvest; however, a meta-analysis of 11 studies encompassing 757 patients could not demonstrate any difference in cancer-/pathology-related outcomes and short-term complications with taTME in comparison with traditional laparoscopic LAR [34].

Results from the International taTME registry seem to indicate that there are more intraoperative adverse events than would be expected for this type of procedure. Many of these events involve serious complications such as bleeding or urethral transection. The taTME is a novel technique with a fairly steep learning curve whose potential benefits have not been clearly demonstrated. Further data needs to mature before the true utility and transferability of this technique can be evaluated [35–37].

Abdominoperineal Resection

The subset of rectal cancer patients who undergo abdominoperineal resection (APR) is decreasing over time, most likely because many patients with ultralow tumors that do not invade the external sphincter muscle, or pelvic floor are now undergoing restorative proctectomy with low colorectal/colo-

anal anastomosis rather than APR. However, patients who have a tumor invading the external sphincter muscle or pelvic floor would be most appropriately treated by APR. Incontinence alone is not an indication for APR, as there is no need to subject the patient to excision of their pelvic floor unless invaded by tumor. Incontinent patients with rectal cancer may be best served by Hartmann resection or intersphincteric proctectomy with preservation of the pelvic floor musculature if blowout of a short rectal stump is of concern.

The abdominal approach to APR is similar to that for restorative proctectomy, using either open, laparoscopic, or robotic techniques described above. The major difference is that the splenic flexure does not need to be mobilized routinely for APR. It is the authors' preference to perform the abdominal portion of the procedure, extending the dissection to the pelvic floor, and then to create the colostomy, close the abdomen, and place the patient in the prone position for the perineal portion of the dissection. Although some surgeons complete the dissection in the lithotomy position, we feel that the exposure afforded by the prone position facilitates accurate dissection and is our favored approach.

Before placing the patient prone, a large cylindrical bump or pillow should be placed on the table to elevate patient's pelvis and buttocks and create flexion at the hip. After the patient is placed prone on the table, the buttocks are taped widely apart, and the perineum is shaved. The anus is sewn shut to prevent fecal soilage. The perineal area is then prepped and draped. The important landmarks for the perineal portion of the case are the tip of the coccyx, the ischial tuberosities, and the midpoint of the perineum. These should be marked prior to incision. An elliptical incision around the anus is made from the coccyx to the midpoint of the perineum, outside of the anal sphincter muscle. The dissection is initiated posteriorly at the level of the coccyx, and the incision is deepened through the anococcygeal ligament and then onto the anterior surface of the coccyx until the pelvis is entered. This is the safest and easiest place enter the pelvis from the perineum. The dissection is then taken posterolaterally through the levators and then laterally from ischial tuberosity to ischial tuberosity [38].

Once the posterior two-thirds of the anus and rectum (including the levators) are liberated, then the specimen can be everted through the perineum, leaving only the distal anterior portion of the rectum and anus still attached

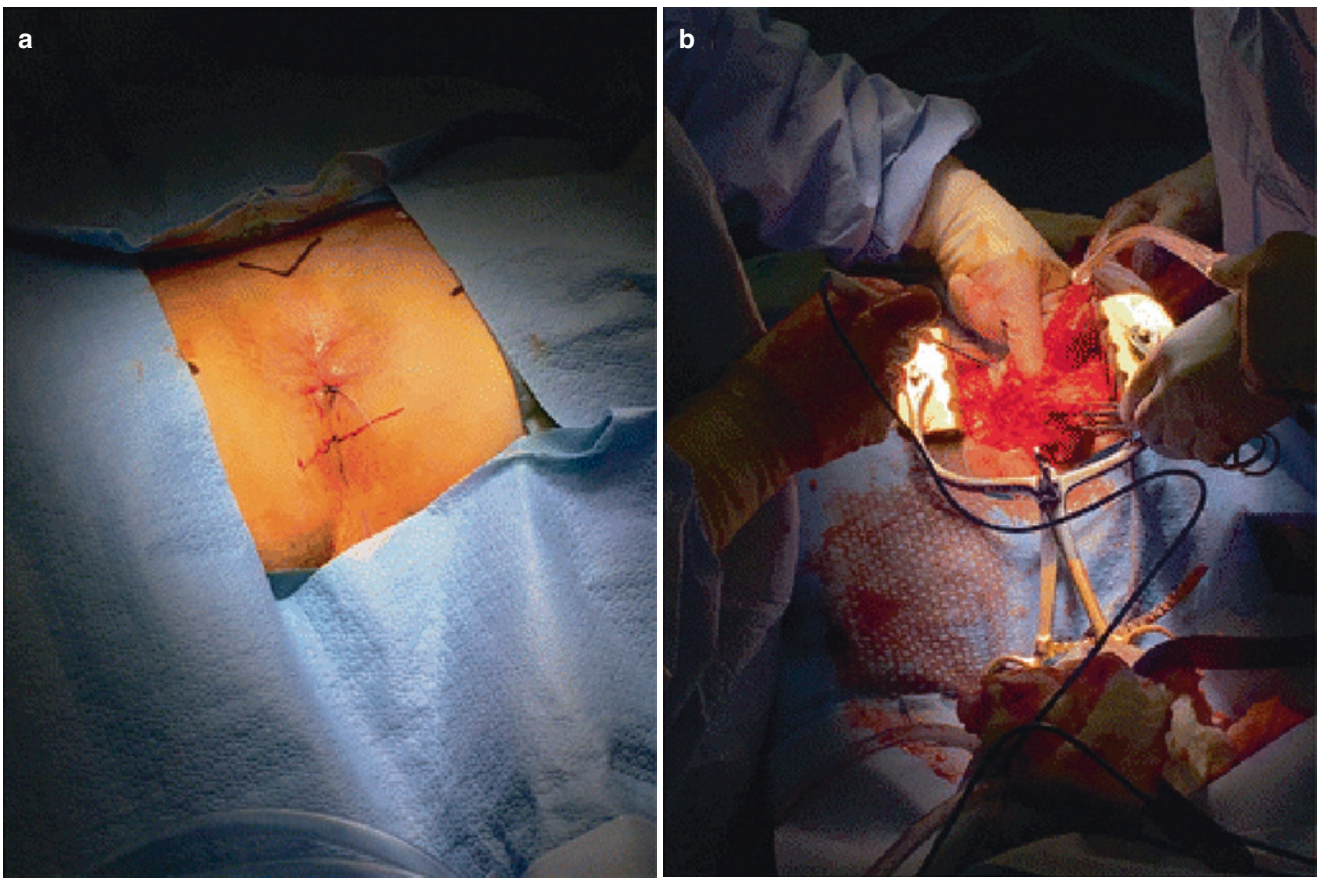

Fig. 29.9 Perineal dissection. (**a**) The anus is sutured closed. The coccyx, perineal body, and ischia are identified. (**b**) The specimen is exteriorized thorough the posterior opening with lateral division of the levators. (Reused with permission [38]. Copyright © 2018 Springer Nature)

(Fig. 29.9). The anterior dissection is performed last as it is typically the most challenging. There are multiple possible pitfalls including injury to the membranous urethra/prostate, inadvertent vaginotomy, or specimen perforation.

Once the specimen is removed, the perineum can be closed primarily in layers or using any number of adjunctive tissue transfer technique described in the next section (Fig. 29.9).

The extralevator abdominoperineal excision (ELAPE) has been described as an alternate method to decrease the likelihood of a positive circumferential resection margin and specimen perforation. This ELAPE or cylindrical APR is meant to be a much wider excision of the pelvic floor and is meant to avoid "the waisting" of the specimen that usually happens when dissecting the distal rectum to the pelvic floor during the abdominal portion. The dissection stops at a much higher point during the abdominal portion, and the cylindrical APR is completed from the perineal portion to create a specimen that is more uniform with less narrowing at the pelvic floor (Fig. 29.10). However, in one of the largest nationwide database studies examining the short-term oncologic outcomes of ELAPE versus traditional APR including 954 patients, there was found to be no benefit to ELAPE [39]. In patients with non-circumferential tumors, there would seem to be no obvious benefit to the wide resection of the pelvic floor contralateral to the tumor. This should be considered during operative planning, as pelvic floor defects after ELAPE can be substantial, most requiring tissue transfer for closure.

Reconstruction After APR

The perineal wound is the most common source of morbidity after APR, with wound complication rates estimated to be as high as 66% with primary closure. Many perineal wound complications are not only attributable to the wound being located in a weight-bearing area, but in addition, the overwhelming majority of these patients have received neoadjuvant radiotherapy to the pelvis. There are many reconstructive options available such as a gracilis flap, vertical rectus myocutaneous muscle (VRAM) flap, anterolateral thigh flap, and gluteal-based fasciocutaneous flaps. Some flaps may be harvested with the associated skin pedicle to reconstruct the posterior vagina after proctectomy with en bloc vaginectomy. Many of the flaps themselves often result in donor site complications or morbidity. For example, a VRAM flap very often results in an abdominal wall hernia but may provide the greatest tissue mass to the pelvis. When considering the use of flap coverage for a perineal wound, consideration should be given to the size of the defect, use of preoperative external beam radiotherapy, and the likelihood and impact of donor site morbidity [40–45].

A well-vascularized omental pedicle flap placed into the pelvis can serve as a very useful adjunct to a primary closure of the perineum, especially in cases of uncertain radial margins where postoperative boost dose radiotherapy is being considered. Filling the pelvis with omentum may help to avoid small bowel toxicity due to radiotherapy. Placement of fiducials guides radiation delivery in these cases. Closed-suction drainage of the pelvis can also prevent excessive fluid buildup which could affect healing of a perineal wound [46–48].

Low Anterior Resection Syndrome

As oncologic outcomes have improved following close adherence to the principles elucidated above, there has been increased focus on function and quality of life following rectal cancer treatment, particularly as it relates to bowel function [49]. There has been persistent controversy as to whether patients with distal rectal cancer have a better quality of life with a restorative or non-restorative proctectomy [50, 51]. There is almost no patient that when initially diagnosed with rectal cancer isn't concerned that they may need a permanent stoma. Yet, it is virtually impossible for the patient to truly comprehend the potential for poor functional outcome that may occur following restorative operations, particularly those with low or ultralow anastomoses (coloanal or intersphincteric), especially following radiotherapy. The patient's

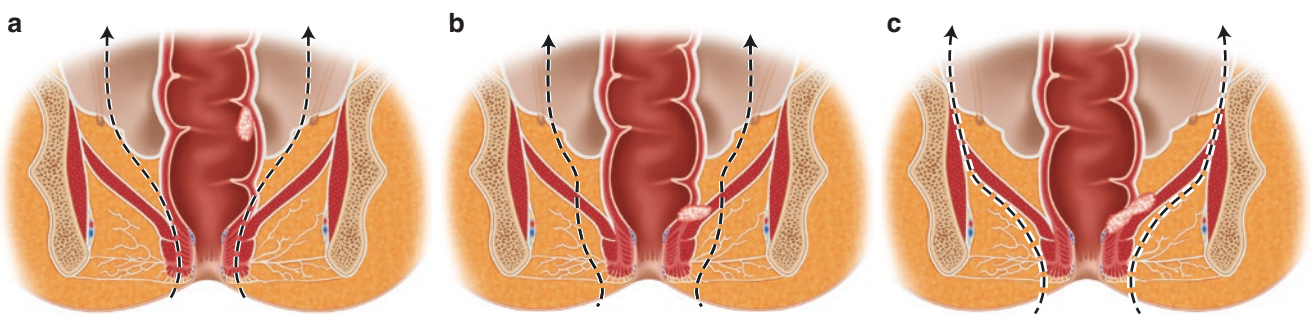

Fig. 29.10 Planes for APR resection. (**a**) Intersphincteric. (**b**) Extrasphincteric. (**c**) Extralevator

desire to avoid a stoma and the surgeons desire to accomplish that goal lead most to choose a restorative operation if it is an option, as opposed to a permanent colostomy.

Studies have shown that when less than 4 cm of native rectum is left in situ following low anterior resection, there is loss of rectal reservoir function and significant alterations in bowel function [52]. As noted previously, surgeons have employed several types of neorectal reservoir configurations including colonic J-pouches, coloplasty pouches, ileocecal reservoirs, and side-to-end anastomoses in an effort to mitigate the effect of rectal loss on bowel function [53–55]. It remains unclear which reconstructive technique offers the best functional outcomes; however, coloplasty pouches have all but been abandoned, as have ileocecal reservoirs, in favor of colonic J-pouches and side-to-end anastomoses. Several recent comparisons of colonic J-pouches and side-to-end anastomoses showed similar long-term function between the two methods with slightly better short-term function (up to 6 months) with a colonic J-pouch [56, 57].

The recognition that patients suffered substantial alterations in bowel function following restorative proctectomy dating back to at least the 1980s was termed "anterior resection syndrome" and described as "disordered bowel function after rectal resection, leading to a detriment in quality of life" [58]. Anterior resection syndrome typically includes some degree of fecal incontinence, incomplete evacuations, clustering of bowel movements, straining at bowel movements, and discomfort associated with bowel movements. Initially thought to be transient and to resolve over time, it is now known that these symptoms may persist indefinitely. Although improvement does occur, it tends to plateau at about 2 years following resection. In addition to loss of rectal reservoir, other potential etiologies for this syndrome include anal sphincter damage and dysfunction, sensory neural dysfunction in the neorectum, and disordered motility of the neorectum.

Recently a Delphi method of consensus among multiple societies considering surgeon, patient, and other healthcare workers' perspectives was published, broadening and better defining the symptoms and consequences of what is now termed "low anterior resection syndrome" (LARS) [59]. In this consensus, eight symptoms and eight consequences were agreed upon, and any given patient must have at least one of each to meet the new definition of having LARS. The symptoms include variable and unpredictable bowel function, emptying difficulties, altered stool consistency, urgency, incontinence, increased stool frequency, repeated painful bowel movements, and soiling. The consequences include toilet dependence, preoccupation with bowel function, dissatisfaction with bowel habits, strategies and compromises to manage symptoms, and adverse impact on mental and emotional well-being, social and daily activities, relationships and intimacy, and roles, commitments, and responsibilities. Having at least once symptom and one consequence would qualify a patient to meet the criteria for having LARS.

The severity of LARS can be determined in part by utilizing a scoring instrument such as the LARS score, initially described in 2012 [60]. The LARS score uses five questions/items (incontinence for flatus, incontinence for liquid stools, clustering, frequency, and urgency) that are scored to come up with a composite score from 0 to 42. A score of 0–20 is not consistent with LARS; a score of 21–29 equates with "minor LARS"; and a score of 30–42 equates with "major LARS." Other scoring systems such as the Bowel Function Instrument (BFI), created by Memorial Sloan Kettering Cancer Center, have not been widely adopted, despite it being more comprehensive than the LARS score [61].

Once diagnosed, a variety of treatment options are available, ranging from simple medical therapy aimed at symptom improvement to redo anastomoses adding some form of rectal reservoir. Some authors have proposed that there are two distinct sets of symptoms and propose classifying patients to guide therapy. One group has incontinence, frequency, and urgency, while the other group has constipation and incomplete evacuation [62]. However, some patients have a combination of symptoms.

Medical therapy should begin with dietary modification, instructing patients to take between 25 and 35 g of dietary fiber daily. This should be accompanied by a fluid intake of 6–8 glasses of a non-caffeinated beverage throughout the day. Depending on the stool consistency, using stool softeners and/or laxatives may also be added to this regime. Dietary consultation for more specific inclusions and exclusions within one's diet may further improve bowel function. If basic therapy should fail, then escalation to other treatments should be considered.

Biofeedback therapy or pelvic floor physical therapy may improve fecal incontinence scores, number of bowel movements, and anal manometry results [63]. Sacral nerve stimulation (SNS) has been reported in seven studies in LARS included as part of a systemic review [64]. SNS had a reported "success rate" of 74%, a result that is comparable to that seen with SNS for fecal incontinence from any cause. Overall, 32 of 34 patients having permanent implantation experienced clinical improvement, and two failed to respond to treatment. Other options include 5HT3-receptor antagonists, transanal lavage, probiotics, and a stoma.

Multivisceral or Extended Resections

Although the need for multivisceral or extended resections occurs more commonly when one is contemplating the surgical management of recurrent rectal cancer, there are times

where these resections need to be considered at the time of initial diagnosis and treatment of primary rectal tumors. Approximately 10% of primary rectal cancers invade other organs [65]. Due to only a few organs or structures in proximity of the rectum, a limited number of multivisceral or extended resections of adjacent organs or structures are performed. Anteriorly the vagina, uterus, prostate, seminal vesicles, and bladder may be involved by direct extension of the cancer. Laterally the ureters and iliac vessels may be involved in upper rectal cancers. Anything more laterally involved and within the pelvic sidewall is usually deemed unresectable. Posteriorly the coccyx or sacrum may be involved. In a single-institution series reporting on 61 patients with locally advanced rectal cancer, multivisceral resection most often involved urogenital structures anteriorly with bladder, prostate, uterus, ovaries, and vagina being the most commonly resected en bloc [66]. This should not be surprising, as tissues anterior to the rectum are soft viscera, while posterolaterally there is bone and pelvic sidewall.

In women, involvement of the uterus, cervix, and/or vagina can typically be managed by en bloc resection of those organs, which usually includes the ovaries and fallopian tubes. Depending on the amount of vagina resected and the size of the residual defect, primary closure vs some form of plastic surgical flap reconstruction may be required. In men, anterior extension of the dissection can be more challenging. En bloc resection of the seminal vesicles and/or prostate is possible, but it is technically more straightforward, with greater likelihood of achieving an R0 resection if pelvic exenteration (proctectomy with en bloc cystoprostatectomy with urinary conduit) is performed. It should be noted that if pelvic exenteration is performed, creation of a colonic urinary conduit is usually straightforward and has the advantage of avoiding intestinal anastomosis, as compared to ileal conduit. Isolated distal ureteral involvement can be managed by en bloc resection and primary ureteral reimplantation into the bladder. If the tumor extends posteriorly to the bony pelvis, more extensive preoperative planning is usually necessary. En bloc coccygectomy is relatively straightforward, but sacrectomy is more complex. Multispecialty planning and operative involvement by an orthopedic oncologist and/or neurosurgeon are paramount to achieving a safe resection (see Chap. 31). Lateral sidewall involvement is the most difficult and often does not allow for an R0 resection. Consideration for intraoperative radiation therapy should be considered in these cases if a resection is attempted in those who appear to have resectable disease [67].

Locally advanced rectal cancers invading other structures are staged as T4b. Patients with T4b rectal cancers often require surgery that has been described as "primary rectal cancer beyond TME planes" (PRCbTME) by the Beyond the Total Mesorectal Excision Collaborative and require surgery outside of the standard planes to achieve an R0 resection [68]. These planes are not well understood by most colorectal surgeons, unless they routinely perform resection of T4b or recurrent rectal cancers. The typical mesorectal plan or "holy plane" described by Heald that all are familiar with is not the plane at least in the area of the en bloc resection that is utilized [69]. Becoming familiar with planes of "extended resections" which would be the plane outside the mesorectal plane lateral to the ureters and the deeper plane exposing the iliac vessels and lateral pelvic nerves and lateral lymph nodes is important so that en bloc resections can be safely and properly performed.

Typically if any of these structures are involved or locally invaded at the time of initial diagnosis of rectal cancer and confirmed by imaging including MRI of the pelvis, there should be strong consideration for some form of neoadjuvant therapy to improve the chance of resectability and increase the chance of an R0 resection. The ability to achieve an R0 resection is paramount to being able to obtain long-term, disease-free survival. A systematic review of multivisceral resections reported a 5-year overall survival of 53% which was higher than resections for recurrent rectal cancers at 20% [70].

Neoadjuvant chemoradiation therapy with long-course radiation, 5400 Gy combined with intravenous 5-fluorouracil or oral capecitabine allows for excellent tumor regression. Regression can lead to higher rates of R0 resection, make borderline resectable tumors resectable, and result in tumor downstaging that may improve overall outcomes. Multiple scoring systems are available that assess tumor response either histologically or radiographically following neoadjuvant chemoradiation therapy. Most commonly some form of tumor regression grade (TRG) is utilized. Regardless of which system is used, there is a positive correlation between TRG grade and outcomes such as local recurrence [71]. Currently the concept of "total neoadjuvant therapy" (TNT) is gaining popularity (See Chap. 26). TNT delivers all adjuvant therapy prior to surgery, typically delivered as short-course radiotherapy or long-course chemoradiotherapy followed by multidrug cytotoxic chemotherapy. This type of regimen is better tolerated, and chemotherapy completion rates are higher than with standard split regimes, and further downstaging and regression can occur [72]. TNT may be considered for any patient with locally advanced primary rectal cancer.

As with all rectal cancer management, presentation at a multidisciplinary tumor board is beneficial, especially when patients require multivisceral or extended resections. Review of treatment planning with colleagues in the fields of medical oncology, radiation oncology, radiology and pathology, as well as other surgical specialists in urology, gynecology, orthopedics or neurosurgery, and plastic surgery is critical to achieving good outcomes [73, 74].

Oncologic Outcomes

As discussed in the introduction, four decades ago the diagnosis of rectal cancer portended an abysmal course with recurrence rates as high as 30% and poor functional outcomes. Fast forward to present day where there is the routine use of chemotherapy and radiation, the routine use of the TME technique for proctectomy and multidisciplinary evaluation. This has resulted in vast improvement in outcomes for locally advanced rectal cancer. The local recurrence rate worldwide is now estimated to be between 4% and 8%. An analysis of 372,130 patients utilizing the SEER database comparing survival of locally advanced rectal cancer patients versus colon cancer patients found that, stage for stage, survival of locally advanced rectal cancer patients was equivalent, if not superior to that of colon cancer patients [75].

The surgical approaches to the treatment of locally advanced rectal cancer over the past decade have increasingly skewed toward minimally invasive surgical approaches. It is concerning that two large randomized controlled trials, ACOSOG Z6051 in the United States and the ALaCaRT trial in Australia and New Zealand failed to demonstrate noninferiority of the laparoscopic approach using a composite assessment measure of successful resection (radial margin negative, distal margin negative, and mesorectal grade complete or nearly complete), all of which have been demonstrated to have prognostic significance in other trials [76, 77]. It is reassuring, however, to note that despite the concerns regarding the quality of the mesorectal dissection in the laparoscopic groups, there have been no demonstrable differences in survival. Review of non-randomized data from the National Cancer Database (NCDB) including 18,765 patients demonstrated equivalence of the MIS and open procedures [78]. Long-term survival outcomes of ACOSOG Z6051, ALaCaRT, and NCDB have demonstrated equivalence between the two techniques [79–85].

Multidisciplinary Rectal Cancer Care

The regionalization of rectal cancer care in Europe and Asia has created national programs that espouse data-driven approaches to rectal cancer care. The OSTRICH consortium queried the NCDB to assess variations across the United States in the appropriate delivery of chemoradiotherapy for patients with LARC. Adherence was highest in high-volume centers in comparison to community centers (78% vs 69%, OR = 1.46, $p < 0.001$) [85]. This same group also found that the rate of circumferential margin positivity was 17.2%, which is double the rate seen in Europe [86]. The Commission on Cancer's National Accreditation Program for Rectal Cancer (NAPRC) will address many of these issues through creating uniformity in the process measures related to rectal cancer care, such as mandatory MRI staging of all new rectal cancers and requiring the discussion of all patients with newly diagnosed rectal tumors at a multispecialty tumor board [87].

Conclusion

The oncologic and functional outcomes following treatment of curable rectal cancer are overwhelmingly dependent on the skill of the surgeon and his/her familiarity with the appropriate conduct of proctectomy using the technique of total mesorectal excision. Strict adherence to these principles not only minimizes the risk of recurrence but also maximizes the likelihood of nerve preservation. Each surgeon's comfort level with open and minimally invasive approaches needs to be understood so that cancer-related outcomes are not jeopardized in the effort to use varying technologies or approaches. Lastly, in absence of the ability to regionalize rectal cancer care in the United States, formal process-oriented measures such as those described by the NAPRC are some important first steps to improving outcomes and care for curable locally advanced rectal cancer.

References

1. Anderson JM. Chemoradiotherapeutic prevention of local recurrence after stapled anastomoses in rectal cancer. Scott Med J. 1981;26(1):21–3.
2. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery – the clue to pelvic recurrence? Br J Surg. 1982;69(10):613–6.
3. Cawthorn SJ, Parums DV, Gibbs NM, A'Hern RP, Caffarey SM, Broughton CI, et al. Extent of mesorectal spread and involvement of lateral resection margin as prognostic factors after surgery for rectal cancer. Lancet. 1990;335(8697):1055–9.
4. Ng IO, Luk IS, Yuen ST, Lau PW, Pritchett CJ, Ng M, et al. Surgical lateral clearance in resected rectal carcinomas. A multivariate analysis of clinicopathologic features. Cancer. 1993;71(6):1972–6.
5. Arbman G, Nilsson E, Hallbook O, Sjodahl R. Local recurrence following total mesorectal excision for rectal cancer. Br J Surg. 1996;83(3):375–9.
6. Martling A, Holm T, Johansson H, Rutqvist LE, Cedermark B, Stockholm Colorectal Cancer Study G. The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. Cancer. 2001;92(4):896–902.
7. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345(9):638–46.
8. Khatri VP, Rodrigues-Bigas MA, Flewell R, Petrelli NJ. Operative approach to rectal cancer: an anatomical and technical description. Surg Oncol. 2018;27(2):A5–A15.
9. Diop M, Parratte B, Tatu L, Vuillier F, Brunelle S, Monnier G. "Mesorectum": the surgical value of an anatomical approach. Surg Radiol Anat. 2003;25(3–4):290–304.

10. Nichols RL, Broido P, Condon RE, Gorbach SL, Nyhus LM. Effect of preoperative neomycin-erythromycin intestinal preparation on the incidence of infectious complications following colon surgery. Ann Surg. 1973;178(4):453–62.
11. Nichols RL, Condon RE, Gorbach SL, Nyhus LM. Efficacy of preoperative antimicrobial preparation of the bowel. Ann Surg. 1972;176(2):227–32.
12. Nichols RL, Gorbach SL, Condon RE. Alteration of intestinal microflora following preoperative mechanical preparation of the colon. Dis Colon Rectum. 1971;14(2):123–7.
13. Nichols RL, Condon RE. Antibiotic preparation of the colon: failure of commonly used regimens. Surg Clin North Am. 1971;51(1):223–31.
14. Nichols RL, Condon RE. Preoperative preparation of the colon. Surg Gynecol Obstet. 1971;132(2):323–37.
15. Cannon JA, Altom LK, Deierhoi RJ, Morris M, Richman JS, Vick CC, et al. Preoperative oral antibiotics reduce surgical site infection following elective colorectal resections. Dis Colon Rectum. 2012;55(11):1160–6.
16. Scarborough JE, Mantyh CR, Sun Z, Migaly J. Combined mechanical and oral antibiotic bowel preparation reduces incisional surgical site infection and anastomotic leak rates after elective colorectal resection: an analysis of colectomy-targeted ACS NSQIP. Ann Surg. 2015;262(2):331–7.
17. Kiran RP, Murray AC, Chiuzan C, Estrada D, Forde K. Combined preoperative mechanical bowel preparation with oral antibiotics significantly reduces surgical site infection, anastomotic leak, and ileus after colorectal surgery. Ann Surg. 2015;262(3):416–25. discussion 23-5
18. Migaly J, Bafford AC, Francone TD, Gaertner WB, Eskicioglu C, Bordeianou L, et al. The American Society of Colon and Rectal Surgeons clinical practice guidelines for the use of bowel preparation in elective colon and rectal surgery. Dis Colon Rectum. 2019;62(1):3–8.
19. Klinger AL, Green H, Monlezun DJ, Beck D, Kann B, Vargas HD, et al. The role of bowel preparation in colorectal surgery: results of the 2012-2015 ACS-NSQIP data. Ann Surg. 2019;269(4):671–7.
20. Zmora O, Wexner SD, Hajjar L, Park T, Efron JE, Nogueras JJ, et al. Trends in preparation for colorectal surgery: survey of the members of the American Society of Colon and Rectal Surgeons. Am Surg. 2003;69(2):150–4.
21. Bertani E, Chiappa A, Biffi R, Bianchi PP, Radice D, Branchi V, et al. Comparison of oral polyethylene glycol plus a large volume glycerine enema with a large volume glycerine enema alone in patients undergoing colorectal surgery for malignancy: a randomized clinical trial. Color Dis. 2011;13(10):e327–34.
22. Platell C, Barwood N, Makin G. Randomized clinical trial of bowel preparation with a single phosphate enema or polyethylene glycol before elective colorectal surgery. Br J Surg. 2006;93(4):427–33.
23. Pittet O, Nocito A, Balke H, Duvoisin C, Clavien PA, Demartines N, et al. Rectal enema is an alternative to full mechanical bowel preparation for primary rectal cancer surgery. Color Dis. 2015;17(11):1007–10.
24. Park JS, Choi GS, Jun SH, Hasegawa S, Sakai Y. Laparoscopic versus open intersphincteric resection and coloanal anastomosis for low rectal cancer: intermediate-term oncologic outcomes. Ann Surg. 2011;254(6):941–6.
25. Park JS, Kim NK, Kim SH, Lee KY, Lee KY, Shin JY, et al. Multicentre study of robotic intersphincteric resection for low rectal cancer. Br J Surg. 2015;102(12):1567–73.
26. Park IJ, Kim JC. Intersphincteric resection for patients with low-lying rectal cancer: oncological and functional outcomes. Ann Coloproctol. 2018;34(4):167–74.
27. Saito N, Ito M, Kobayashi A, Nishizawa Y, Kojima M, Nishizawa Y, et al. Long-term outcomes after intersphincteric resection for low-lying rectal cancer. Ann Surg Oncol. 2014;21(11):3608–15.
28. Park JS, Park SY, Kim HJ, Cho SH, Kwak SG, Choi GS. Long-term oncologic outcomes after neoadjuvant chemoradiation followed by intersphincteric resection with coloanal anastomosis for locally advanced low rectal cancer. Dis Colon Rectum. 2019;62(4):408–16.
29. Rubin F, Douard R, Wind P. The functional outcomes of coloanal and low colorectal anastomoses with reservoirs after low rectal cancer resections. Am Surg. 2014;80(12):1222–9.
30. Ulrich A, Z'Graggen K, Schmitz-Winnenthal H, Weitz J, Buchler MW. The transverse coloplasty pouch. Langenbeck's Arch Surg. 2005;390(4):355–60.
31. Grimaldi G, Eberspacher C, Romani AM, Merletti D, Maturo A, Pontone S, et al. Modified transverse coloplasty pouch: new reconstruction techniques after total mesorectal excision. Our experience. G Chir. 2017;38(6):285–90.
32. Huttner FJ, Tenckhoff S, Jensen K, Uhlmann L, Kulu Y, Buchler MW, et al. Meta-analysis of reconstruction techniques after low anterior resection for rectal cancer. Br J Surg. 2015;102(7):735–45.
33. Arroyave MC, DeLacy FB, Lacy AM. Transanal total mesorectal excision (TaTME) for rectal cancer: step by step description of the surgical technique for a two-teams approach. Eur J Surg Oncol. 2017;43(2):502–5.
34. Zhang X, Gao Y, Dai X, Zhang H, Shang Z, Cai X, et al. Short- and long-term outcomes of transanal versus laparoscopic total mesorectal excision for mid-to-low rectal cancer: a meta-analysis. Surg Endosc. 2019;33(3):972–85.
35. Adamina M, Buchs NC, Penna M, Hompes R, St.Gallen Colorectal Consensus Expert G. St.Gallen consensus on safe implementation of transanal total mesorectal excision. Surg Endosc. 2018;32(3):1091–103.
36. Koedam TWA, Veltcamp Helbach M, Penna M, Wijsmuller A, Doornebosch P, van Westreenen HL, et al. Short-term outcomes of transanal completion total mesorectal excision (cTaTME) for rectal cancer: a case-matched analysis. Surg Endosc. 2019;33(1):103–9.
37. Roodbeen SX, Penna M, Mackenzie H, Kusters M, Slater A, Jones OM, et al. Transanal total mesorectal excision (TaTME) versus laparoscopic TME for MRI-defined low rectal cancer: a propensity score-matched analysis of oncological outcomes. Surg Endosc. 2019;33(8):2459–67.
38. Hawkins AT, Albutt K, Wise PE, Alavi K, Sudan R, Kaiser AM, et al. Abdominoperineal resection for rectal cancer in the twenty-first century: indications, techniques, and outcomes. J Gastrointest Surg. 2018;22(8):1477–87.
39. Klein M, Fischer A, Rosenberg J, Gogenur I, Danish Colorectal Cancer G. Extralevatory abdominoperineal excision (ELAPE) does not result in reduced rate of tumor perforation or rate of positive circumferential resection margin: a nationwide database study. Ann Surg. 2015;261(5):933–8.
40. Kokosis G, Phillips BT, Soo J, Poveromo L, Erdmann D, Mantyh CR, et al. Modified V-Y fasciocutaneous flap reconstruction after abdominoperineal resection in irradiated patients prevents wound dehiscence and associated complications: a retrospective analysis and Benchtop confirmation. Ann Plast Surg. 2019;82(2):218–23.
41. Kokosis G, Sun Z, Avashia YJ, Adam MA, Levinson H, Erdmann D, et al. V-Y fasciocutaneous flap closure technique is a safe and efficacious alternative to primary closure of the perineal wound following abdominoperineal resection. Am J Surg. 2017;213(2):371–6.
42. Devulapalli C, Jia Wei AT, DiBiagio JR, Baez ML, Baltodano PA, Seal SM, et al. Primary versus flap closure of perineal defects following oncologic resection: a systematic review and meta-analysis. Plast Reconstr Surg. 2016;137(5):1602–13.
43. Butler CE, Rodriguez-Bigas MA. Pelvic reconstruction after abdominoperineal resection: is it worthwhile? Ann Surg Oncol. 2005;12(2):91–4.
44. Singh M, Kinsley S, Huang A, Ricci JA, Clancy TE, Irani J, et al. Gracilis flap reconstruction of the perineum: an outcomes analysis. J Am Coll Surg. 2016;223(4):602–10.

45. Butler CE, Gundeslioglu AO, Rodriguez-Bigas MA. Outcomes of immediate vertical rectus abdominis myocutaneous flap reconstruction for irradiated abdominoperineal resection defects. J Am Coll Surg. 2008;206(4):694–703.
46. Chaudhry A, Oliver JD, Vyas KS, Tran NV, Martinez-Jorge J, Larson D, et al. Comparison of outcomes in oncoplastic pelvic reconstruction with VRAM versus omental flaps: a large cohort analysis. J Reconstr Microsurg. 2019;35(6):425–9.
47. Killeen S, Devaney A, Mannion M, Martin ST, Winter DC. Omental pedicle flaps following proctectomy: a systematic review. Color Dis. 2013;15(11):e634–45.
48. Hultman CS, Sherrill MA, Halvorson EG, Lee CN, Boggess JF, Meyers MO, et al. Utility of the omentum in pelvic floor reconstruction following resection of anorectal malignancy: patient selection, technical caveats, and clinical outcomes. Ann Plast Surg. 2010;64(5):559–62.
49. Denlinger CS, Barsevick AM. The challenges of colorectal cancer survivorship. J Natl Compr Cancer Netw. 2009;7(8):883–93; quiz 94.
50. Feddern ML, Emmertsen KJ, Laurberg S. Life with a stoma after curative resection for rectal cancer: a population-based cross-sectional study. Color Dis. 2015;17(11):1011–7.
51. Nasvall P, Dahlstrand U, Lowenmark T, Rutegard J, Gunnarsson U, Strigard K. Quality of life in patients with a permanent stoma after rectal cancer surgery. Qual Life Res. 2017;26(1):55–64.
52. Matzel KE, Stadelmaier U, Muehldorfer S, Hohenberger W. Continence after colorectal reconstruction following resection: impact of level of anastomosis. Int J Color Dis. 1997;12(2):82–7.
53. Hamel CT, Metzger J, Curti G, Degen L, Harder F, von Flue MO. Ileocecal reservoir reconstruction after total mesorectal excision: functional results of the long-term follow-up. Int J Color Dis. 2004;19(6):574–9.
54. Z'Graggen K, Maurer CA, Birrer S, Giachino D, Kern B, Buchler MW. A new surgical concept for rectal replacement after low anterior resection: the transverse coloplasty pouch. Ann Surg. 2001;234(6):780–5; discussion 5–7.
55. Parc R, Tiret E, Frileux P, Moszkowski E, Loygue J. Resection and colo-anal anastomosis with colonic reservoir for rectal carcinoma. Br J Surg. 1986;73(2):139–41.
56. Parc Y, Ruppert R, Fuerst A, Golcher H, Zutshi M, Hull T, et al. Better function with a colonic J-pouch or a side-to-end anastomosis?: a randomized controlled trial to compare the complications, functional outcome, and quality of life in patients with low rectal cancer after a J-pouch or a side-to-end anastomosis. Ann Surg. 2019;269(5):815–26.
57. Ribi K, Marti WR, Bernhard J, Grieder F, Graf M, Gloor B, et al. Quality of life after total mesorectal excision and rectal replacement: comparing side-to-end, colon J-pouch and straight colorectal reconstruction in a randomized, phase III trial (SAKK 40/04). Ann Surg Oncol. 2019;26(11):3568–76.
58. Bryant CL, Lunniss PJ, Knowles CH, Thaha MA, Chan CL. Anterior resection syndrome. Lancet Oncol. 2012;13(9):e403–8.
59. Keane C, Fearnhead NS, Bordeianou LG, Christensen P, Basany EE, Laurberg S, et al. International consensus definition of low anterior resection syndrome. Dis Colon Rectum. 2020;63(3):274–84.
60. Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. Ann Surg. 2012;255(5):922–8.
61. Temple LK, Bacik J, Savatta SG, Gottesman L, Paty PB, Weiser MR, et al. The development of a validated instrument to evaluate bowel function after sphincter-preserving surgery for rectal cancer. Dis Colon Rectum. 2005;48(7):1353–65.
62. Liu CH, Chen CH, Lee JC. Rehabilitation exercise on the quality of life in anal sphincter-preserving surgery. Hepato-Gastroenterology. 2011;58(110–111):1461–5.
63. Liang Z, Ding W, Chen W, Wang Z, Du P, Cui L. Therapeutic evaluation of biofeedback therapy in the treatment of anterior resection syndrome after sphincter-saving surgery for rectal cancer. Clin Colorectal Cancer. 2016;15(3):e101–7.
64. Thin NN, Horrocks EJ, Hotouras A, Palit S, Thaha MA, Chan CL, et al. Systematic review of the clinical effectiveness of neuromodulation in the treatment of faecal incontinence. Br J Surg. 2013;100(11):1430–47.
65. Amshel C, Avital S, Miller A, Sands L, Marchetti F, Hellinger M. T4 rectal cancer: analysis of patient outcome after surgical excision. Am Surg. 2005;71(11):901–3; discussion 4.
66. Crawshaw BP, Augestad KM, Keller DS, Nobel T, Swendseid B, Champagne BJ, et al. Multivisceral resection for advanced rectal cancer: outcomes and experience at a single institution. Am J Surg. 2015;209(3):526–31.
67. Haddock MG. Intraoperative radiation therapy for colon and rectal cancers: a clinical review. Radiat Oncol. 2017;12(1):11.
68. Beyond TMEC. Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. Br J Surg. 2013;100(8):E1–33.
69. Heald RJ. The 'Holy Plane' of rectal surgery. J R Soc Med. 1988;81(9):503–8.
70. Mohan HM, Evans MD, Larkin JO, Beynon J, Winter DC. Multivisceral resection in colorectal cancer: a systematic review. Ann Surg Oncol. 2013;20(9):2929–36.
71. Rodel C, Martus P, Papadoupolos T, Fuzesi L, Klimpfinger M, Fietkau R, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol. 2005;23(34):8688–96.
72. Glynne-Jones R, Anyamene N, Moran B, Harrison M. Neoadjuvant chemotherapy in MRI-staged high-risk rectal cancer in addition to or as an alternative to preoperative chemoradiation? Ann Oncol. 2012;23(10):2517–26.
73. Richardson B, Preskitt J, Lichliter W, Peschka S, Carmack S, de Prisco G, et al. The effect of multidisciplinary teams for rectal cancer on delivery of care and patient outcome: has the use of multidisciplinary teams for rectal cancer affected the utilization of available resources, proportion of patients meeting the standard of care, and does this translate into changes in patient outcome? Am J Surg. 2016;211(1):46–52.
74. Obias VJ, Reynolds HL Jr. Multidisciplinary teams in the management of rectal cancer. Clin Colon Rectal Surg. 2007;20(3):143–7.
75. Lee YC, Lee YL, Chuang JP, Lee JC. Differences in survival between colon and rectal cancer from SEER data. PLoS One. 2013;8(11):e78709.
76. Fleshman J, Branda M, Sargent DJ, Boller AM, George V, Abbas M, et al. Effect of laparoscopic-assisted resection vs open resection of stage II or III rectal cancer on pathologic outcomes: the ACOSOG Z6051 randomized clinical trial. JAMA. 2015;314(13):1346–55.
77. Stevenson AR, Solomon MJ, Lumley JW, Hewett P, Clouston AD, Gebski VJ, et al. Effect of laparoscopic-assisted resection vs open resection on pathological outcomes in rectal cancer: the ALaCaRT randomized clinical trial. JAMA. 2015;314(13):1356–63.
78. Nussbaum DP, Speicher PJ, Ganapathi AM, Englum BR, Keenan JE, Mantyh CR, et al. Laparoscopic versus open low anterior resection for rectal cancer: results from the national cancer data base. J Gastrointest Surg. 2015;19(1):124–31; discussion 31–2.
79. Gilmore B, Adam MA, Rhodin K, Turner MC, Ezekian B, Mantyh CR, et al. Evolution of minimally invasive surgery for rectal cancer: update from the national cancer database. Surg Endosc. 2021;35(1):275–90.
80. Sun Z, Kim J, Adam MA, Nussbaum DP, Speicher PJ, Mantyh CR, et al. Minimally invasive versus open low anterior resection: equivalent survival in a national analysis of 14,033 patients with rectal cancer. Ann Surg. 2016;263(6):1152–8.

81. Speicher PJ, Englum BR, Ganapathi AM, Nussbaum DP, Mantyh CR, Migaly J. Robotic low anterior resection for rectal cancer: a national perspective on short-term oncologic outcomes. Ann Surg. 2015;262(6):1040–5.
82. Fleshman J, Branda ME, Sargent DJ, Boller AM, George VV, Abbas MA, et al. Disease-free survival and local recurrence for laparoscopic resection compared with open resection of stage II to III rectal cancer: follow-up results of the ACOSOG Z6051 randomized controlled trial. Ann Surg. 2019;269(4):589–95.
83. Stevenson ARL, Solomon MJ, Brown CSB, Lumley JW, Hewett P, Clouston AD, et al. Disease-free survival and local recurrence after laparoscopic-assisted resection or open resection for rectal cancer: the Australasian laparoscopic cancer of the rectum randomized clinical trial. Ann Surg. 2019;269(4):596–602.
84. Bagshaw PF, Allardyce RA, Frampton CM, Frizelle FA, Hewett PJ, McMurrick PJ, et al. Long-term outcomes of the australasian randomized clinical trial comparing laparoscopic and conventional open surgical treatments for colon cancer: the Australasian Laparoscopic Colon Cancer Study trial. Ann Surg. 2012;256(6):915–9.
85. Monson JR, Probst CP, Wexner SD, Remzi FH, Fleshman JW, Garcia-Aguilar J, et al. Failure of evidence-based cancer care in the United States: the association between rectal cancer treatment, cancer center volume, and geography. Ann Surg. 2014;260(4):625–31; discussion 31–2.
86. Rickles AS, Dietz DW, Chang GJ, Wexner SD, Berho ME, Remzi FH, et al. High rate of positive circumferential resection margins following rectal cancer surgery: a call to action. Ann Surg. 2015;262(6):891–8.
87. Brady JT, Xu Z, Scarberry KB, Saad A, Fleming FJ, Remzi FH, et al. Evaluating the current status of rectal cancer care in the US: where we stand at the start of the commission on Cancer's National Accreditation Program for Rectal Cancer. J Am Coll Surg. 2018;226(5):881–90.
88. Fleshman J. Current status of minimally invasive surgery for rectal cancer. J Gastrointest Surg. 2016;20:1056–4.

Colorectal Cancer: Postoperative Adjuvant Therapy and Surveillance

30

David A. Kleiman and David W. Larson

Key Concepts

- All patients with resected stage III, and most with high-risk stage II, colon cancer should be considered for adjuvant chemotherapy for 3–6 months.
- Adjuvant therapy for rectal cancer is more complex. Multiple options exist with regard to the order and timing of multimodal therapy.
- Patients with clinical stage II and III rectal cancer should be considered for preoperative radiotherapy and systemic chemotherapy for a total of 4–6 months of treatment.
- Radiotherapy used as an adjunct to proctectomy for rectal cancer is more effective and less toxic if it is given preoperatively, as compared to postoperative administration. Postoperative radiotherapy should be avoided if possible.
- Intensive postoperative surveillance has not been proven to be associated with improved survival, as compared to less intense surveillance or no surveillance.
- Surveillance is only indicated in patients who wish to undergo treatment for recurrent tumor, *and* who are candidates for liver, lung, and/or intestinal resection, and/or multidrug chemotherapy. Patient desires, age, and comorbidities should be considered prior to initiating a surveillance plan.
- Detection of asymptomatic liver metastasis and local regional recurrence are more likely to be amenable to curative-intent salvage resection than symptomatic recurrences, although it is unclear whether this strategy improves survival when compared with no surveillance.
- Use of carcinoembryonic antigen (CEA) testing and computed tomography (CT) scans is associated with increased detection of asymptomatic recurrence. However, there remains no evidence to support the use of other laboratory or image-guided testing in routine surveillance.
- Risk of locoregional recurrence is higher in patients with advanced rectal cancer compared to colon cancer. Risk factors include the omission of chemoradiotherapy, positive circumferential margin, and T4 and N2 histology.
- Surveillance after resection of stage I colorectal cancer remains controversial. Typically, colonoscopy to look for metachronous neoplasia is the only test recommended.

Introduction

Colorectal cancer is the fourth most common cancer in the United States among men and women and is the second leading cause of cancer-related death [1]. Although surgery is the mainstay of treatment, recurrence following curative-intent surgery for stage II and III colorectal cancer can be as high as 40%. Patients at highest risk of recurrence (high-risk stage II and all stage III) should be considered for adjuvant therapy. Treatment of recurrent disease may prolong survival. Therefore, otherwise healthy colorectal cancer patients with reasonable life expectancy should be considered for regular postoperative surveillance. This chapter will review the role of adjuvant therapy following curative-intent resection of colorectal cancer and will discuss surveillance strategies.

First, we would like to offer a few general comments regarding the concept of cancer "recurrence." Although commonly referred to as such, there is no evidence that true "recurrence" ever occurs. Rather, the malignant cells responsible for the "recurrence" were present at the time of initial treatment, but of such small volume as to render them undetectable by current technology. Thus, it is more proper to refer to tumor detected subsequent to primary therapy as either local or distant "failure" of treatment. Throughout this chapter, the term "recurrence" is utilized, as it has become embedded in the common lexicon. However, the treating physician should realize the limitations of the term.

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Second, our ability to detect distant disease, or locally recurrent disease, depends upon the sensitivity and specificity of the diagnostic testing modalities of the time. As sensitivity of tests improves, and more patients undergo more frequent testing, results of non-randomized clinical trials of surveillance and/or treatment will be subject to both stage migration and lead-time bias. This is especially true when comparing more recent results with historical controls.

Colon Cancer

Stage III Colon Cancer

Patients undergoing curative-intent resection of stage III colon cancer should be considered for adjuvant chemotherapy, as it has been consistently shown to decrease recurrence and increase survival compared to surgery alone [2]. The overall 5-year survival following surgery alone for stage III colon cancer is 40–60%, whereas modern chemotherapy regimens have increased the expected overall survival to 70–80% [3, 4].

The benefits of adjuvant chemotherapy for stage III colon cancer have been demonstrated since 1990, when Moertel et al. reported a 41% relative reduction in cancer recurrence and a 33% relative improvement in overall survival with 12 months of postoperative adjuvant fluorouracil and levamisole [5]. The International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators pooled data from three prospective randomized controlled trials comparing surgery alone to surgery followed by six cycles of 5-fluorouracil (5-FU)/leucovorin. This demonstrated an increase in 3-year overall survival from 62% to 71% with <3% incidence of WHO grade 4 toxicities [6]. Several subsequent trials then demonstrated that 5-FU combined with leucovorin was superior to levamisole and that 6 months of adjuvant therapy achieved similar survival benefits compared to 12 months [7–9]. Thus, 6 months of adjuvant 5-FU plus leucovorin became the accepted standard of care for stage III colon cancer from the early 1990s until the late 2000s.

Oxaliplatin was introduced as adjuvant chemotherapy for colon cancer in 2004. It inhibits DNA synthesis by forming inter- and intra-strand DNA cross-links, preventing transcription and replication. Several studies demonstrated the benefits of oxaliplatin when added to a regimen of 5-FU and leucovorin [10, 11]. In the landmark MOSAIC trial, 2246 patients with stage II or III colon cancer were randomly assigned to receive either 5-FU and leucovorin (LV5FU2) or 5-FU and leucovorin plus oxaliplatin (FOLFOX4) for 6 months following curative surgery [3]. When comparing FOLFOX4 to LV5FU2 in patients with stage III disease, a 5-year disease-free survival was 73% versus 67% ($p = 0.003$), and a 6-year overall survival was 73% versus 69% ($p = 0.023$). No differences were seen in the stage II population.

Capecitabine is an oral 5-FU prolog that works via the same mechanism as 5-FU. Its oral dosing makes it an appealing alternative to infusional 5-FU and leucovorin. Oral capecitabine alone was shown to be at least equivalent to infusional 5-FU and leucovorin with regard to disease-free survival and is associated with fewer adverse effects [12]. Adjuvant capecitabine combined with oxaliplatin (CAPOX) has been demonstrated to improve 3-year disease-free survival following curative-intent resection in stage III colon cancer patients from 67% to 71% when compared to 5-FU and leucovorin [13]. Given that the relative improvement in survival was similar with both CAPOX and FOLFOX in the adjuvant setting, CAPOX is considered an equivalent alternative (although with slightly different durations of therapy) to FOLFOX for patients with stage III colon cancer.

The duration of adjuvant chemotherapy for stage III colon cancer had traditionally been 6 months for all patients. However, toxicity of oxaliplatin (particularly peripheral neuropathy) becomes more severe (and potentially permanent) with longer courses of treatment [14]. In the International Duration Evaluation of Adjuvant Therapy (IDEA) collaboration, nearly 13,000 patients with stage III colon cancer were randomized to either 3 or 6 months of adjuvant FOLFOX or CAPOX in a non-inferiority trial design [15]. Overall, 3 months of treatment failed to meet the criteria for non-inferiority as compared to 6 months of treatment, when 3-year disease-free survival was utilized as the outcome variable. However, subgroup analysis showed that among low-risk tumors (T1–3N1), 3 months of CAPOX was non-inferior to 6 months of treatment. Non-inferiority could not be proven for 3 months of FOLFOX versus 6 months. Among high-risk tumors (T4 and/or N2), non-inferiority could not be proven with 3 months of CAPOX versus 6 months, and 3 months of FOLFOX was inferior to 6 months. Therefore, the 2020 National Collaborative Cancer Network (NCCN)® colon cancer guidelines now recommend either 3 months of CAPOX or 3–6 months of FOLFOX for low-risk stage III colon cancer (T1–3N1), whereas high-risk stage III cancer (T4 and/or N2) is recommended to receive CAPOX for 3–6 months (with category 1 data supporting 6 months) or 6 months of FOLFOX [16].

Stage II Colon Cancer

Several landmark adjuvant chemotherapy trials included both patients with stage II and stage III disease, and subgroup analysis of the stage II patients has offered conflicting data on the efficacy of adjuvant chemotherapy. The IMPACT B2 (International Multicentre Pooled Analysis of B2 Colon Cancer Trials) found no difference in 5-year overall survival

(OS) in patients with stage II resected colon cancer who were randomized to 5-FU-leucovorin versus observation (82% vs. 80%, $p = 0.57$) [17]. In the intergroup analysis, the subset of stage II colon cancer who received adjuvant 5-FU-leucovorin had a 4% improvement in disease-free survival (DFS) (76% vs. 72%, $p = 0.049$) but no difference in OS (81% vs. 76%, $p = 0.113$) [18]. In the QUASAR (Leucovorin and Fluorouracil Compared with Observation in Treating Patients with Colorectal Cancer That Has Been Surgically Removed) trial, patients who received adjuvant chemotherapy had a 22% decrease in recurrence ($p = 0.001$) and an 18% reduction in death ($p = 0.008$), but the 5-year OS absolute benefit was only 3–4% [19]. Two landmark trials, MOSAIC and NSABP C-07, were both designed to investigate the added efficacy of oxaliplatin to 5-FU in resected stage II and III colon cancer [3, 11]. In both trials, subgroup analysis of patients with stage II disease found no difference in DFS or OS with the addition of oxaliplatin to 5-FU. In summary, when considered as a uniform group, there has been at best a very modest and inconsistent benefit of adjuvant 5-FU-leucovorin for patients with resected stage II colon cancer, with no additional benefit of oxaliplatin.

The American Society of Clinical Oncology and the European Society for Medical Oncology both recognize the broad range of presentations among stage II colon cancers. Both groups have published similar definitions of high-risk clinicopathologic features [20, 21], as outlined in Table 30.1, that should prompt consideration of adjuvant chemotherapy. However, at present, there are no definitive data to support the utilization of adjuvant chemotherapy for stage II colon cancer patients.

Analysis of the tumor for microsatellite instability (MSI), immunohistochemistry for expression of mismatch repair (MMR) proteins, and BRAF mutational analysis also play important roles in risk stratification for stage II colon cancer. MSI-high/MMR-deficient tumors generally have improved overall survival and lower risk of lymph node and distant metastases compared to MSI-low/MMR-proficient tumors [22]. Furthermore, MSI-high/MMR-deficient tumors tend to be resistant to 5-FU therapy, and oxaliplatin is typically required to confer treatment response [23]. Therefore, assessment of MSI/MMR status can help avoid administering cytotoxic chemotherapy to patients unlikely to benefit from it. The BRAF (V600E) mutation is associated with worse OS, and there is an additive prognostic significance with MMR status. In pooled analysis of two NSABP trials, patients who had BRAF wild-type and MMR-deficient tumors had the highest 5-year OS (89.7%), whereas patients who had BRAF-mutant and MMR-proficient tumors had the worst 5-year OS (69.1%) [24]. Therefore, the presence of the BRAF (V600E) mutation should prompt consideration for adjuvant chemotherapy. As such, routine assessment of MSI/MMR status with reflex testing for BRAF (V600E) has become standard for all colorectal cancer resection specimens in many institutions.

There are several commercially available multigene assays available to predict the risk of recurrence of stage II colon cancer. These are discussed in more detail later in this chapter ("Molecular Profiling" section). This information can be useful in deciding who should be offered adjuvant chemotherapy.

Table 30.1 High-risk features of stage II colon cancer

T4 tumor
Poor differentiation
Lymphovascular invasion
Perineural invasion
Close or positive margin
Bowel obstruction
<12 lymph nodes harvested

Radiation for Colon Cancer

There is a very limited role of adjuvant radiotherapy for colon cancer. Unlike the rectum, which is fixed within the pelvis allowing for precise targeting of the tumor and surrounding lymph nodes with minimal risk to surrounding structures, most of the colon is intraperitoneal and/or closely approximated by loops of the small bowel. Therefore, the risk of inadvertent radiation enteritis is unacceptably high, and therefore it is not routinely recommended [25]. Moreover, the primary benefit of radiation is to improve local control. This is much more problematic for rectal cancer, in which positive circumferential resection margins (CRM) can be seen in upward of 17% of cases, whereas the risk of a positive CRM in colon cancer is much lower.

To date, there has only been one prospective randomized trial investigating the use of adjuvant chemoradiation in addition to chemotherapy for high-risk stage II (T4) or stage III colon cancers [26]. No difference was seen in 5-year OS or DFS between the groups, although the study was terminated early due to slow accrual. Furthermore, significant toxicity was seen in 54% of the patients who received radiation.

A situation where adjuvant radiation may be considered is for T4 colon cancers that invade adjacent solid organs and have a close or positive margin following surgery. However, a recent study using the National Cancer Database (NCDB) and Surveillance, Epidemiology, and End Results (SEER) Program data analyzed over 28,000 patients with T4 colon cancer treated with adjuvant chemotherapy either with or without radiation, and no difference in OS or DSS (disease specific survival) was observed [27]. Therefore, even this may have limited utility. If a close or positive radial margin is suspected at the time of surgery, the margins of the area of

concern should be marked with surgical clips or fiducials to help define the radiation field postoperatively. Rotation of an omental flap to cover the area may help isolate the area from direct small bowel adhesion and minimize radiation damage.

Neoadjuvant Chemotherapy and Radiation for Colon Cancer

Neoadjuvant systemic chemotherapy can be considered for locally advanced colon cancers. It has been demonstrated that neoadjuvant chemotherapy is more effective than postoperative adjuvant chemotherapy in locally advanced esophageal, gastric, and rectal cancer, and it is now utilized routinely for these tumor types. The potential benefits of neoadjuvant chemotherapy include earlier systemic treatment and more effective eradication of occult micrometastatic disease, improved tolerability and dose intensity, and assessment of response to guide adjuvant therapy decisions. Theoretically, chemically debulking tumors before surgery may reduce the frequency of tumor cell shedding during surgery and improve R0 resection rates. Data from the FOxTROT Collaborative Group showed significant tumor downstaging, less apical node involvement, and fewer positive margins, favoring preoperative treatment in patients with locally advanced, resectable colon cancer [28]. Neoadjuvant chemotherapy seems to be well tolerated and safe, with no increase in perioperative morbidity and a trend toward fewer serious postoperative complications. There are also data that suggest that neoadjuvant chemotherapy in clinical T4b colon cancer may improve survival, although this benefit was not seen in T3 or T4a disease [29].

Neoadjuvant chemoradiotherapy can be considered in highly select patients, such as those with sigmoid tumors invading the bladder or other pelvic organs, provided that the radiation dose to surrounding small bowel can be limited. Neoadjuvant chemoradiotherapy can also be considered for highly select patients with more proximal colon tumors invading other vital structures such as the duodenum and pancreas, although data are limited to case reports and small series, and thus no definitive conclusions can be made regarding relative efficacy. As chemotherapy becomes more effective, it is likely that neoadjuvant chemotherapy will supplant chemoradiotherapy in these highly select situations, as risk of small bowel radiotherapy damage would be eliminated.

Figure 30.1 shows a treatment algorithm for adjuvant therapy for stage II and III colon cancer.

Rectal Cancer

Compared to colon cancer, the multimodal management of rectal cancer is far more complex, primarily due to the fact that the fixed location of the rectum in the pelvis allows for the safe delivery of targeted radiotherapy to the operative field with minimal risk of collateral damage to adjacent structures. Furthermore, the risk of local recurrence following curative resection for rectal cancer is significantly higher than for colon cancer, and so great effort has been placed on developing a multimodal treatment approach to reduce the risk of local recurrence as well as to improve overall survival.

Multimodal treatment of rectal cancer may include chemotherapy, radiation, local excision, proctectomy, or some

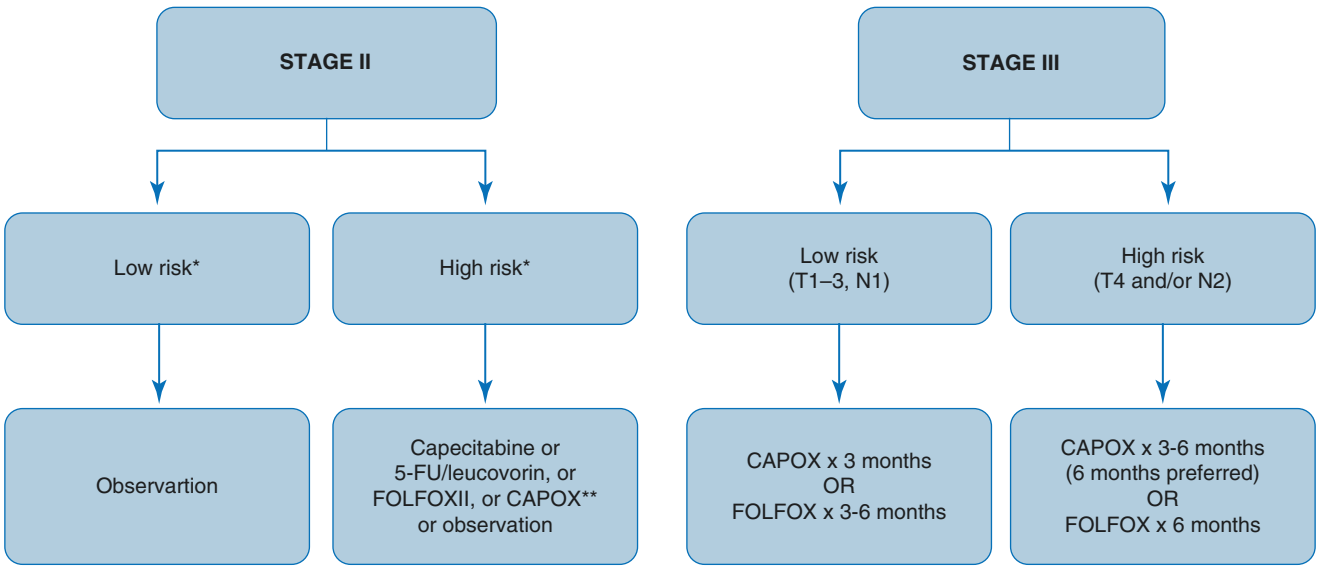

Fig. 30.1 Treatment algorithm for adjuvant therapy for stage II and III colon cancer following surgery with curative intent. (*High-risk features include T4 tumor, poor differentiation, lymphovascular invasion, perineural invasion, close or positive margin, bowel obstruction, and <12 lymph nodes harvested. **Oxaliplatin required if MSI-L or MMR proteins are expressed)

combination of the above. There are also a multitude of options available for the order in which multimodal therapy can be delivered, often resulting in great confusion for surgeons and patients alike. Some of the most significant changes in treatment algorithms in recent years have involved moving adjuvant chemotherapy forward in the treatment schematic so that systemic chemotherapy and radiotherapy are both administered prior to surgery (total neoadjuvant therapy). There has also been a rapid evolution of the role of non-operative management ("watch-and-wait") for rectal cancer. Both of these concepts are covered elsewhere in the textbook; thus we will focus the discussion here to only adjuvant treatment options following curative-intent surgery.

Adjuvant Chemotherapy Following Neoadjuvant Radiation

A series of landmark prospective randomized clinical trials in the 1990s and early 2000s established that treating stage II and III mid and low rectal cancers with preoperative radiation given as either short course (5 Gy/day × 5 days followed by surgery) or long course (1.8–2.0 Gy/day × 5 days a week to a total dose of 45–50 Gy along with a sensitizing agent such as 5-FU or capecitabine) is associated with significant improvement in local pelvic control, although improvement in overall survival was only demonstrated in the first of these three trials [30–32]. Therefore, for stage II or III mid and low rectal cancer, the 2020 NCCN® guidelines recommend neoadjuvant radiation (short course or long course) followed by surgery, as well as additional systemic chemotherapy given either before or after surgery for a total of 6 months of perioperative therapy [33].

Neoadjuvant radiation often downstages the tumor, and therefore it has been a matter of debate as to whether to determine the need for adjuvant chemotherapy based on initial clinical stage or final histologic stage. Although not supported by definitive data, the current NCCN® guidelines recommend adjuvant chemotherapy for patients with clinical stage II/III rectal cancer who received neoadjuvant radiation, regardless of final histology [33].

Data are conflicting with regard to who benefits from adjuvant chemotherapy as well as what the ideal chemotherapy regimen is. Two prospective randomized clinical trials demonstrated a modest disease-free survival advantage with FOLFOX compared to 5-FU/leucovorin without oxaliplatin for stage II and III rectal cancer following neoadjuvant chemoradiation and surgery [34, 35]. However, a recent meta-analysis of nearly 1200 patients with stage II and III rectal cancers who received 5-FU-based chemotherapy following neoadjuvant chemoradiation and surgery showed no difference in overall survival, disease-free survival, or distant recurrences with adjuvant therapy [36].

One reason why there has been inconsistency with demonstrating the benefits of adjuvant chemotherapy is that many such studies were plagued with treatment interruptions, thereby diminishing the incremental benefits of the additional chemotherapy. In fact, it has been estimated that only 50% of patients complete the full prescribed course of adjuvant chemotherapy without interruption and that each 4-week delay in treatment can decrease survival by 14% [37]. This has caused many to advocate for moving the adjuvant chemotherapy forward in the sequence of multimodal therapy, to be given prior to radiotherapy/chemoradiotherapy (induction chemotherapy), the entire regimen referred to as "total neoadjuvant therapy." Multiple studies have demonstrated fewer treatment interruptions, increased pathologic complete response (pCR) rates, and less chemotherapy-related toxicity with induction chemotherapy compared to conventionally sequenced multimodal therapy [38, 39]. Since 2015, NCCN® guidelines have included induction chemotherapy followed by chemoradiation and then surgery as an option for management of locally advanced rectal cancer [33].

Adjuvant Therapy Without Neoadjuvant Radiation

One of the inherent difficulties of determining the optimal treatment for patients with rectal cancer is the dependence upon preoperative imaging to determine clinical stage. Even with modern high-resolution MRI, it is estimated that the specificity of MRI for determining T category is only 75% and lymph node status is only 71% [40]. Therefore, tumor mis-staging can occur in upward of 20–25% of cases, and patients who undergo upfront surgery and are found to have stage II/III rectal cancer may not have received any neoadjuvant therapy prior to surgery. The treatment team is then faced with the dilemma of whether to offer adjuvant radiation, systemic chemotherapy, both, or neither. Unfortunately, there are limited data available to guide such decisions, and the latest NCCN guidelines leave several options available to the clinicians since high-level data are lacking.

Postoperative adjuvant radiation is associated with considerable morbidity. Adjuvant radiation may damage loops of the small bowel that may have fallen into the pelvis within the radiation field, resulting in radiation enteritis. Postoperative radiation is especially morbid if a restorative proctectomy has been performed. Radiation may damage the colonic conduit, remaining the rectum and anal sphincter, especially given that higher doses of postoperative radiotherapy are required to achieve similar oncologic benefit as compared to neoadjuvant radiotherapy. Chronic inflammation, poor function, stricture, and subacute perforation with abscess/fistula can result. Furthermore, tumoricidal effects of radiation may be diminished when it is administered in the postoperative period, as

the tissues surrounding the operative field are not as well oxygenated as naïve tissues prior to surgery.

The rationale for utilizing postoperative radiotherapy/chemotherapy derives from trials that accrued patients in the 1980s, a time when surgical technique and pathology processing were not standardized and often were what would be considered suboptimal today. The efficacy of adjuvant radiation for stage II/III rectal cancer was established in two studies showing that adjuvant 5-FU-based chemotherapy plus radiation leads to improved local control and decreased distant recurrence compared to radiation or surgery alone [41, 42]. In another prospective randomized trial, 694 patients with stage II/III rectal cancer who went straight to curative surgery were randomized to receive chemotherapy alone or chemotherapy with adjuvant radiation [9]. There were no differences observed in disease-free survival or overall survival, but the cumulative incidence of locoregional relapse at 5 years was significantly lower in the group that received adjuvant radiation (8% vs. 13%, $p = 0.02$). However, all three of these studies were conducted at a time when less attention was paid to maintaining sound oncologic principles of mesorectal excision and ensuring negative circumferential margins. Therefore, it is unclear if adjuvant radiation would confer the same benefits in modern practice with experienced surgeons performing high-quality proctectomy utilizing the principles of "total mesorectal excision" (TME).

NCCN® guidelines for adjuvant therapy after curative resection without neoadjuvant therapy distinguish between low-risk stage II tumors and high-risk stage II/any stage III tumors [33]. For low-risk stage II disease (pT3N0M0, negative CRM), adjuvant chemoradiation followed by 5-FU/leucovorin or capecitabine is preferred, but observation alone is also an option. For high-risk stage II (pT4N0M0 or positive CRM) or any stage III tumor (pT1–4N1–2), adjuvant chemoradiation followed by oxaliplatin-based chemotherapy (FOLFOX or CAPOX) is preferred. Total duration of adjuvant treatment is typically 6 months. However, many experienced surgeons would argue that the benefit of postoperative radiotherapy may be minimal if negative CRM is achieved as compared to the toxicity of therapy and that current chemotherapy regimens are highly effective. Thus, another reasonable strategy is to treat patients with node-positive disease with negative CRM with postoperative chemotherapy only.

Adjuvant Therapy Following Local Excision of Early-Stage Rectal Cancer

The significant morbidity associated with proctectomy makes local excision for low-risk early-stage (cT1–2N0M0) rectal cancers an appealing option. However, beginning in the early 2000s, there was an increased awareness that local excision was associated with significantly worse oncologic outcomes compared to proctectomy. Five separate institutional series published between 2000 and 2009 reported local recurrence rates of 7–23% following local excision compared to 0–9% following proctectomy and 5-year overall survival rates of 70–92% versus 80–96% following proctectomy [43–47]. This has led many to revisit this approach and look to multimodal therapy to try to improve oncologic outcomes while maintaining organ preservation.

Table 30.2 High-risk features of early-stage rectal cancers following local excision

Poor differentiation
Lymphovascular invasion
R1 resection
Tumor fragmentation during local invasion
Margins positive or <1 mm

An improved understanding of high-risk histopathologic features of early-stage rectal cancer has allowed for better patient selection and identification of those at highest risk of recurrence who may benefit from additional treatment following local excision [43, 45, 48, 49]. A list of these features can be found in Table 30.2. If any of these features are present, proctectomy should be considered. However, if the patient is unwilling or unable to tolerate major abdominal surgery, then treatment with adjuvant chemoradiation and possibly chemotherapy could be considered.

The use of neoadjuvant chemoradiation for cT2N0M0 rectal cancers treated with local excision was examined in the ACOSOG Z6041 trial [50]. In this multicenter phase 2 single-arm trial, 79 patients with cT2N0M0 distal rectal cancer were treated with chemoradiation followed by local excision. The 3-year DFS was 87%, which was significantly lower than what would be expected for similarly staged patients who underwent proctectomy. Therefore, this approach should be considered an oncologic compromise for carefully selected patients who are unable or unwilling to undergo proctectomy.

The current NCCN® guidelines recommend proctectomy or chemoradiation with either capecitabine or infusional 5-FU along with radiotherapy for pT2Nx and pT1Nx locally excised tumors with high-risk features [33]. Proctectomy is the preferred option for pT2Nx tumors in otherwise healthy patients.

Figure 30.2 shows treatment options for multimodal treatment of locally advanced stage II or III rectal cancer.

Targeted Chemotherapy Options

Several targeted chemotherapeutic agents have been evaluated in the adjuvant setting, including bevacizumab (anti-VEGF antibody) and cetuximab (anti-EGFR antibody).

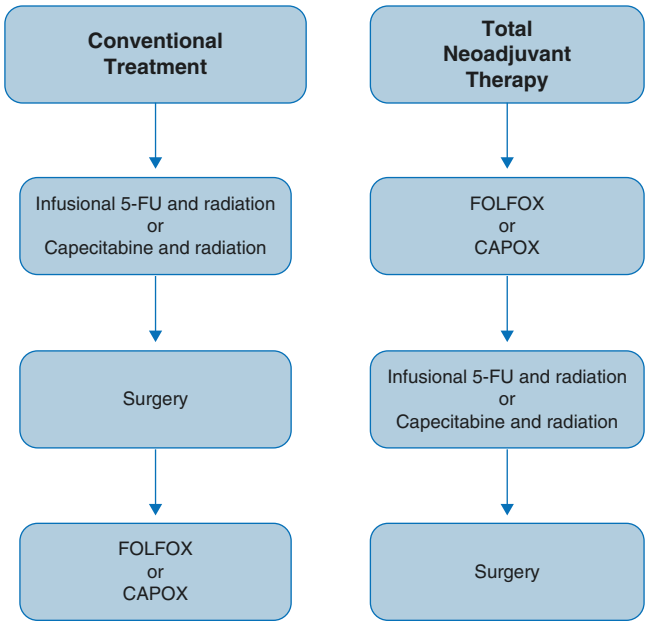

Fig. 30.2 Two treatment options for multimodal treatment of locally advanced stage II or III rectal cancer. Total duration of perioperative therapy should be 6 months

Unfortunately, neither has been shown to be beneficial for routine adjuvant therapy following curative resection. In the AVANT trial, patients with resected stage II/III colon cancer were randomized to either FOLFOX, FOLFOX plus bevacizumab, or XELOX plus bevacizumab [51]. After a minimum follow-up of 60 months, there were no differences in disease-free survival, but there were more grade 3–5 adverse events in the bevacizumab groups, and therefore it was not routinely recommended to use bevacizumab in the adjuvant setting following curative surgery. Similarly, the PETACC-8 and N0147 trials randomized patients with KRAS wild-type tumors to adjuvant FOLFOX with or without cetuximab [52, 53]. Both studies found no difference in disease-free survival with the addition of cetuximab, and the N0147 trial demonstrated increased incidence of grade 3–5 adverse events and lower likelihood of completing the full 12 cycles.

Molecular Profiling

Although a complete understanding of the molecular pathways and genetic mutations that drive the pathogenesis of colorectal cancer remains elusive, significant advances in the understanding of several key pathways have been achieved in recent years [54]. Molecular profiling has now entered routine clinical practice to help identify patients who are at increased risk for tumor recurrence or who may benefit from certain chemotherapy regimens.

DNA mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2) are responsible for the detection and correction of nucleotide pairing errors that occur during DNA replication. Mutations in the DNA mismatch repair proteins may be inherited (i.e., Lynch syndrome) or sporadic [55]. Alternatively, abnormal protein expression may be the result of epigenetic modification, either through silencing by the BRAF (V600E) mutation or through promoter hypermethylation.

Screening for DNA mismatch repair protein expression can help identify patients most likely to benefit from oxaliplatin-based adjuvant chemotherapy. In general, MMR-deficient tumors have a better prognosis and are less responsive to chemotherapy with 5-FU/leucovorin [23]. Therefore, MMR testing can identify patients who will derive little benefit from chemotherapy and who can thus avoid the toxicity of therapy.

Several multigene assays have been developed for risk stratification of colon cancer recurrence. The best studied to date is Oncotype DX®. This is a 12-gene assay used to calculate a recurrence score to predict risk of recurrence following potentially curative resection. Its ability to risk stratify for recurrence has been evaluated in 3 prospective studies and 1 retrospective cohort study including a total of nearly 3000 patients with stage II or III colon cancer [56–59]. However, this test and others like it are unable to accurately predict response to adjuvant therapy, and so their clinical utility is limited.

Surveillance After Curative-Intent Therapy

Introduction

Given the improvements in screening, diagnostics, surgery, and adjuvant therapy, most patients suffering from colorectal cancer will survive, resulting in an ever-increasing survivor population [60]. The 1.3 million adults living with a history of colorectal cancer represent a large group of cancer survivors in which appropriate follow-up and survivorship care is a priority to identify cancer recurrence, treat long-term consequences of therapy, as well as to address the psychosocial needs of survivorship [61]. Unfortunately, there remains little consensus regarding best practice for surveillance and survivorship care [62, 63].

The goal of surveillance is the detection of treatable recurrence or metachronous colorectal primary malignancy while improving the patient's opportunities for curative intervention and survival. For those patients with suspected or known genetic syndromes, appropriate strategies must consider the risk of other associated cancers, as well as address appropriate screening of at-risk relatives. It should be understood that the appropriateness of surveillance must take the patient's age, comorbid conditions, functional status, life expectancy, and goals of care into consideration.

Active surveillance to detect recurrent or metastatic disease should only be performed if the patient is willing and able to undergo aggressive treatment. Otherwise, surveillance is simply an economic and emotional burden that the patient must bear, solely to satisfy the intellectual curiosity of the ordering physician.

Decisions regarding surveillance should be based in part on the demonstrated magnitude of improvement in overall survival, cancer-specific survival, quality of life, and function. Unfortunately, it is difficult to interpret and synthesize the findings of published series on surveillance, as they are plagued with heterogeneity regarding interventions and comparisons, where one trial's "more intensive regimen" may be virtually identical to another trial's "less intensive regimen." In addition, few series have adequate power to detect meaningful differences in survival and other objective measures of outcome.

National organizations, such as the American Society of Colon and Rectal Surgeons, the American and European Society of Clinical Oncology, and the National Comprehensive Cancer Network, have published surveillance testing guidelines for primary colorectal cancer (Table 30.3). In general terms, surveillance includes history and physical examination as well as laboratory testing [carcinoembryonic antigen (CEA) measurement every 3–6 months for 5 years] and image-guided testing [computed tomography (CT) scans of the chest, abdomen, and pelvis every 6–12 months for 3–5 years] along with colonoscopy at 1-, 3-, and then 5-year intervals. Variation in the recommended frequency of tests is common when comparing various society recommendations and those of authors of primary studies on the topic in the published literature.

While historical evidence has suggested intensive follow-up improves the detection of early disease which may be amenable to additional therapeutic and surgical measures, newer evidence is calling this paradigm into question. Historically, improvements in overall survival hinged on the detection of treatable disease. Newer data suggests that less intensive follow-up results in similar overall and cancer-specific survival, suggesting that the previously perceived benefits of intensive surveillance were due to lead-time bias or stage migration. This shift in surveillance recommendations is critical for the third of patients who suffer from recurrence, many of whom undergo salvage resection with a median survival in excess of 3–5 years [61, 64–66]. Throughout this chapter, we will discuss past and current literature regarding the surveillance of patients with colorectal malignancy who undergo curative-intent resection of their primary tumors.

Timing and Choice of Surveillance Modalities

Historical Literature

There have been eight prospective randomized trials addressing outcomes of surveillance after curative resection published from 1995 to 2014 [67–74]. These series are all limited by their heterogeneity of surveillance regimes, diagnostic and therapeutic modalities, and the varying time periods in which the study was conducted [75].

Table 30.3 National organization surveillance testing guidelines for primary colorectal cancer [16, 21, 33, 96, 139, 140]

Organization	History/physical	CEA	CT scan	Endoscopy
ASCO 2013 (stages II–III)	q 3–6 mos. for 5 yrs.	q 3–6 mos. for 5 yrs.	Chest/abdomen/pelvis (if rectal) q yr. for 3–5 yrs.	Colonoscopy at 1 yr., if negative, every 5 yrs. Rectal cancer, proctosigmoidoscopy q 6 mos. for 2–5 yrs. if now pelvic RT
ESMO 2013 (stages I, II, III)	q 3–6 mos. for 3 yrs. and then q 6–12 mos. for 2 yrs.	q 3–6 mos. for 3 yrs. and then q 6–12 mos. for 2 yrs.	Chest/abdomen q 6–12 mos. for 3 yrs.	Colonoscopy at 1 yr., if negative, every 3–5 yrs.
ESMO 2017 (stages I, II, III)	q 6 mos. for 2 yrs.	q 6 mos. for 3 yrs.	2× chest/abdomen/pelvis during the first 3 yrs.	Colonoscopy at 1 yr., if negative, every 5 yrs. till age 75
NCCN 2020 colon	q 3–6 mos. for 2 yrs., q 6 mos. for 5 yrs.	q 3–6 mos. for 2 yrs. and then q 6 mos. for 5 yrs.	Chest/abdomen q 6–12 mos. for 5 yrs.	Colonoscopy at 1 yr., repeat q 1 yr. if adenoma, otherwise repeat 3 yrs. and then every 5 yrs.
NCCN 2020 rectum	q 3–6 mos. for 2 yrs., q 6 mos. for 5 yrs.	q 3–6 mos. for 2 yrs. and then q 6 mos. for 5 yrs.	Stages II and III chest/abdomen/pelvis q 6–12 mos. for 5 yrs.	Transanal: EUS or MRI q 3–6 mos. for 2 yrs. and then q 6 mos. for 5 yrs., colonoscopy at 1 yr. and then 3 yrs. and then repeat q 5 yrs. Stages II–III: q 1 yr., repeat q 1 yr. if adenoma, otherwise repeat 3 yrs. and then every 5 yrs.
ASCRS 2015	q 3–6 mos. for 2 yrs., q 6 mos. for 5 yrs.	q 3–6 mos. for 2 yrs. and then q 6 mos. for 5 yrs.	Chest/abdomen/pelvis q 1 yr. for 5 yrs.	1 yr. after surgery, for rectum, the same or proctoscopy +/- ERUS q 6–12 mos. for those undergoing resection or q 6 mos. for those with local excision for 3–5 yrs.

Tjandra and Chan [76] reviewed seven of the eight studies noted above [67–71, 73] concluding that intensive surveillance resulted in earlier asymptomatic detection of resectable recurrences, as well as a statistically significant improvement in survival during follow-up (78% vs. 74%, $p = 0.01$). This was followed by a systemic review of 11 trials by Pita-Fernandez et al. [77] with more than 4055 patients which demonstrated a small but significant improvement in overall survival, as well as a higher probability of identifying asymptomatic recurrence (RR 2.59), higher rates of curative surgery (RR 1.98), and improved overall survival after recurrence (RR 2.59) [77]. However, the common theme of all of these trials is the finding of no significant difference in cancer-specific survival when compared to less intensive strategies.

FACS Trial

The eighth trial mentioned above is the FACS trial. In this landmark study published in 2014 [74], 1202 patients from the United Kingdom between the years of 2003 and 2009 from 39 national health service hospitals with primary colorectal cancer treated with curative-intent surgery were randomized to 4 combinations of testing. The four groups included minimal (clinical-only) follow-up, CEA only (every 3 months for 2 years and then semiannually out to 5 years), CT only (every 6 months for 2 years, done annually for 5 years), and both CEA and CT. Colonoscopy was performed at 5 years in the group without CT and at 2 and 5 years in the CT group. For those with minimal follow-up, additional testing was utilized only if symptoms occurred. The active surveillance group resulted in more curative-intent salvage operations (7% CEA alone, 8% CT alone, 7% CEA + CT) than the minimal follow-up group (2%, $p = 0.02$); however, there was no improvement in survival (82% active regimens vs. 84% no surveillance). Moreover, the addition of both CT and CEA did not increase detection rates of resectable disease. These findings challenged the notion that intensive surveillance and aggressive treatment of recurrence are of benefit.

Modern Literature

Modern surveillance trials from 2014 to 2018 as well as future trials (PRODIGE, expected to be completed by 2021) [78] have the potential to alter our understanding of these issues. These studies, which will be discussed, present evidence suggesting that more frequent testing or intensive surveillance may not be associated with any clinically meaningful benefit to patients (Table 30.4).

CEA Watch Trial

The Watch trial published in 2015 with follow-up in 2017 [79, 80] was not powered to assess overall survival but is important in terms of the information one can glean about the ability to detect recurrent disease. This randomized multicenter prospective study was designed to transition from a limited follow-up regime to an intensified follow-up for those with resected colorectal cancer. The less intensive protocol included outpatient clinic visits with liver ultrasound and chest x-ray every 6 months and CEA every 3–6 months for 3 years. The intensive follow-up protocol included bimonthly CEA measurements and annual CT imaging of the chest and abdomen for 3 years. As a part of this protocol,

Table 30.4 Colorectal cancer trials [74, 81, 82]

Trial	Setting	Population	Intensive group	Control group	Results
FACS (JAMA 2014)	United Kingdom	1201 stages I–III	Either CEA every 3 mos. for 2 yrs. and then every 6 mos. for 3 yrs., with a single chest, abdomen, and pelvis CT scan at 12–18 months if requested; CT of the chest/abdomen/ pelvis q 6 mos. for 2 yrs. and then q 1 yr. for 3 yrs.; both CEA and CT as above	No scheduled follow-up except single CT of the chest/abdomen/pelvis at 12–18 mos. if requested	No difference in mortality for combined CEA/ CT compared to control
GILDA (Ann Oncol 2016)	Italy	1228 Dukes B2–C (high-risk stages II and III)	CEA, CBC, liver tests, and CA 19-9 q 4 mos. for 2 yrs. and then q 6 mos. for 2 yrs. and then at 5 yrs.; colonoscopy and chest x-ray q yr. for 5 yrs.; liver ultrasound at 4, 8, 12, 16, 24, 36, 48, and 60 mos.	CEA q 4 mos. for 2 yrs. and then q 6 mos. for 2 yrs. and then at 5 yrs.; colonoscopy at 1 yr. and at 4 yrs.; liver ultrasound at 8 and 20 mos.	No difference in overall survival or health-related quality-of-life scores
COLFOL (JAMA 2018)	24 centers in Sweden, Denmark, and Uruguay	2509 stages II and III	CEA and CT of the chest/abdomen at 6, 12, 18, 24, and 36 mos.	CEA and CT of the chest/ abdomen at 12 mos. and 36 mos.	No difference in overall mortality, cancer-specific mortality, and cancer recurrence

additional imaging was obtained if the CEA increased by 20% or more over two consecutive measurements. The more intensive surveillance protocol detected a higher percentage of recurrent disease, 57% versus 43%. This resulted in a greater proportion of recurrences being treated with curative intent in the intensive surveillance group, 42% versus 30%. One potential limitation, which must be discussed, is the low overall recurrence rate of 8%, which is far lower than many published results, which average around 20%. This fact limits the generalizability of these findings.

GILDA

The GILDA trial published in 2016 included 1228 patients with resected stage II/III colorectal cancer from 1998 to 2006 [81]. Patients were randomized to intensive or minimal surveillance. The intensive protocol included annual colonoscopy with ultrasound and chest imaging every 6 months. The minimal follow-up protocol included two ultrasounds within 16 months with colonoscopy performed at years 1 and 4. Despite detecting recurrence an average of 6 months earlier, there remained no statistical difference in disease-free survival or overall survival. Moreover, there were no differences in health-related quality-of-life scores among treatment groups.

COLOFOL Trial

This randomized multicenter trial published in the *Journal of the American Medical Association* in 2018 evaluated 2509 patients [82]. All patients had stage II and III colorectal cancer and were treated at 24 centers in Sweden, Denmark, and Uruguay from 2006 to 2010. These patients were randomized to follow-up testing with chest and abdomen CT scans and CEA every 6 months for 3 years versus the CT and CEA at 12 and 36 months after initial resection. Recurrence rates were equivalent between the intensive and low-frequency testing groups (22% versus 19%). Moreover, disease-specific and overall mortality were equivalent at 11% versus 11% and 13% versus 14%, respectively.

Alliance and CoC Collaboration

A collaborative effort between the Alliance Surveillance Optimization Work Group and the Commission on Cancer in 2018 published a large series comparing surveillance testing intensity within the National Cancer Database [83]. Those patients treated from 2006 to 2007 with follow-up through 2014 were included. 8529 patients were identified and evaluated with the aim to determine if intensity of follow-up was associated with time to detection of CRC recurrence, rate of recurrence, resection of recurrence, and overall survival. Those patients with high-intensity follow-up included a mean of 2.9 imaging tests and 4.3 CEA evaluations during follow-up. Patients undergoing low-intensity treatment underwent a mean of 1.6 imaging tests and 1.6 CEA evaluations during follow-up. Frequency of imaging and CEA surveillance was not associated with differences in recurrence rates [HR 0.98 (95% CI 0.89–1.09) and 1.00 (95% CI 0.90–1.10)], resection of recurrence [HR 0.99 (95% CI 0.89–1.09) and 1.00 (95% CI 0.90–1.10)], or overall survival [HR 1.00 (95% CI 0.94–1.08) and 0.96 (95% CI 0.89–1.03)]. The conclusion of the authors was that there was no perceived benefit to more intensive follow-up.

PRODIGE

This French and Belgium trial will be randomizing 1750 patients with resected stage II and III colorectal cancer to intensive follow-up versus minimal follow-up. The results should be available sometime in the year 2021 [78].

Other Works

Despite the findings of a previous Cochrane collaborative meta-analysis of pre-FACS study findings, which demonstrated improved salvage surgery rates and a 27% reduction in odds of mortality, updated versions of similar analyses reveal alternative findings [75]. A review in 2019 demonstrated no overall survival benefit associated with intensive surveillance [75]. This new analysis of 13,216 patients from 16 previous studies demonstrated no statistical significance in overall survival, cancer-specific survival, or relapse-free survival for intensive follow-up. Moreover, compliance with best practice remains a real-world issue. A recent Canadian study of 408 patients revealed a disturbing fact that only 14%, 33%, and 24% completed their recommended CT imaging, colonoscopy, and CEA testing, respectively. Ultimately only 50% of all patients enrolled received all three follow-up tests at any time. Investigators in the Netherlands [84, 85] and Norway [86] found significant variability in surveillance when providers were compared. There is little consensus regarding who should coordinate cancer surveillance. Two randomized trials have compared surveillance by general practitioners and surgeons. In both series, surgeons were costlier, using intensive diagnostic testing with no associated difference in recurrence, time to recurrence, survival, or quality of life [87, 88]. Patient followed by their primary care doctors also reported a high emphasis on preventive health maintenance over surgical consultation [89]. A recent publication of the Optum®, a database with

180 million patient claim records, 80 million with EHR, and 12 million with deterministically linked claims and EHR, reviewed 6921 patient which demonstrated strikingly low levels of compliance with recommended surveillance examination during follow-up [90]. They concluded that low levels of compliance led to decreasing frequencies of CT imaging in surveillance programs. They also made recommendations to study further why providers are not adhering to aspects of surveillance. In the United States, there is substantial geographic variation in the intensity of surveillance, with both undertreatment in 40% and overtreatment in 23% based on published guidelines [91]. Similarly, a survey of ASCRS (American Society of Colon and Rectal Surgeons) membership concluded that surgeons engage in a variety of surveillance approaches, with only 30% following formal national guidelines [92]. Ultimately, implementing best practice and guideline recommendations from both a provider and a patient perspective remains challenging.

Specific Tests and Recommendations

Eighty percent of recurrence is detected within 2–3 years following initial curative surgical therapy. Therefore, most guidelines include more intensive surveillance during the first 2–3 years, with diminishing intensity over the remaining years of surveillance (typically a total of 5 years of surveillance testing) [65, 93–95]. The data associated with any specific surveillance test are generally of poor quality and often derived from larger trials using different testing at varying frequencies. Substantial variability exists in the use of clinical, laboratory, radiologic, and endoscopic methods to evaluate patients with colorectal cancer as part of "routine surveillance." Therefore, the recommendations within this section reflect that which is presented in Table 30.3 along with the best evidence for such recommendation.

Physical Examination

The American Society of Colon and Rectal Surgeons (ASCRS) recommends physical exam every 3–6 months for 2 years and then every 6 months until 5 years [96]. The physical exam should focus on the abdomen, the wound, the rectal examination, and the perineal wound if an abdominoperineal resection was performed. Not surprisingly, there are virtually no data to support the contention that physical examination provides any benefit to patients undergoing curative-intent resection of intraperitoneal colon cancer. It would seem logical that patients undergoing restorative proctectomy for rectal cancer may benefit from physical examination to detect pelvic recurrence; however, definitive data are lacking. More important may be that patient complaints possibly associated with tumor are voiced during an office visit and investigated appropriately.

Probably more important than detection of recurrence during an office visit is attention to the psychosocial issues that accompany colorectal resection. There are many physical, functional, and emotional challenges that affect patients post resection. A majority (50%) of patients who undergo rectal resection suffer from low anterior resection syndrome and defecatory dysfunction [97, 98]. Moreover, many patients suffer from depression after colorectal resection, and therefore it remains important to address these issues as well as encourage patients to engage in healthy eating and exercise [99–101].

Laboratory Testing

The evaluation of CEA (an oncofetal protein) levels is recommended by most societies and guidelines. CEA alone may detect up to 30–60% of recurrences [16, 33, 65, 102–104]; however, more than 15% of patients will have falsely elevated CEA in the absence of recurrence [105]. CEA elevation may identify disease in the setting of normal conventional imaging in up to 23% of patients [103]. Typically, one third of primary colorectal cancers do not produce CEA, yet overall, CEA elevation remains an independent predictor of recurrence [102]. There remains some controversy about the use of CEA in those patients with normal preoperative CEA levels at diagnosis, although some metastatic tumors will release CEA into the circulation even when the primary tumor did not. Elevations of CEA should be confirmed and then prompt evaluation with physical examination, colonoscopy, and typically CT of the chest, abdomen, and pelvis [96]. If conventional testing is non-diagnostic, then one may consider the use of combined positron emission tomography/CT (PET/CT). If no tumor is detected, CEA and imaging can be repeated every 3 months until levels decline or recurrence is detected [96].

Abdominal Imaging

The most common metastatic site of metachronous colorectal cancer is the liver (50) although the lung is increasing in frequency, particularly in cases of rectal cancer. Past recommendations for routine imaging include ultrasonography and CT imaging. However, current recommendations have reduced their emphasis on ultrasound to diagnose liver disease. In general, ultrasound has been replaced with CT due to its greater sensitivity [96].

Although observational studies [95, 106] have supported the use of frequent advanced liver imaging to improve the opportunity for further salvage surgery, few modern trials

suggest improved survival with such a strategy. In a meta-analysis of five surveillance trials, Renehan et al. [107] concluded that the regimen most consistently associated with improved survival included both CT and frequent CEA testing. This combination of testing is common among consensus recommendations. The routine use of PET/CT or liver magnetic resonance imaging (MRI) has not been endorsed by any current organizations [96]. One fundamental limitation of PET remains its low spatial resolution in combination with low-quality CT imaging without contrast for combined cases. A meta-analysis using PET demonstrated inadequate support for its use in routine surveillance [108].

Colonoscopy

The primary purpose of colonoscopy in surveillance algorithms is to detect metachronous neoplasia. If primary resection was accomplished with negative margins, luminal recurrence should be a relatively rare and late event, only occurring after extraluminal tumor has grown through the wall of the colon or rectum. If surgery was performed skillfully at the initial operation, usually the detection of luminal recurrence portends unresectable disease, as the local recurrence presumably arose from micrometastases beyond the normal planes of resection. Table 30.3 outlines current recommendations for colonoscopy surveillance from multiple societies and guidelines. Anastomotic recurrence is a rare event representing less than 4% of all recurrences [107, 109, 110]. The risk of metachronous cancer found within 2 years after surgery with colonoscopy is also low with an incidence of 0.7% [111–114]. Cone et al. [109] demonstrated an incidence of neoplastic polyps in 18% of patients undergoing first surveillance colonoscopy at a mean of 478 (± 283) days post resection, but only a 3% rate of polyps >1 cm in size. It thus is reasonable to defer colonoscopy to 2–3 years following resection, provided that the patient has a good-quality colonoscopy prior to resection and there is no suggestion of Lynch syndrome. A second primary colorectal cancer is found at 5–10 years in 2–3% of patients [112, 115–117]. It should be emphasized that patients with limited life expectancy should refrain from endoscopic surveillance in the absence of symptoms [118–120].

Special Circumstances

Stage I Colon Cancer

Patients with stage I tumors have been largely excluded from randomized trials of surveillance. Several of the consensus guidelines recommend against routine CEA testing or imaging [16, 21], advising only endoscopic surveillance to look for metachronous neoplasia. In general terms, the number needed to treat for a potential survival advantage to be demonstrated for CEA and imaging testing would not be consistent with healthcare value for patients or society.

Stage I Rectal Cancer

Typically, surveillance is used to identify distant disease. Updated guidelines from NCCN® in 2020 recommend only colonoscopy at 1 year after surgery with repeat at 3 years and then every 5 years after that for those cases with full surgical staging [33]. However, in locally transanally resected rectal cancer, the highest risk component of recurrence is local disease, estimated to be 4–33% [45, 121, 122]. Therefore, an emphasis on local site surveillance takes precedence over traditional modalities. Identification of local recurrence may allow for curative-intent salvage resection, especially if patients were initially treated with local excision. Therefore, surveillance including endoscopic and pelvic imaging is recommended. Endorectal ultrasound (ERUS) has been identified as a sensitive imaging modality for detection of recurrence in expert hands, exceeding other forms of follow-up such as digital exam, endoscopy, CT, and CEA in about 30% of cases in some studies [123–125]. Moreover, ERUS-guided biopsy can obtain histological confirmation of extraluminal recurrence [126–128].

MRI of the pelvis can also be used as a highly accurate diagnostic pelvic modality to detect recurrence [129]. However, its use in routine surveillance did not improve the detection of resectable recurrences in one trial [130], and its cost-effectiveness has not been formally evaluated. Kwakye et al. [131] recently evaluated 114 patients in which 11% suffered from local recurrence. In the series, it was suggested that traditional surveillance methods such as laboratory testing or imaging are actually responsible for a minority of positive findings. On the other hand, ERUS was able to identify the majority of recurrences. Although it is difficult to prove that this more intensive surveillance results in improved outcomes, some have suggested that a novel approach to detect pelvic recurrence following treatment of rectal cancer may be needed. ERUS or MRI every 3–6 months for the first 2 years and then every 6 months for a total of 5 is the recommendation from this series and the new 2020 NCCN® guidelines [33, 131]. In addition, surveillance is recommended to extend beyond the 5-year window because local recurrence has been observed beyond 7 years.

Quality of Life

In addition to cancer-specific outcomes of surveillance, the psychological health and quality of life of patients are of critical significance. Most patients in surveillance report that

the anxieties, which may be potentiated by intensive follow-up, are outweighed by the reassurance of negative results [132]. The randomized trial by Kjeldsen et al. [133] reported that patients had greater confidence in the surveillance process and less worry about test results. Likewise, Stiggelbout et al. [134] reported on 212 patients undergoing surveillance with positive attitude toward surveillance. Although difficult to prove through research, it is likely to assume that patients simply desire a standardized approach, which is known and executed on their behalf.

Cost

Given the myriad of proposed recommendations, the cost of surveillance testing, correlation with patient outcomes, and availability of healthcare resources are of paramount concern. Between 1999 and 2000, the use of CT and MRI scans increased more than 5% annually, with the use of PET scans tripling in the same time period [135]. Among a cohort of Italian patients undergoing surveillance with clinical examination, CEA, abdominal ultrasound, chest radiograph, and colonoscopy, the 5-year cost of surveillance averaged $5400 per patient but more than $100,000 per detected case of potentially curable recurrence [136]. Similarly, Renehan et al. [137] estimate the average cost of surveillance at almost £2500 per patient or about £3000 per year of life saved, within the range of acceptable cost-effectiveness for the United Kingdom's National Health Service. A comparative study in France estimated that intense surveillance cost an additional €3144 for quality-adjusted year of life gained over a minimal surveillance strategy. Wanis et al. [138], using a mathematical Markov model, demonstrated that the effectiveness of routine surveillance and the treatment of recurrent colorectal cancer is on average small.

Overall, assessments of cost-effectiveness for colorectal cancer surveillance would suggest that it provides low value. Current NCCN recommendations for stage II and III colorectal cancer patients promote costly surveillance testing with minimal to no demonstrated improvement in overall outcomes. Therefore, although the cost-effectiveness of colorectal cancer surveillance is within the range of other interventions considered acceptable by many Western cultures, it is highly likely that this intensity of practice leads to an overall elevated utilization healthcare and surgical services, without substantial benefit.

Conclusions

Although surgery remains the mainstay of treatment of non-metastatic colorectal cancer, recurrence following surgery with curative intent remains relatively high. Adjuvant systemic chemotherapy offers clear advantages in terms of reduced risk of recurrence and improved survival following surgery for stage III colon cancer and stage II and III rectal cancer, but its benefits for stage II colon cancer remain unclear. Adjuvant radiotherapy has a role in the treatment of rectal cancer, but it is ideally used in the neoadjuvant setting, and it is rarely used for colon cancer. Molecular profiling can be helpful in predicting risk of recurrence and identifying potential candidates for targeted therapies, but its routine use following curative-intent surgery remains limited.

The optimal frequency and modalities of surveillance testing remain a question. There appears to be a growing consensus regarding the lack of benefit from intensive surveillance for colorectal cancer. Despite the growing array of management options and diagnostic testing, the ability to identify early recurrence appears to provide patients little benefit in terms of cancer-specific survival. It is time to reevaluate US consensus guidelines to more closely reflect current evidence.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67(1):7–30.
2. Vogel JD, et al. The American Society of Colon and Rectal Surgeons clinical practice guidelines for the treatment of colon cancer. Dis Colon Rectum. 2017;60(10):999–1017.
3. Andre T, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009;27(19):3109–16.
4. Jemal A, et al. Cancer statistics, 2006. CA Cancer J Clin. 2006;56(2):106–30.
5. Moertel CG, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med. 1990;322(6):352–8.
6. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Lancet. 1995;345(8955):939–44.
7. Haller DG, et al. Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of Intergroup 0089. J Clin Oncol. 2005;23(34):8671–8.
8. O'Connell MJ, et al. Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. J Clin Oncol. 1997;15(1):246–50.
9. Wolmark N, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. J Clin Oncol. 1993;11(10):1879–87.
10. Andre T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004;350(23):2343–51.
11. Kuebler JP, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol. 2007;25(16):2198–204.
12. Twelves C, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med. 2005;352(26):2696–704.
13. Haller DG, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol. 2011;29(11):1465–71.

14. Zedan AH, et al. Oxaliplatin-induced neuropathy in colorectal cancer: many questions with few answers. Clin Colorectal Cancer. 2014;13(2):73–80.
15. Grothey A, et al. Duration of adjuvant chemotherapy for stage III colon cancer. N Engl J Med. 2018;378(13):1177–88.
16. Benson AB, et al. Colon cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. 2020 5/6/2020 [cited 2020 5/10/2020]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
17. Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer. International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) Investigators. J Clin Oncol. 1999;17(5):1356–63.
18. Gill S, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J Clin Oncol. 2004;22(10):1797–806.
19. Quasar Collaborative, G, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet. 2007;370(9604):2020–9.
20. Benson AB 3rd, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol. 2004;22(16):3408–19.
21. Labianca R, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi64–72.
22. Gryfe R, et al. Tumor microsatellite instability and clinical outcome in young patients with colorectal cancer. N Engl J Med. 2000;342(2):69–77.
23. Sargent DJ, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol. 2010;28(20):3219–26.
24. Gavin PG, et al. Mutation profiling and microsatellite instability in stage II and III colon cancer: an assessment of their prognostic and oxaliplatin predictive value. Clin Cancer Res. 2012;18(23):6531–41.
25. Benson AB 3rd, et al. Colon cancer, version 1.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2017;15(3):370–98.
26. Martenson JA Jr, et al. Phase III study of adjuvant chemotherapy and radiation therapy compared with chemotherapy alone in the surgical adjuvant treatment of colon cancer: results of intergroup protocol 0130. J Clin Oncol. 2004;22(16):3277–83.
27. Sebastian NT, et al. Surgery with and without adjuvant radiotherapy are associated with similar survival in T4 colon cancer. Color Dis. 2020;22:779.
28. Zhou Z, Nimeiri HS, Benson AB 3rd. Preoperative chemotherapy for locally advanced resectable colon cancer - a new treatment paradigm in colon cancer? Ann Transl Med. 2013;1(2):11.
29. Dehal A, et al. Neoadjuvant chemotherapy improves survival in patients with clinical T4b colon cancer. J Gastrointest Surg. 2018;22(2):242–9.
30. Swedish Rectal Cancer, T, et al. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med. 1997;336(14):980–7.
31. Sauer R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351(17):1731–40.
32. Peeters KC, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg. 2007;246(5):693–701.
33. Benson AB, et al. Rectal cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. 2020 5/6/2020 [cited 2020 5/10/2020]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf.
34. Hong YS, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. Lancet Oncol. 2014;15(11):1245–53.
35. Rodel C, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol. 2012;13(7):679–87.
36. Breugom AJ, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol. 2015;16(2):200–7.
37. Biagi JJ, et al. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. JAMA. 2011;305(22):2335–42.
38. Fernandez-Martos C, et al. Chemoradiation, surgery and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: long-term results of the Spanish GCR-3 phase II randomized trial†. Ann Oncol. 2015;26(8):1722–8.
39. Nogue M, et al. Addition of bevacizumab to XELOX induction therapy plus concomitant capecitabine-based chemoradiotherapy in magnetic resonance imaging-defined poor-prognosis locally advanced rectal cancer: the AVACROSS study. Oncologist. 2011;16(5):614–20.
40. Al-Sukhni E, et al. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. Ann Surg Oncol. 2012;19(7):2212–23.
41. Fisher B, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. J Natl Cancer Inst. 1988;80(1):21–9.
42. Krook JE, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med. 1991;324(11):709–15.
43. Mellgren A, et al. Is local excision adequate therapy for early rectal cancer? Dis Colon Rectum. 2000;43(8):1064–71. discussion 1071-4
44. Endreseth BH, et al. Transanal excision vs. major surgery for T1 rectal cancer. Dis Colon Rectum. 2005;48(7):1380–8.
45. Nash GM, et al. Long-term survival after transanal excision of T1 rectal cancer. Dis Colon Rectum. 2009;52(4):577–82.
46. Bentrem DJ, et al. T1 adenocarcinoma of the rectum: transanal excision or radical surgery? Ann Surg. 2005;242(4):472–7. discussion 477-9
47. Nascimbeni R, et al. Long-term survival after local excision for T1 carcinoma of the rectum. Dis Colon Rectum. 2004;47(11):1773–9.
48. Borschitz T, Heintz A, Junginger T. The influence of histopathologic criteria on the long-term prognosis of locally excised pT1 rectal carcinomas: results of local excision (transanal endoscopic microsurgery) and immediate reoperation. Dis Colon Rectum. 2006;49(10):1492–506. discussion 1500-5
49. Junginger T, et al. Long-term oncologic outcome after transanal endoscopic microsurgery for rectal carcinoma. Dis Colon Rectum. 2016;59(1):8–15.
50. Garcia-Aguilar J, et al. Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial. Lancet Oncol. 2015;16(15):1537–46.
51. de Gramont A, et al. Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. Lancet Oncol. 2012;13(12):1225–33.
52. Alberts SR, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. JAMA. 2012;307(13):1383–93.

53. Taieb J, et al. Oxaliplatin, fluorouracil, and leucovorin with or without cetuximab in patients with resected stage III colon cancer (PETACC-8): an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15(8):862–73.
54. Markowitz SD, Bertagnolli MM. Molecular origins of cancer: molecular basis of colorectal cancer. N Engl J Med. 2009;361(25):2449–60.
55. Ionov Y, et al. Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis. Nature. 1993;363(6429):558–61.
56. Gray RG, et al. Validation study of a quantitative multigene reverse transcriptase-polymerase chain reaction assay for assessment of recurrence risk in patients with stage II colon cancer. J Clin Oncol. 2011;29(35):4611–9.
57. Venook AP, et al. Biologic determinants of tumor recurrence in stage II colon cancer: validation study of the 12-gene recurrence score in cancer and leukemia group B (CALGB) 9581. J Clin Oncol. 2013;31(14):1775–81.
58. Yamanaka T, et al. 12-gene recurrence score assay stratifies the recurrence risk in stage II/III colon cancer with surgery alone: the SUNRISE study. J Clin Oncol. 2016;34(24):2906–13.
59. Yothers G, et al. Validation of the 12-gene colon cancer recurrence score in NSABP C-07 as a predictor of recurrence in patients with stage II and III colon cancer treated with fluorouracil and leucovorin (FU/LV) and FU/LV plus oxaliplatin. J Clin Oncol. 2013;31(36):4512–9.
60. DeSantis CE, et al. Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin. 2014;64(4):252–71.
61. Buie WD, Attard JA. Follow-up recommendations for colon cancer. Clin Colon Rectal Surg. 2005;18(3):232–43.
62. Grossmann EM, et al. Follow-up of colorectal cancer patients after resection with curative intent-the GILDA trial. Surg Oncol. 2004;13(2–3):119–24.
63. Vernava AM 3rd, et al. Current follow-up strategies after resection of colon cancer. Results of a survey of members of the American Society of Colon and Rectal Surgeons. Dis Colon Rectum. 1994;37(6):573–83.
64. Fong Y, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999;230(3):309–18. discussion 318-21
65. Kobayashi H, et al. Characteristics of recurrence after curative resection for T1 colorectal cancer: Japanese multicenter study. J Gastroenterol. 2011;46(2):203–11.
66. Tsikitis VL, et al. Postoperative surveillance recommendations for early stage colon cancer based on results from the clinical outcomes of surgical therapy trial. J Clin Oncol. 2009;27(22):3671–6.
67. Ohlsson B, et al. Follow-up after curative surgery for colorectal carcinoma. Randomized comparison with no follow-up. Dis Colon Rectum. 1995;38(6):619–26.
68. Makela JT, Laitinen SO, Kairaluoma MI. Five-year follow-up after radical surgery for colorectal cancer. Results of a prospective randomized trial. Arch Surg. 1995;130(10):1062–7.
69. Kjeldsen BJ, et al. A prospective randomized study of follow-up after radical surgery for colorectal cancer. Br J Surg. 1997;84(5):666–9.
70. Schoemaker D, et al. Yearly colonoscopy, liver CT, and chest radiography do not influence 5-year survival of colorectal cancer patients. Gastroenterology. 1998;114(1):7–14.
71. Rodriguez-Moranta F, et al. Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: a prospective, multicenter, randomized, controlled trial. J Clin Oncol. 2006;24(3):386–93.
72. Pietra N, et al. Role of follow-up in management of local recurrences of colorectal cancer: a prospective, randomized study. Dis Colon Rectum. 1998;41(9):1127–33.
73. Secco GB, et al. Efficacy and cost of risk-adapted follow-up in patients after colorectal cancer surgery: a prospective, randomized and controlled trial. Eur J Surg Oncol. 2002;28(4):418–23.
74. Primrose JN, et al. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. JAMA. 2014;311(3):263–70.
75. Jeffery M, Hickey BE, Hider PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev. 2019;9:CD002200.
76. Tjandra JJ, Chan MK. Follow-up after curative resection of colorectal cancer: a meta-analysis. Dis Colon Rectum. 2007;50(11):1783–99.
77. Pita-Fernandez S, et al. Intensive follow-up strategies improve outcomes in nonmetastatic colorectal cancer patients after curative surgery: a systematic review and meta-analysis. Ann Oncol. 2015;26(4):644–56.
78. Lepage C, et al. Effect of 5 years of imaging and CEA follow-up to detect recurrence of colorectal cancer: the FFCD PRODIGE 13 randomised phase III trial. Dig Liver Dis. 2015;47(7):529–31.
79. Verberne CJ, et al. Intensified follow-up in colorectal cancer patients using frequent Carcino-Embryonic Antigen (CEA) measurements and CEA-triggered imaging: results of the randomized "CEAwatch" trial. Eur J Surg Oncol. 2015;41(9):1188–96.
80. Verberne CJ, et al. Survival analysis of the CEAwatch multicentre clustered randomized trial. Br J Surg. 2017;104(8):1069–77.
81. Rosati G, et al. A randomized trial of intensive versus minimal surveillance of patients with resected Dukes B2-C colorectal carcinoma. Ann Oncol. 2016;27(2):274–80.
82. Wille-Jorgensen P, et al. Effect of more vs less frequent follow-up testing on overall and colorectal cancer-specific mortality in patients with stage II or III colorectal cancer: the COLOFOL randomized clinical trial. JAMA. 2018;319(20):2095–103.
83. Snyder RA, et al. Association between intensity of posttreatment surveillance testing and detection of recurrence in patients with colorectal cancer. JAMA. 2018;319(20):2104–15.
84. Grossmann I, et al. Results of a national survey among Dutch surgeons treating patients with colorectal carcinoma. Current opinion about follow-up, treatment of metastasis, and reasons to revise follow-up practice. Color Dis. 2007;9(9):787–92.
85. van Steenbergen LN, et al. Large variation between hospitals in follow-up for colorectal cancer in southern Netherlands. Int J Color Dis. 2013;28(9):1257–65.
86. Soreide K, et al. Adherence to national guidelines for surveillance after curative resection of nonmetastatic colon and rectum cancer: a survey among Norwegian gastrointestinal surgeons. Color Dis. 2012;14(3):320–4.
87. Wattchow DA, et al. General practice vs surgical-based follow-up for patients with colon cancer: randomised controlled trial. Br J Cancer. 2006;94(8):1116–21.
88. Augestad KM, et al. Cost-effectiveness and quality of life in surgeon versus general practitioner-organised colon cancer surveillance: a randomised controlled trial. BMJ Open. 2013;3(4):e002391.
89. Haggstrom DA, et al. Follow-up care delivery among colorectal cancer survivors most often seen by primary and subspecialty care physicians. J Gen Intern Med. 2009;24(Suppl 2):S472–9.
90. Durani U, et al. Use of imaging during staging and surveillance of localized colon cancer in a large insured population. J Natl Compr Cancer Netw. 2019;17(11):1355–61.
91. Cooper GS, Kou TD, Reynolds HL Jr. Receipt of guideline-recommended follow-up in older colorectal cancer survivors: a population-based analysis. Cancer. 2008;113(8):2029–37.
92. Giordano P, et al. Strategies of follow-up for colorectal cancer: a survey of the American Society of Colon and Rectal Surgeons. Tech Coloproctol. 2006;10(3):199–207.

93. Sargent D, et al. Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol. 2009;27(6):872–7.
94. Seo SI, et al. Comparison of recurrence patterns between </=5 years and >5 years after curative operations in colorectal cancer patients. J Surg Oncol. 2013;108(1):9–13.
95. Fora A, et al. Intensive radiographic and biomarker surveillance in stage II and III colorectal cancer. Oncology. 2012;82(1):41–7.
96. Steele SR, et al. Practice guideline for the surveillance of patients after curative treatment of colon and rectal cancer. Dis Colon Rectum. 2015;58(8):713–25.
97. Juul T, et al. International validation of the low anterior resection syndrome score. Ann Surg. 2014;259(4):728–34.
98. Peeters KC, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients – a Dutch colorectal cancer group study. J Clin Oncol. 2005;23(25):6199–206.
99. Meyerhardt JA, et al. Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer. JAMA. 2007;298(7):754–64.
100. McCullough ML, et al. Association between red and processed meat intake and mortality among colorectal cancer survivors. J Clin Oncol. 2013;31(22):2773–82.
101. Meyerhardt JA, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. J Clin Oncol. 2006;24(22):3535–41.
102. Irvine T, Scott M, Clark CI. A small rise in CEA is sensitive for recurrence after surgery for colorectal cancer. Color Dis. 2007;9(6):527–31.
103. Verberne CJ, et al. Detection of recurrences during follow-up after liver surgery for colorectal metastases: both carcinoembryonic antigen (CEA) and imaging are important. Ann Surg Oncol. 2013;20(2):457–63.
104. Goslin R, et al. Correlation of Plasma CEA and CEA tissue staining in poorly differentiated colorectal cancer. Am J Med. 1981;71(2):246–53.
105. Moertel CG, et al. An evaluation of the carcinoembryonic antigen (CEA) test for monitoring patients with resected colon cancer. JAMA. 1993;270(8):943–7.
106. Arriola E, et al. Imaging techniques contribute to increased surgical rescue of relapse in the follow-up of colorectal cancer. Dis Colon Rectum. 2006;49(4):478–84.
107. Renehan AG, et al. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. BMJ. 2002;324(7341):813.
108. Patel K, et al. The lack of evidence for PET or PET/CT surveillance of patients with treated lymphoma, colorectal cancer, and head and neck cancer: a systematic review. J Nucl Med. 2013;54(9):1518–27.
109. Cone MM, et al. Timing of colonoscopy after resection for colorectal cancer: are we looking too soon? Dis Colon Rectum. 2013;56(11):1233–6.
110. Ohlsson B, Palsson B. Follow-up after colorectal cancer surgery. Acta Oncol. 2003;42(8):816–26.
111. Rex DK, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2006;130(6):1865–71.
112. Cali RL, et al. Cumulative incidence of metachronous colorectal cancer. Dis Colon Rectum. 1993;36(4):388–93.
113. Wang T, et al. The role of postoperative colonoscopic surveillance after radical surgery for colorectal cancer: a prospective, randomized clinical study. Gastrointest Endosc. 2009;69(3 Pt 2):609–15.
114. Lan YT, et al. Metachronous colorectal cancer: necessity of post-operative colonoscopic surveillance. Int J Color Dis. 2005;20(2):121–5.
115. Green RJ, et al. Surveillance for second primary colorectal cancer after adjuvant chemotherapy: an analysis of Intergroup 0089. Ann Intern Med. 2002;136(4):261–9.
116. Mulder SA, et al. The incidence and risk factors of metachronous colorectal cancer: an indication for follow-up. Dis Colon Rectum. 2012;55(5):522–31.
117. Bouvier AM, et al. The lifelong risk of metachronous colorectal cancer justifies long-term colonoscopic follow-up. Eur J Cancer. 2008;44(4):522–7.
118. Battersby NJ, et al. Metachronous colorectal cancer: a competing risks analysis with consideration for a stratified approach to surveillance colonoscopy. J Surg Oncol. 2014;109(5):445–50.
119. Day LW, Walter LC, Velayos F. Colorectal cancer screening and surveillance in the elderly patient. Am J Gastroenterol. 2011;106(7):1197–206; quiz 1207.
120. Tran AH, Man Ngor EW, Wu BU. Surveillance colonoscopy in elderly patients: a retrospective cohort study. JAMA Intern Med. 2014;174(10):1675–82.
121. You YN, et al. Is the increasing rate of local excision for stage I rectal cancer in the United States justified?: a nationwide cohort study from the National Cancer Database. Ann Surg. 2007;245(5):726–33.
122. Paty PB, et al. Long-term results of local excision for rectal cancer. Ann Surg. 2002;236(4):522–9. discussion 529-30
123. Lohnert MS, Doniec JM, Henne-Bruns D. Effectiveness of endoluminal sonography in the identification of occult local rectal cancer recurrences. Dis Colon Rectum. 2000;43(4):483–91.
124. de Anda EH, et al. Endorectal ultrasound in the follow-up of rectal cancer patients treated by local excision or radical surgery. Dis Colon Rectum. 2004;47(6):818–24.
125. Ramirez JM, et al. Endoluminal ultrasonography in the follow-up of patients with rectal cancer. Br J Surg. 1994;81(5):692–4.
126. Morken JJ, et al. Endorectal ultrasound-directed biopsy: a useful technique to detect local recurrence of rectal cancer. Int J Color Dis. 2006;21(3):258–64.
127. Gleeson FC, et al. Local recurrence detection following transanal excision facilitated by EUS-FNA. Hepato-Gastroenterology. 2012;59(116):1102–7.
128. Maleki Z, et al. Endorectal ultrasound-guided fine-needle aspiration: a useful diagnostic tool for perirectal and intraluminal lesions. Acta Cytol. 2013;57(1):9–18.
129. Lambregts DM, et al. Value of MRI and diffusion-weighted MRI for the diagnosis of locally recurrent rectal cancer. Eur Radiol. 2011;21(6):1250–8.
130. Titu LV, et al. Routine follow-up by magnetic resonance imaging does not improve detection of resectable local recurrences from colorectal cancer. Ann Surg. 2006;243(3):348–52.
131. Kwakye G, et al. Locally excised T1 rectal cancers: need for specialized surveillance protocols. Dis Colon Rectum. 2019;62(9):1055–62.
132. Papagrigoriadis S, Heyman B. Patients' views on follow up of colorectal cancer: implications for risk communication and decision making. Postgrad Med J. 2003;79(933):403–7.
133. Kjeldsen BJ, et al. Influence of follow-up on health-related quality of life after radical surgery for colorectal cancer. Scand J Gastroenterol. 1999;34(5):509–15.
134. Stiggelbout AM, et al. Follow-up of colorectal cancer patients: quality of life and attitudes towards follow-up. Br J Cancer. 1997;75(6):914–20.
135. Dinan MA, et al. Changes in the use and costs of diagnostic imaging among Medicare beneficiaries with cancer, 1999-2006. JAMA. 2010;303(16):1625–31.

136. Audisio RA, et al. Follow-up in colorectal cancer patients: a cost-benefit analysis. Ann Surg Oncol. 1996;3(4):349–57.
137. Renehan AG, O'Dwyer ST, Whynes DK. Cost effectiveness analysis of intensive versus conventional follow up after curative resection for colorectal cancer. BMJ. 2004;328(7431):81.
138. Wanis KN, et al. Health and economic impact of intensive surveillance for distant recurrence after curative treatment of colon cancer: a mathematical modeling study. Dis Colon Rectum. 2019;62(7):872–81.
139. Liu SL, Cheung WY. Role of surveillance imaging and endoscopy in colorectal cancer follow-up: quality over quantity? World J Gastroenterol. 2019;25(1):59–68.
140. Glimelius B, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi81–8.

Colorectal Cancer: Management of Distant Metastases

31

Traci L. Hedrick

Key Concepts

- Treatment of advanced colorectal cancer has evolved significantly over time, reflecting a shift toward more aggressive therapy recognizing the potential for long-term survival.
- The liver is the most common site of metastatic disease followed by the lung. The brain, bone, ovary, peritoneum, and adrenals make up the remaining less common sites of metastatic disease.
- Treatment options depend on the functional status and primary goals of the patient, site and volume of metastatic disease, as well as the degree of symptoms from the primary tumor.
- Treatment of the patient with metastatic colorectal cancer requires a comprehensive multidisciplinary approach to develop an individualized treatment scheme integrating quality of life and patient needs.

Introduction

The majority of CRC-related deaths are attributable to metastatic disease, with up to 22% of patients exhibiting evidence of metastatic disease at initial presentation [1–4]. The overall 5-year survival rate in the setting of Stage IV CRC is 10–14% [2, 5]. However, this is highly dependent on the extent and site of metastases with 5-year survival ranging from 24% to 58% (averaging 40%) in patients with resectable hepatic metastases. The liver is the dominant site of metastatic disease, accounting for 75% of patients with CRC metastases, followed by the lung in 22% [5]. Over 70% of patients with lung metastases have synchronous liver metastases as well [5]. The brain, bone, ovary, peritoneum, and adrenals make up the remaining less common sites of metastatic disease. Prognosis relates to volume and site of metastases with oligometastases portending a worse prognosis than single-organ metastases. Wang et al. demonstrated a 3-year overall survival (OS) for patients with solitary metastasis to the liver and lung of 26.8% (95% CI, 25.8–27.8%) and 34.0% (95% CI, 29.9–38.1%), respectively, using the Surveillance, Epidemiology, and End Results (SEER) database [5].

Multidisciplinary Evaluation

Treatment of metastatic CRC has evolved over time with a shift toward more aggressive therapy in recognition of the potential for long-term survival. There are innumerable factors to consider in the management of the patient with metastatic CRC. The National Comprehensive Cancer Network (NCCN) and American Society of Colon and Rectal Surgeons (ASCRS) guidelines do not recommend one treatment strategy over the other, particularly in the patient with resectable metastatic disease [6, 7]. Rather, treatment of the patient with metastatic CRC requires a comprehensive multidisciplinary approach to develop an individualized treatment scheme, integrating quality of life and patient needs [6]. Shared decision-making strategies between the patient and the team result in better alignment between medical decisions and patient care preferences [8–10].

Synchronous Metastases

The patient presenting with metastatic disease at the time of initial diagnosis requires a sophisticated individualized approach based on a multitude of factors. Treatment options depend on the functional status and primary goals of the patient, site and volume of metastatic disease, as well as the degree of symptoms from the primary tumor. An algorithm is presented in Fig. 31.1 to guide clinical decision-making in patients presenting with synchronous colorectal primary tumor and liver or lung metastases.

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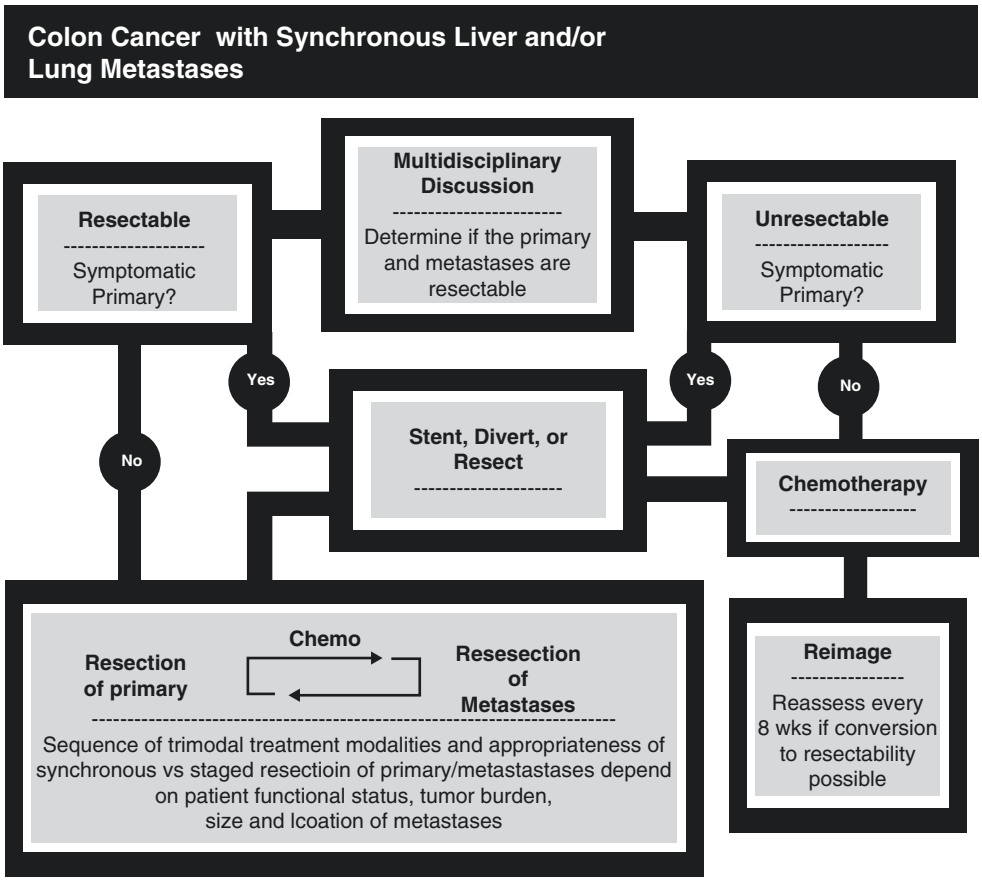

Fig. 31.1 Treatment algorithm to guide clinical decision-making in patients with synchronous CRC metastases

Management of Primary Tumor

Management of the primary tumor requires thoughtful clinical judgment to ascertain the degree of primary tumor-related symptoms during the initial evaluation.

Bleeding Many patients suffer from symptomatic anemia at the time of diagnosis. Given that the ongoing blood loss from the primary tumor is typically low volume, symptomatic anemia can usually be managed non-operatively. Rarely, however, patients exhibit significant blood loss necessitating surgery, particularly in the setting of mandatory chronic anticoagulation (e.g., mechanical valve/pulmonary embolus) or tumor involvement of a mesenteric or surrounding vascular structure (Fig. 31.2). Management of bleeding depends on the location and size of the tumor as well as the rate of bleeding. Radiation provides relatively quick and effective palliation for surface bleeding at the site of the tumor, particularly within the rectum [11, 12]. Resection is the preferred approach, if possible, for more proximal cancers or in the setting of significant hemorrhage. However, this decision will depend on the local invasion of the tumor into adjacent structures, the functional status of the patient, and the volume of metastatic disease. Endovascular procedures (e.g., embolization, covered stent placement) are also available in the palliative setting for bleeding from advanced CRC [13, 14].

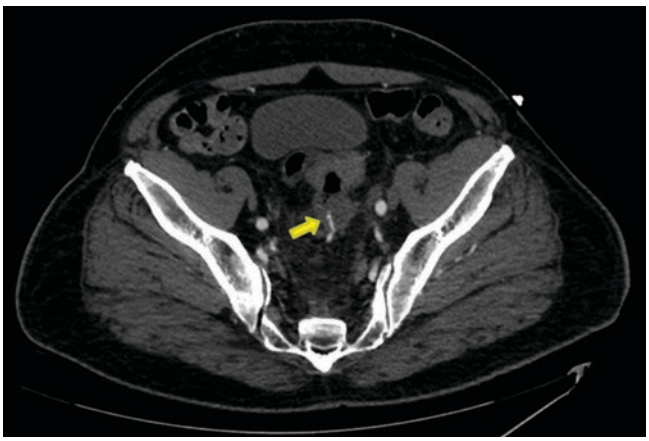

Fig. 31.2 Computed tomography image demonstrating active extravasation from the inferior mesenteric artery (arrow) into a necrotic rectosigmoid tumor causing significant intraluminal bleeding requiring resection

Obstruction Between 8% and 30% of patients with colorectal cancer present with a partial or completely obstructing primary lesion [15]. While recognition of a complete obstruction is straightforward, recognition and management of a patient with an impending obstruction can be more nuanced. Patients may complain of constipation, diarrhea or tenesmus, weight loss, post-prandial colicky abdominal pain, and abdominal distention. Failure to pass the endoscope past the primary lesion is an obvious indicator of pending obstruction. However, many patients (particularly right-sided) remain surprisingly asymptomatic in this situation and do not require immediate intervention. Alternatively, there are patients who will clinically obstruct despite passage of the endoscope through the primary lesion, particularly when the tumor is in the left colon. A stool column proximal to the primary lesion on cross-sectional imaging, and absence of stool distally, can be a subtle harbinger of impending obstruction, even in the absence of colonic dilation.

The size and location of the primary tumor dictate the interventional options for an obstructing tumor. ASCRS guidelines recommend considering decompressive stent insertion prior to colectomy or diversion in patients with an obstructing colon cancer in the setting of incurable metastatic disease. Compared to surgery, colonic stenting reduces short-term morbidity and the interval to chemotherapy initiation with no impact on OS [6, 16–19]. Anecdotally however, institutional capabilities and experience with colonic stenting seem highly variable. The ability to successfully stent an obstructing tumor is also dependent on anatomic considerations, such as acute angulation of the colon or location in the colon. For example, distal rectal tumors are often not amenable to stenting as the distal end of the stent may sit on the anorectal muscular ring and cause severe discomfort. One must also consider the patients' overall life expectancy when contemplating palliative intervention given that the median duration of stent patency is 106 (68–288) days [20, 21]. In addition, stents may ultimately erode through the bowel wall with resultant abscess and fistula.

Resection may be preferable in the patient with an easily resectable primary tumor who is expected to live for at least 6 months. The threshold should be low for fecal diversion with the possibility of staged reconstruction (either Hartman's or primary anastomosis with proximal diversion) in the newly diagnosed patient with obstruction and metastatic CRC. There are significant implications of an anastomotic leak on receipt of chemotherapy [6]. This is not the time nor the place to be cavalier, given that surgical complications are a leading cause of adjuvant chemotherapy delays/omission which could adversely affect oncologic outcomes [22]. Resection should follow oncologic principles to the extent possible [6].

Proximal diversion is a valuable option for locally invasive or rectal lesions that would be difficult to resect. The distal portion of the bowel should always be vented, either as loop stoma or divided end-loop stoma, to avoid closed-loop obstruction and perforation. It is also wise to anticipate the ultimate definitive resection when considering proximal diversion in a patient with potentially resectable disease. A misplaced stoma can significantly interfere with future reconstructive options (e.g., a distal transverse or mid-/proximal descending loop colostomy in the rectal cancer patient). In addition to restricting colonic mobility, damage to the marginal artery can occur during transverse/descending colostomy creation or reversal. This would devascularize the distal colon once a high ligation of the inferior mesenteric artery is performed during a low anterior resection. Therefore, it is best to use the mid-/proximal sigmoid colon (preferably) or the proximal transverse colon just to the patient's right of the middle colic artery for diversion of obstructing rectal tumors. If a sigmoid colostomy is performed, the colon and mesentery can simply be transected distal to the stoma at time of subsequent proctosigmoidectomy. A transverse colostomy placed in the right upper quadrant facilitates access to the splenic flexure during subsequent proctosigmoidectomy, whereas a distal loop transverse colostomy may impede it. A loop ileostomy, which has the least influence on the "next" operation, is another valuable consideration. However, caution is warranted in this scenario. Diversion with a loop ileostomy could create a closed-loop obstruction physiology within the colon if the ileocecal valve is competent and the distal tumor is completely obstructing. In addition, ileostomy carries with it the risk of dehydration, which can be magnified by chemotherapy-induced enteritis.

Perforation Similar to the principles described above, exploration for perforation warrants resection versus diversion based on the feasibility of resection. Resection should follow oncologic principles if possible. However, aggressive en bloc resection of vital structures is rarely indicated in the setting of a perforated tumor and metastatic disease, given the overall poor prognosis [23]. Rather, priority should be placed on obtaining source control of the intra-abdominal infection. This may include simple diversion if the perforation is contained and can be percutaneously or surgically drained.

Unresectable Synchronous Metastases

Survival is closely linked to control and treatment of the distant disease in patients with Stage IV CRC. Therefore, control of metastatic disease should be prioritized [24]. Within this context, early determination of whether the patient has

potentially curable metastases is necessary to determine the appropriate treatment strategy (Fig. 31.1).

In the setting of unresectable synchronous metastases, NCCN and ASCRS guidelines recommend systemic chemotherapy for patients with minimal symptoms from the primary tumor [6, 7]. Surgery is reserved for patients with an imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms. This is based on evidence demonstrating that few patients (<20%) with metastatic CRC require palliative intervention of the primary tumor during chemotherapy [25]. There has been a philosophical shift away from prophylactic resection of the primary lesion in asymptomatic patients with unresectable metastatic disease (84% in 2000 vs 52% in 2011) toward upfront systemic chemotherapy [26]. It remains unclear whether resection of the primary tumor ultimately improves survival in patients with unresectable metastatic disease after treatment response to systemic therapy. There are retrospective data suggesting a significant survival benefit from chemotherapy and surgical resection of the primary tumor compared to chemotherapy alone in patients with unresectable synchronous CRC metastases [5, 27, 28]. Improvements in disease-free survival (DFS) and OS ranging from 6 to 14 months have been reported with resection plus chemotherapy compared to chemotherapy alone in patients with unresectable metastatic disease [27, 29–31]. However, all studies are retrospective with regard to the operative decision-making and therefore inherently plagued with selection bias. There are several ongoing prospective clinical trials (JCOG1007, CAIRO4, and GRECCAR 8) which may elucidate the efficacy of resection in the future [32–34]. For now, however, the decision should be individualized based on response to chemotherapy, estimated prognosis, and patient preference.

In the setting of unresectable synchronous metastases, chemotherapy options include FOLFOX or FOLFIRI or CAPEOX or FOLFOXIRI ± bevacizumab [7]. An additional option for KRAS/NRAS/BRAF WT gene left-sided tumors only is FOLFIRI or FOLFOX or FOLFOXIRI ± panitumumab or cetuximab. NCCN recommends reevaluation with cross-sectional imaging to monitor for conversion to resectable disease every 2 months if conversion to resectability is a possibility [7]. In the event of planned operation, a 6-week interval between the last dose of bevacizumab and elective surgery with re-initiation at least 6–8 weeks postoperatively is recommended [7].

Resectable Synchronous Metastases

Approximately 20% of patients with CRC metastases have resectable or potentially resectable disease [35]. There are numerous treatment options involving resection of the primary tumor, resection/ablation of metastases, and 6 months of chemotherapy with varying sequences. Neither NCCN nor ASCRS guidelines recommend one strategy over the other but stipulate that treatment should be individualized and determined by multidisciplinary consensus [6, 7]. This is based on systematic reviews and meta-analysis showing equivalent oncologic outcomes between treatment strategies in the patient with resectable synchronous metastatic disease [6, 7]. FOLFOX or CAPOX are the preferred chemotherapeutic agents over capecitabine or 5-FU/leucovorin alone in the patient with resectable metastatic disease unless the patient cannot tolerate oxaliplatin (7). Surgery should be delayed 4 weeks after the last dose of FOLFOX or CAPOX.

The ideal sequencing of surgery and chemotherapy remains unclear. There are advantages and disadvantages to each approach which must be carefully weighed by the multidisciplinary tumor board. Advantages for the resection-first strategy include elimination of tumor shedding of metastatic cells from the primary tumor during systemic treatment and avoidance of emergent surgery in the event of primary tumor progression while on treatment [25]. Additionally, there are reports of increased perioperative morbidity and liver toxicity (steatohepatitis, sinusoidal obstruction syndrome, noncirrhotic portal hypertension) following neoadjuvant therapy [36–39]. Alternatively, advantages of neoadjuvant chemotherapy include elimination of micrometastatic disease, cytoreduction facilitating R0 resection, or potential conversion from unresectable to resectable disease. An additional advantage is avoidance of potential surgical complications from upfront surgery which could delay initiation of chemotherapy [22, 40]. Finally, initial treatment with chemotherapy may uncover the natural history of the individual's cancer with avoidance of futile surgery in patients with aggressive tumor biology who progress on systemic therapy. Regardless of the specific regimen chosen, NCCN guidelines recommend limiting the duration of neoadjuvant chemotherapy to 2–3 months in the patient with clearly resectable disease. The remaining 3 months of perioperative chemotherapy are then administered after surgery [7].

Although each patient will require individual evaluation by the multidisciplinary team to determine the optimal treatment scheme, the following vignettes are provided to illustrate possible options within the NCCN guideline framework (Fig. 31.3) [7].

Synchronous or staged colectomy with liver or lung resection (preferred) and/or local ablative procedures followed by 6 months adjuvant chemotherapy. Patients with small solitary metastases in the periphery of the liver or the lung are at lowest risk for surgical morbidity and mortality. Assuming the patient is otherwise healthy and the colon resection appears straightforward, the patient with a solitary peripheral liver metastasis would be a candidate for a combined upfront resection followed by adjuvant chemotherapy.

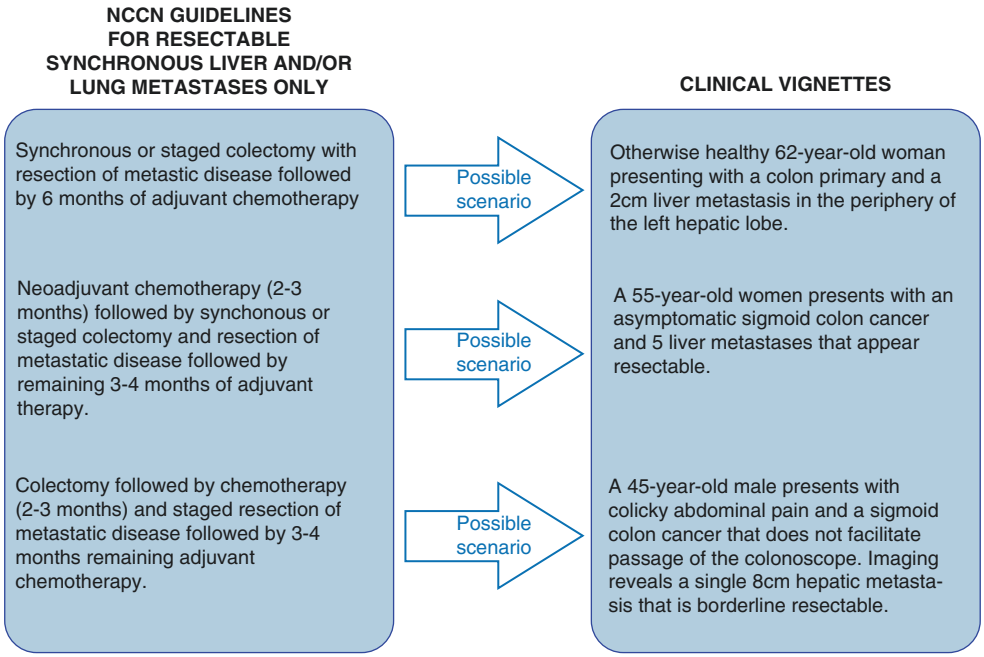

Fig. 31.3 NCCN guidelines for resectable synchronous liver and/or lung metastases with clinical vignettes highlighting possible scenarios

Neoadjuvant chemotherapy [2–3 months] followed by synchronous or staged colectomy and resection of metastatic disease followed by remaining the 3–4 months of adjuvant therapy. The patient with multiple (>4) liver metastases and an asymptomatic primary is an appropriate candidate to start with neoadjuvant chemotherapy. The increasing number of hepatic metastases puts a patient in the high-risk category for recurrence following hepatic resection [41]. Assuming a patient is fit for surgery and the liver lesions respond (or at least fail to progress) to neoadjuvant therapy, this patient may be a candidate for a simultaneous liver and colon resection followed by 3 months additional adjuvant chemotherapy.

Colectomy followed by chemotherapy (2–3 months) and staged resection of metastatic disease followed by 3–4 months remaining adjuvant chemotherapy. A 45-year-old male presents with colicky abdominal pain and a sigmoid colon cancer that does not facilitate passage of the colonoscope. Imaging reveals a single 8-cm hepatic metastasis that is borderline resectable. This patient is not an ideal candidate for combined upfront resection of the colon and hepatic metastasis, given the extent of the hepatic metastasis. Rather, in the setting of a potential impending obstruction, this patient would likely benefit from upfront colon resection and 2–3 months of chemotherapy with reevaluation for resectability. Assuming he is medically fit and the tumor responds to chemotherapy, the patient could then undergo hepatic resection followed by additional adjuvant chemotherapy. Alternatively, an endoscopic stent could also be used to alleviate the obstruction while the patient receives neoadjuvant chemotherapy.

Rectal Cancer

The patient with locally advanced rectal cancer and synchronous resectable metastases is further complicated by the possible addition of pelvic radiotherapy to the treatment armamentarium. Treatment options include upfront chemotherapy followed by short-course radiotherapy or long-course chemoradiotherapy and then resection (synchronous or staged) or upfront short-course radiotherapy or long-course chemoradiotherapy followed by chemotherapy and then resection. If radiotherapy is given first, short-course radiotherapy is an attractive option as it allows institution of multi-drug chemotherapy much sooner than if long-course chemoradiotherapy is utilized. Giving radiotherapy first allows for more accurate assessment of response of the primary tumor [42]. There may be patients with resectable metastases (particularly those facing an abdominoperineal resection) who would choose a "wait-and-watch" approach for the primary tumor in the event of a complete clinical response. It is important to recognize however that prior studies evaluating the "wait-and-watch" approach exclude patients with Stage IV disease [43–45]. Therefore, the oncologic outcomes of a "wait-and-watch" approach in the setting of synchronous resectable metastatic disease have not been evaluated. This further exemplifies the need for shared decision-making based on an in-depth discussion with the patient about their goals of treatment [8–10].

There is some concern that delaying hepatic resection until completion of, and recovery from, systemic chemotherapy may worsen chemotherapy-induced liver changes and increase the risk of postoperative liver failure. If pelvic

radiotherapy is planned after chemotherapy, then short-course radiotherapy after chemotherapy, followed by immediate surgery, is the preferred option to shorten the time to resection in this setting [7].

Another appropriate option in this case is to the treat the patient with 2–3 months of neoadjuvant chemotherapy followed by liver resection. After recovery from the liver resection, the patient would then receive the additional 3 months of perioperative chemotherapy and chemoradiation or short-course radiation prior to resection of the rectal primary. A further consideration is the risk of abdominal adhesions and radiation enteritis. As such, another option is to administer short-course radiotherapy prior to liver resection in the above algorithm. This would allow radiotherapy to occur prior to any surgical intervention and also allow for better assessment of the clinical response of the primary tumor to radiotherapy.

Metachronous Metastases

Roughly 20% of patients with CRC present with synchronous metastases at the time of initial diagnosis. Another 20% of patients go on to develop metachronous metastases after initial curative treatment [37, 46]. Over 85% of metachronous metastases are diagnosed within 3 years of initial curative treatment, and the most common site of disease is the liver (60%), followed by the lungs (39%), extra-regional lymph nodes (22%), and peritoneum (19%) [46, 47]. Predictors of metachronous metastases include male gender (HR = 1.2, 95%CI 1.03–1.32), advanced primary T-stage (T4 vs. T3 HR = 1.6, 95%CI 1.32–1.90) and N-stage (N1 vs. N0 HR = 2.8, 95%CI 2.42–3.30 and N2 vs. N0 HR = 4.5, 95%CI 3.72–5.42), high-grade tumor differentiation (HR = 1.4, 95%CI 1.17–1.62), and a positive (HR = 2.1, 95%CI 1.68–2.71) and unknown (HR = 1.7, 95%CI 1.34–2.22) resection margin [47]. Many of the same treatment principles apply in the setting of metachronous disease, depending on whether or not the disease is resectable and adjuvant therapy was received within the previous 12 months [7]. In general, patients with metachronous disease have a better prognosis than patients with synchronous metastases. [48]

Liver Metastases

Resection

Surgical resection is associated with the highest cure rates of the available treatment modalities in patients with hepatic metastases. Five-year survival ranges from 24% to 58% (averaging 40%), and 30-day mortality rates are less than 3% [39]. This compares to 5-year survival rates of 10–11% for patients who received systemic chemotherapy alone, although, obviously, this finding is heavily influenced by selection bias [49]. Approximately 20% of patients with hepatic metastases are considered resectable at the time of initial presentation. Another 10% may become resectable after induction chemotherapy [35].

What constitutes "resectable disease" has broadened significantly over time through adoption of a more aggressive surgical approach [50]. Initially, criteria for resection was limited to small, easily resectable, low-volume (<4) lesions in the absence of extrahepatic disease [41]. However, criteria have expanded to include multiple/bilobar metastases of varying size in the setting of extrahepatic disease (particularly the lung) (Fig. 31.4). Close margins and difficult-to-reach lesions can be managed with ablation (cryosurgery or radiofrequency ablation) or en bloc vascular resection with reconstruction to achieve an R0 resection. Additionally, the use of three-dimensional (3D) imaging technology, portal vein embolization, and liver partition and portal venous ligation for staged hepatectomy (ALPPS) have expanded resection possibilities through more precise assessment and optimization of the future liver remnant [51]. In the modern environment, patients are considered resectable if they are fit enough to tolerate surgery, and an R0 resection can be achieved with preservation of enough viable hepatic parenchyma to sustain life [50].

Future liver remnant (FLR) volume and the degree of hypertrophy achieved after portal vein embolization (PVE) can be measured through a variety of imaging modalities, serving as important predictors of surgical outcomes in

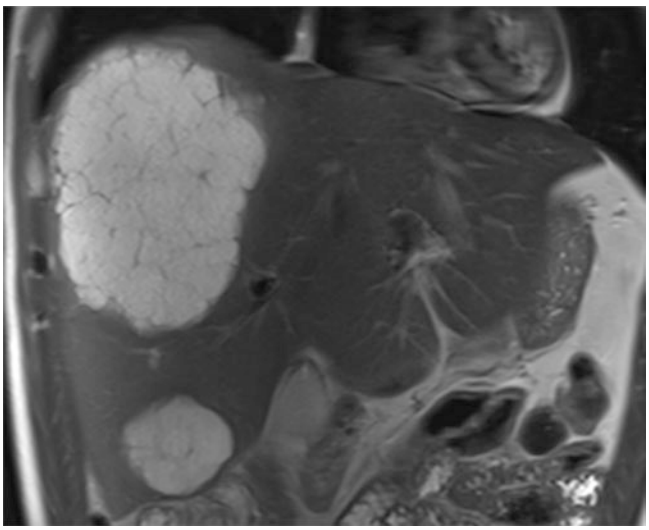

Fig. 31.4 Magnetic resonance imaging demonstrating multiple large hepatic CRC metastases that previously would have been considered unresectable. Criteria for resection have expanded with neoadjuvant chemotherapy, three-dimensional imaging technology, and portal vein embolization facilitating more precise assessment and optimization of the future liver remnant

patients undergoing major liver resection. 3D reconstruction of computed tomography (CT) images is one of the most common techniques for measuring the future liver remnant. A FLR >30% of the total hepatic volume is generally regarded as the minimum FLR volume for patients who have received chemotherapy for longer than 12 weeks [52].

The patient with extensive bilobar hepatic metastases presents an additional challenge given the risk of hepatic failure with resection. Previously, these patients were considered unresectable. However, resection criteria have expanded over time to include a select group of these patients in which an R0 resection can be achieved. This is accomplished with portal vein occlusion, either via embolization or ligation, resulting in hypertrophy within the liver remnant to reduce the risk of hepatic failure. In the patient with extensive bilobar disease, resection may be undertaken in stages. In the first stage, partial hepatectomies are performed to clear the FLR of disease in conjunction with portal vein ligation. This can be performed with resection of the primary tumor in the case of synchronous disease. Formal anatomic resection of the remaining diseased lobe is undertaken in a second-stage operation after the FLR has achieved adequate hypertrophy in the absence of metastatic progression. Alternatively, portal vein embolization is performed up front with a single-stage hepatectomy after adequate hypertrophy is achieved [53]. Embolization/ligation of the portal vein can expand functional liver volume by 39% over 4–8 weeks, although occasionally it can take longer to achieve adequate hypertrophy [54]. The risks of this method include cancer progression during the waiting period and insufficient hypertrophy. Not surprisingly, there are a substantial number of patients (25–38%) who progress and fail to undergo the staged hepatectomy [53–55].

Associating liver partition and portal venous ligation for staged hepatectomy (ALPPS) is an emerging technique in the treatment of CRC metastases [56]. With the ALPPS procedure, the portal vein is occluded either operatively with portal vein ligation or through percutaneous embolization. In the first stage, the liver is incised (partitioned) at the site of the future transection which theoretically produces much more rapid regrowth of the liver compared to portal vein occlusion alone. The patient undergoes 3D reconstruction and volumetric analysis within 1–2 weeks of the first stage to ensure adequate hepatic parenchyma. Staged hepatectomy is performed when adequate volume in the FLR is achieved (as soon as 7–10 days). The initial clinical series suggested increased liver growth rate and volume, rendering more patients resectable in a quicker amount of time [56]. However, there was significant morbidity and mortality, which has limited widespread adoption of the technique. The LIGRO Trial was a Scandinavian multicenter randomized controlled trial randomizing 100 patients with advanced colorectal liver metastases to ALPPS versus conventional two-stage hepatectomy with either portal vein ligation or embolization. ALPPS was associated with both a higher resection rate (92% vs 80%, $P = 0.091$) and estimated median survival (46 months vs 26, $P = 0.028$) compared to conventional staged hepatectomy [57]. There were no differences in complication rates or 90-day mortality between groups. Interestingly, the ALPPS procedure has been coined the "hepatobiliary controversy of the decade," testifying to the polarizing view of the procedure by many leaders of the field [58]. Further studies are needed to fully evaluate the efficacy of the technique. For now, portal vein embolization remains the standard care in patients with resectable liver metastases and FLR of less than 30%.

The majority of liver resections are performed via an open approach. However, the randomized OSLO-COMET trial demonstrated shorter hospital stays (2 days vs 4 days; $P < 0.001$), lower complication rates (19% vs 31%; $P = 0.021$), and better quality of life in patients with CRC metastases undergoing laparoscopic compared to open liver resection. Long-term oncologic outcomes were similar between groups with median overall survival (OS) of 80 months (95% CI, 52–108) in patients who underwent laparoscopic surgery compared with 81 months (95% CI, 42–120) in patients who underwent open surgery ($P = 0.91$). Therefore, a laparoscopic approach should be considered when anatomically feasible.

Locoregional Therapies

Per NCCN guidelines, resection is preferred over locoregional therapies in the management of CRC metastases given better DFS and OS [59]. However, approximately 80% of patients will have unresectable disease and may benefit from alternative locoregional therapies including percutaneous ablative treatments (radiofrequency ablation, microwave ablation) and transcatheter intra-arterial therapies [transarterial chemoembolization (TACE), and radioembolization with yttrium-90 (^{90}Y)]. Many of these image-guided ablative therapies can also be used in conjunction with resection to improve resectability. Table 31.1 provides an overview of the available locoregional treatment modalities in comparison with resection and systemic chemotherapy.

Radiofrequency Ablation

Radiofrequency ablation (RFA) causes thermal damage through high-frequency alternating current (375–500 kHz) from monopolar or bipolar radiofrequency systems inducing cytotoxicity within the few millimeters of the surrounding thermal zone. As the surrounding tissue reaches 100 °C, cells die and irreversible coagulation ensues. However, water evaporation causing desiccation results in electrical impedance which limits the volume of thermal transmission. Thus,

Table 31.1 Treatment options in patients with hepatic CRC metastases

Modality	Mechanism	Indication	Adv/dis	Survival	Risks
Resection	Partial hepatectomy, lobectomy, PVE, ALLPS	R0 resection can be achieved, pt fit for surgery	Only 20% of pts resectable	5-yr OS 24–58%	Morbidity <15%, Mortality <3%
Radiofrequency Ablation (RFA)	Thermal damage via high-frequency alternating current	Unresectable, peripheral lesions <3 cm, pt not surgical candidate	Not effective near vascular structure or lesions >3 cm	OS 28–53 mo, 5-yr OS 43%	Morbidity <2%, Mortality <1%, post ablation syndrome
Microwave Ablation (MWA)	Electromagnetic signal generates heat via molecular friction	Unresectable, pt not surgical candidate	Effective for larger and more central lesions than RFA	5-yr OS 37%	Morbidity <2%, Mortality <1%, post ablation syndrome
Transarterial chemoembolization ± drug eluding beads (TACE)	Delivers chemotherapy into hepatic arteries supplying tumor	Unresectable, not candidate for ablation, failed chemotherapy	Toxicity, limited efficacy	OS 8–14 mo, 5-yr OS 6%	Post-embolization syndrome in 60–80%
Transarterial radioembolization (TARE) or Selective internal radiotherapy (SIRT)	Microspheres loaded with radioisotope (^{90}Y) deliver high dose radiation to tumor	Unresectable, not candidate for ablation, failed chemotherapy	Toxicity, limited efficacy	OS 8–14 mo, 5-yr OS 4–7%	Better tolerated than TACE
Stereotactic body radiation therapy (SBRT)	Precise external beam radiation using 4D imaging	Unresectable, pt not surgical candidate	Unclear advantage over ablation or chemo	OS 24–27 mo	20% hepatic toxicity
Chemotherapy	FOLFOX or FOLFIRI or CAPEOX or FOLFOXIRI ± bevacizumab	Unresectable, pt not surgical candidate	Noninvasive	5-yr OS 20%, OS 23 mo	Neutropenia, neuropathy; perforation and bleeding (bevacizumab)

Abbreviations: *Adv* advantages, *Dis* disadvantages, *PVE* portal vein embolization, *ALLPS* liver partition and portal venous ligation for staged hepatectomy, *pt* patient, *OS* overall survival, *yr* year, *mo* month

RFA is limited to a relatively small-size treatment zone. Additionally, flowing blood within large vessels adjacent to the target causes a cooling effect, thereby reducing the ablation volume and lowering the efficacy near large vessels (heat sink effect) [60]. Generally, RFA is well tolerated with major complication rates ranging from 6% to 9% and mortality rates <2% [61]. RFA may be performed through an open, laparoscopic, or percutaneous approach and can be combined with surgical resection [62]. RFA is most effective for peripheral lesions less than 3 cm in diameter [63]. Median OS following RFA ranges widely throughout the literature between 28 and 53 months and seems superior to treatment with chemotherapy alone but inferior to surgical resection [59, 64–66].

Microwave Ablation

Microwave ablation (MWA) utilizes electromagnetic signal to general heat via molecular friction with frequencies between 900 and 2450 MHz resulting in cellular death via coagulation necrosis. MWA has gain acceptance as an alternative to RFA with faster heating over larger volumes of tissue and resistance to heat sink effect. Therefore, as opposed to RFA, MWA can be used to treat tumors larger than 3 cm and those near hepatic vessels with similar to improved recurrence rates [60]. Given these technical advantages, in addition to ease of use and shorter ablation time resulting in less procedural pain, there has been a shift from RFA toward MWA over the past few years [60]. In a recent meta-analysis, median 5-y OS was 43% for RFA versus 55% for MWA compared to 20% for chemotherapy alone [59].

Transcatheter Intra-arterial Techniques

Transcatheter intra-arterial techniques are reserved for patients with unresectable oligometastatic disease who are not candidates for ablative therapy and have failed systemic chemotherapy [7]. Transarterial chemoembolization (TACE) delivers chemotherapeutic agents (mitomycin, doxorubicin, cisplatin) emulsified with lipiodol, followed by delivery of an embolic agent, (traditionally polyvinyl alcohol or gelfoam) into the hepatic arteries supplying the liver tumors. Pioneered initially in the treatment of hepatocellular carcinoma, it is considered a salvage option for patients with liver-limited mCRC who fail systemic chemotherapy. Not surprisingly, OS rates are low with median survival between 8 and 9 months [59, 67, 68]. Side effects include fever, right upper quadrant pain, nausea, and vomiting known collectively as "post-embolization syndrome."

Recently, drug-eluting beads (DEBs) have replaced polyvinyl alcohol or gelfoam as embolic agents, allowing a slower and more sustained release of chemotherapeutic drugs directly

into the liver tumors, theoretically reducing systemic drug exposure and side effects (DEB-TACE) [59, 69]. Irinotecan-loaded DEBs (DEBIRI) are the most widely studied for the treatment of liver metastases in CRC. Toxicity rates average 10% with OS of 16 months [69]. Martin et al. [70] randomized 70 chemo-naïve patients with unresectable CRC hepatic metastases to FOLFOX+bevacizumab vs FOLFOX+bevacizumab+DEBIRI (FOLFOX-DEBIRI). Higher response rates were demonstrated in the FOLFOX-DEBIRI group at 6 months (P = 0.05) with a significant improvement in downsizing to resection in the FOLFOX-DEBIRI arm (35%) versus the FOLFOX-alone control arm (6%; P = 0.05). However, there was no difference in progression-free survival and no data presented on OS. Further studies are needed to define the role of DEB-TACE in the treatment of patients with hepatic CRC metastases.

Transarterial radioembolization (TARE), also known as selective internal radiotherapy (SIRT), utilizes microspheres loaded with a radioisotope to deliver high doses of radiation to liver tumors through an intra-arterial, catheter-based technique. The commonly used radioisotope is ß emitter yttrium-90 (^{90}Y). TARE was one of the initial transcatheter techniques utilized as a salvage option for patients who failed systemic chemotherapy. Response rates vary between 35% and 40% with a median survival between 8 and 14 months [59]. Recent analysis of three RCTs (FOXFIRE, SIRFLOX, and FOXFIRE-Global) demonstrated higher toxicity and no difference in OS with the addition of SIRT ^{90}Y compared to FOLFOX alone in 1103 patients with liver-only and liver-dominant metastatic CRC [71]. As such, the exact role of this technique in the armamentarium of treatment modalities for patients with metastatic CRC remains to be seen.

Stereotactic Body Radiation Therapy

Stereotactic body radiation therapy (SBRT) is an extremely precise form of external beam radiation that utilizes sophisticated 4D CT imaging to deliver intense doses of radiation (Fig. 31.5). In the case of hepatic metastases, patients are immobilized in a thermoplastic body mask using a Styrofoam block for abdominal compression and receive 25Gy in three consecutive daily fractions for a total dose of 75Gy to the target [72]. Five-year follow-up from a Phase II trial on SBRT for unresectable liver metastases demonstrated median OS of 27.6 months with 5-yr survival rates of 18% [72]. Recently published data from two large international registries including over 400 patients with hepatic CRC metastases demonstrates median OS between 24 and 27 months after SBRT [73, 74]. These results are comparable to a median OS of 23.3 months demonstrated with oxaliplatin-based chemotherapy alone in patients with unresectable CRC metastases [71]. Therefore, it is unclear whether SBRT contributes to better survival over modern chemotherapeutic regimens in patients with unresectable hepatic CRC metastases.

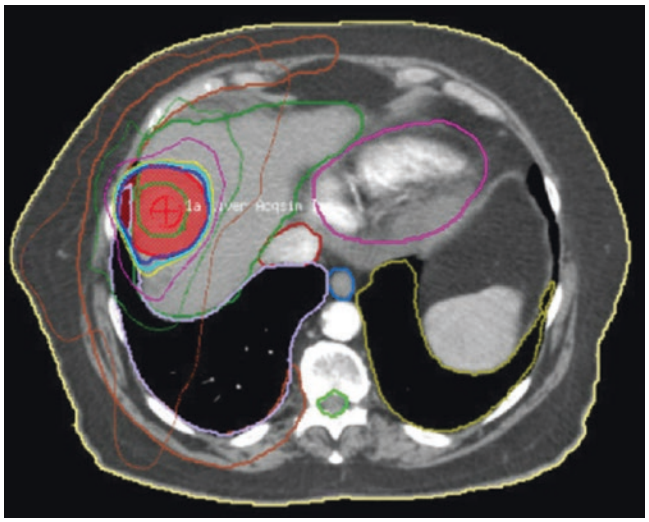

Fig. 31.5 Computed tomography image demonstrating the planning field for stereotactic body radiation therapy (SBRT) in a patient with hepatic metastases unfit to tolerate surgical resection

Lung Metastases

The lung is the second most common site of CRC metastatic disease, accounting for 22% of CRC metastases. In general, isolated lung metastases are associated with a better prognosis than isolated liver metastases with 5-yr OS up to 68% [5, 75]. Many of the same treatment modalities utilized with hepatic metastases are available for the treatment of pulmonary metastases including resection, ablative techniques, radiotherapy, and chemotherapy. Similarly, multidisciplinary input is essential.

Surgical resection of pulmonary metastases is a common practice. However, surprisingly there has not been a single prospective trial to evaluate the effectiveness of pulmonary metastasectomy (PM). Instead, practice patterns have been defined through retrospective series and several international registries, which are limited by selection bias, inconsistent systemic treatment, variable follow-up length, and a lack of comparative survival analyses [76]. There is an ongoing trial in patients with metastatic CRC randomizing patients to resection or surveillance (PulMiCC trial) [77]. Management decisions will depend on expert consensus and retrospective series until data from this and other prospective trials are available.

The Society of Thoracic Surgeons (STS) put together an Expert Consensus Task Force on Pulmonary Metastasectomy, which published a consensus document with treatment recommendations utilizing the modified Delphi method [76]. In addition, NCCN guidelines provide specific recommendations pertaining to pulmonary resection [7]. The goal of PM is complete resection based on the location and extent of the tumor with preservation of adequate functional lung. Most

pulmonary tumors are amendable to metastasectomy as opposed to formal lobectomy, while pneumonectomy is generally discouraged in the context of metastatic disease. There is no defined contraindication to PM based on the number of pulmonary metastases as long as an R0 resection can be achieved. Re-resection is appropriate in select patients assuming extrapulmonary disease is manageable [78].

Minimally invasive techniques for PM are preferred over the open approach [76]. The minimally invasive thoracoscopic technique presents a challenge for localization of small lesions. There are many different techniques for localization including finger or instrument palpation through port sites, percutaneous coils, wire localization, agar injection, and dyes. However, there does not seem to be a demonstrable difference between techniques [79].

Mediastinal LN metastases occur in up to 44% of patients with pulmonary metastases and are associated with worse survival [80]. Some advocate for routine LN sampling/dissection at the time of PM to provide prognostic information and influence decision-making with regard to systemic therapy following surgery [80]. STS guidelines suggest consideration of LN sampling/dissection at the time of PM. However, there was no uniform agreement with this recommendation [76].

PM is associated with low rates of morbidity (11%) and mortality (1.1%), with average LOS between 4 and 7 days in properly selected patients [81, 82]. As is the case with hepatic metastasectomy, chemotherapy can be administered before or after surgery based on multidisciplinary input.

STS guidelines suggest that ablative techniques and SBRT are both reasonable therapy for patients with oligometastases, particularly for high-risk patients or those who refuse resection. Compared to hepatic metastases, NCCN guidelines are not as definitive in recommending resection over other locoregional modalities in the management of pulmonary metastases. Rather, it is suggested that ablative techniques may be considered alone or in conjunction with resection for resectable pulmonary metastases [7].

Other Sites of Metastases

Ovarian Metastases

Approximately 5–10% of women with CRC develop ovarian metastases, with preponderance toward younger patients. The development of ovarian metastases is associated with a median survival of 19–27 months. Ovarian metastases can reach significant size before becoming symptomatic and are disproportionately unresponsive to chemotherapy compared to other sites of disease [83].

The term Krukenberg tumor has been loosely (and incorrectly) applied to all metastatic tumors of the ovary. However, true Krukenberg tumors are secondary carcinomas of the ovary that contain >10% mucin-filled signet-ring cells and are most commonly gastric in origin [84]. Hematologic spread accounts for the most common route of metastases in CRC as evident by the association of ovarian metastases with vascular invasion and low rate of lympho-angio invasion [85]. Primary ovarian metastases spread by transcoelomic dissemination, the spreading of tumor cells across the peritoneal cavity [86]. However, this does not seem to play a role in the majority of CRC metastases as evident by the smooth capsular surface of affected ovaries in the absence of surface tumor deposits.

It can be difficult to distinguish ovarian CRC metastases from a primary ovarian malignancy given that both ovarian primaries and CRC ovarian metastases tend to be large and unilateral. On histopathology, mucinous adenocarcinomas can be misinterpreted as ovarian primaries. Immunohistochemistry can help elucidate the diagnosis with ovarian adenocarcinomas typically exhibiting CK7+, CA 125+, CK20−, CEA−, and CDX2−, while the converse immunophenotype (CK20+, CEA+, CDX2+, CK7−, and CA 125−) is observed in metastatic CRC [87].

Synchronous ovarian metastases are more commonly encountered than metachronous ovarian metastases [88]. The indication for oophorectomy in the synchronous setting includes grossly abnormal ovaries or contiguous extension of the colorectal cancer into the ovarian capsule. While prophylactic oophorectomy of normal appearing ovaries was traditionally advocated to remove potential microscopic "undetectable" synchronous disease, this practice is no longer recommended. Specifically, NCCN guidelines state that "routine prophylactic oophorectomy is not necessary" [7]. It is reasonable to consider reoperation for oophorectomy in the metachronous setting given that ovarian metastases are less responsive to chemotherapy than other sites of disease and can grow quite large and symptomatic. This will, of course, depend on the performance status of the patient and the tumor burden elsewhere. The majority of patients with ovarian metastases will have extraovarian metastases, and residual disease after surgery is associated with worse survival. As with all other sites of metastases, overall survival is improved if an R0/R1 resection can be achieved [83].

Brain Metastases

Approximately 1–4% of patients with CRC will develop brain metastases, which are generally seen in the context of diffuse widespread metastases. Rarely, patients can present with isolated brain metastases. Given the infrequency of brain metastases, brain imaging is not routinely performed on initial staging or during metastatic workup in the absence of neurologic signs or symptoms. Treatment options for patients with

brain metastases include a combination of surgery, whole-brain radiation therapy (WBRT), and stereotactic radiosurgery (SRS). Surgery is preferred in the case of an isolated brain metastasis. However, surgical resection of a single brain metastasis is associated with a 50–60% risk of local recurrence within 1 year [89]. SRS has replaced WBRT in the adjuvant setting to reduce the risk of local recurrence due to its improved side effect profile [89, 90]. SRS is also indicated for small unresectable solitary tumors or in patients with a limited number of brain metastases that are <3 cm in diameter. WBRT is an option for patients with multiple intracranial metastases who are not candidates for surgery or SRS. However, it is associated with significant side effects (fatigue, alopecia, neurocognitive decline), and does not improve OS [91]. Palliative options include steroids to reduce peritumoral edema and anticonvulsants for seizure prophylaxis.

Adrenal Metastases

Adrenal metastases are uncommon in the setting of metastatic colorectal cancer and usually develop late in the course of the disease. Surgery is rarely an option, although there are case reports of prolonged survival following resection of isolated adrenal metastases [92].

Surveillance

There is a paucity of data to guide posttreatment surveillance in patients with metastatic CRC who were treated with curative intent. NCCN guidelines suggest utilizing the same strategy as for Stages II and III CRC with the exception of more frequent cross-sectional imaging [7]:

- History and physical every 3–6 months for 2 years and then every 6 months for a total of 5 years
- CEA every 3–6 months for 2 years and then every 6 months for a total of 5 years
- Chest/abdominal/pelvic CT scan every 3–6 months for 2 years and then every 6–12 months for a total of 5 year
- Colonoscopy 1 year after surgery

Conclusion

Treatment of advanced colorectal cancer has evolved significantly over time reflecting a shift toward more aggressive therapy recognizing the potential for long-term survival. The complexity involved in managing patients with advanced colorectal cancer relies on multidisciplinary collaboration to develop an individualized treatment scheme that takes into account the patient's goals and objectives.

References

1. Hu CY, Bailey CE, You YN, et al. Time trend analysis of primary tumor resection for stage IV colorectal cancer: less surgery, improved survival. JAMA Surg. 2015;150(3):245–51.
2. Brouwer NPM, Bos A, Lemmens V, et al. An overview of 25 years of incidence, treatment and outcome of colorectal cancer patients. Int J Cancer. 2018;143(11):2758–66.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7–34.
4. Ansa BE, Coughlin SS, Alema-Mensah E, Smith SA. Evaluation of colorectal cancer incidence trends in the United States (2000–2014). J Clin Med. 2018;7(2)
5. Wang J, Li S, Liu Y, Zhang C, Li H, Lai B. Metastatic patterns and survival outcomes in patients with stage IV colon cancer: a population-based analysis. Cancer Med. 2020;9(1):361–73.
6. Vogel JD, Eskicioglu C, Weiser MR, Feingold DL, Steele SR. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Treatment of Colon Cancer. Dis Colon Rectum. 2017;60(10):999–1017.
7. Benson AB 3rd, Venook AP, Cederquist L, et al. Colon cancer, version 1.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2017;15(3):370–98.
8. Morris AM. Shared decision making for rectal cancer care: a long way forward. Dis Colon Rectum. 2016;59(10):905–6.
9. Hawley ST, Jagsi R. Shared decision making in cancer care: does one size fit all? JAMA Oncol. 2015;1(1):58–9.
10. Ellis PG, O'Neil BH, Earle MF, et al. Clinical pathways: management of quality and cost in oncology networks in the metastatic colorectal cancer setting. J Oncol Pract. 2017;13(5):e522–9.
11. Cameron MG, Kersten C, Vistad I, Fossa S, Guren MG. Palliative pelvic radiotherapy of symptomatic incurable rectal cancer – a systematic review. Acta Oncol. 2014;53(2):164–73.
12. Cameron MG, Kersten C, Vistad I, et al. Palliative pelvic radiotherapy for symptomatic rectal cancer - a prospective multicenter study. Acta Oncol. 2016;55(12):1400–7.
13. Corvino F, Giurazza F, Cangiano G, et al. Endovascular treatment of peripheral vascular blowout syndrome in end-stage malignancies. Ann Vasc Surg. 2019;58:382 e381–5.
14. Tan KK, Strong DH, Shore T, Ahmad MR, Waugh R, Young CJ. The safety and efficacy of mesenteric embolization in the management of acute lower gastrointestinal hemorrhage. Ann Coloproctol. 2013;29(5):205–8.
15. Deans GT, Krukowski ZH, Irwin ST. Malignant obstruction of the left colon. Br J Surg. 1994;81(9):1270–6.
16. van Hooft JE, van Halsema EE, Vanbiervliet G, et al. Self-expandable metal stents for obstructing colonic and extracolonic cancer: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2014;46(11):990–1053.
17. Fiori E, Lamazza A, Schillaci A, et al. Palliative management for patients with subacute obstruction and stage IV unresectable rectosigmoid cancer: colostomy versus endoscopic stenting: final results of a prospective randomized trial. Am J Surg. 2012;204(3):321–6.
18. Gianotti L, Tamini N, Nespoli L, et al. A prospective evaluation of short-term and long-term results from colonic stenting for palliation or as a bridge to elective operation versus immediate surgery for large-bowel obstruction. Surg Endosc. 2013;27(3):832–42.
19. Young CJ, De-Loyde KJ, Young JM, et al. Improving quality of life for people with incurable large-bowel obstruction: randomized control trial of colonic stent insertion. Dis Colon Rectum. 2015;58(9):838–49.
20. van den Berg MW, Ledeboer M, Dijkgraaf MG, Fockens P, ter Borg F, van Hooft JE. Long-term results of palliative stent placement for acute malignant colonic obstruction. Surg Endosc. 2015;29(6):1580–5.

21. Watt AM, Faragher IG, Griffin TT, Rieger NA, Maddern GJ. Self-expanding metallic stents for relieving malignant colorectal obstruction: a systematic review. Ann Surg. 2007;246(1):24–30.
22. Gao P, Huang XZ, Song YX, et al. Impact of timing of adjuvant chemotherapy on survival in stage III colon cancer: a population-based study. BMC Cancer. 2018;18(1):234.
23. Daniels M, Merkel S, Agaimy A, Hohenberger W. Treatment of perforated colon carcinomas-outcomes of radical surgery. Int J Color Dis. 2015;30(11):1505–13.
24. Lam VW, Laurence JM, Pang T, et al. A systematic review of a liver-first approach in patients with colorectal cancer and synchronous colorectal liver metastases. HPB. 2014;16(2):101–8.
25. Poultsides GA, Servais EL, Saltz LB, et al. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. J Clin Oncol. 2009;27(20):3379–84.
26. Birkett RT, O'Donnell MMT, Epstein AJ, Saur NM, Bleier JIS, Paulson EC. Elective colon resection without curative intent in stage IV colon cancer. Surg Oncol. 2019;28:110–5.
27. Faron M, Pignon JP, Malka D, et al. Is primary tumour resection associated with survival improvement in patients with colorectal cancer and unresectable synchronous metastases? A pooled analysis of individual data from four randomised trials. Eur J Cancer. 2015;51(2):166–76.
28. Shida D, Boku N, Tanabe T, et al. Primary tumor resection for stage IV colorectal cancer in the era of targeted chemotherapy. J Gastrointest Surg. 2019;23(11):2144–50.
29. Ahmed S, Leis A, Chandra-Kanthan S, et al. Surgical management of the primary tumor in stage IV colorectal cancer: a confirmatory retrospective cohort study. J Cancer. 2016;7(7):837–45.
30. Clancy C, Burke JP, Barry M, Kalady MF, Calvin CJ. A meta-analysis to determine the effect of primary tumor resection for stage IV colorectal cancer with unresectable metastases on patient survival. Ann Surg Oncol. 2014;21(12):3900–8.
31. Ducreux M, Bouche O, Pignon JP, et al. Randomised trial comparing three different schedules of infusional 5FU and raltitrexed alone as first-line therapy in metastatic colorectal cancer. Final results of the Federation Francophone de Cancerologie Digestive (FFCD) 9601 trial. Oncology. 2006;70(3):222–30.
32. Moritani K, Kanemitsu Y, Shida D, et al. A randomized controlled trial comparing primary tumour resection plus chemotherapy with chemotherapy alone in incurable stage IV colorectal cancer: JCOG1007 (iPACS study). Jpn J Clin Oncol. 2020;50(1):89–93.
33. Cotte E, Villeneuve L, Passot G, et al. GRECCAR 8: impact on survival of the primary tumor resection in rectal cancer with unresectable synchronous metastasis: a randomized multicentre study. BMC Cancer. 2015;15:47.
34. t Lam-Boer J, Mol L, Verhoef C, et al. The CAIRO4 study: the role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of colorectal cancer–a randomized phase III study of the Dutch Colorectal Cancer Group (DCCG). BMC Can. 2014;14:741.
35. Line PD, Hagness M, Dueland S. The potential role of liver transplantation as a treatment option in colorectal liver metastases. Can J Gastroenterol Hepatol. 2018;2018:8547940.
36. Fernandez FG, Ritter J, Goodwin JW, Linehan DC, Hawkins WG, Strasberg SM. Effect of steatohepatitis associated with irinotecan or oxaliplatin pretreatment on resectability of hepatic colorectal metastases. J Am Coll Surg. 2005;200(6):845–53.
37. Simpson AL, Leal JN, Pugalenthi A, et al. Chemotherapy-induced splenic volume increase is independently associated with major complications after hepatic resection for metastatic colorectal cancer. J Am Coll Surg. 2015;220(3):271–80.
38. Khan AZ, Morris-Stiff G, Makuuchi M. Patterns of chemotherapy-induced hepatic injury and their implications for patients undergoing liver resection for colorectal liver metastases. J Hepato-Biliary-Pancreat Surg. 2009;16(2):137–44.
39. Duwe G, Knitter S, Pesthy S, et al. Hepatotoxicity following systemic therapy for colorectal liver metastases and the impact of chemotherapy-associated liver injury on outcomes after curative liver resection. Eur J Surg Oncol. 2017;43(9):1668–81.
40. Jamnagerwalla M, Tay R, Steel M, et al. Impact of surgical complications following resection of locally advanced rectal adenocarcinoma on adjuvant chemotherapy delivery and survival outcomes. Dis Colon Rectum. 2016;59(10):916–24.
41. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999;230(3):309–18; discussion 318–321.
42. Habr-Gama A, Sao Juliao GP, Fernandez LM, et al. Achieving a complete clinical response after neoadjuvant chemoradiation that does not require surgical resection: it may take longer than you think! Dis Colon Rectum. 2019;62(7):802–8.
43. Dattani M, Heald RJ, Goussous G, et al. Oncological and survival outcomes in watch and wait patients with a clinical complete response after neoadjuvant chemoradiotherapy for rectal cancer: a systematic review and pooled analysis. Ann Surg. 2018;268(6):955–67.
44. Renehan AG, Malcomson L, Emsley R, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol. 2016;17(2):174–83.
45. Smith JJ, Strombom P, Chow OS, et al. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. JAMA Oncol. 2019;5(4):e185896.
46. Elferink MA, de Jong KP, Klaase JM, Siemerink EJ, de Wilt JH. Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands. Int J Color Dis. 2015;30(2):205–12.
47. van Gestel YR, de Hingh IH, van Herk-Sukel MP, et al. Patterns of metachronous metastases after curative treatment of colorectal cancer. Cancer Epidemiol. 2014;38(4):448–54.
48. Okholm C, Mollerup TK, Schultz NA, Strandby RB, Achiam MP. Synchronous and metachronous liver metastases in patients with colorectal cancer. Dan Med J. 2018;65(12)
49. Ferrarotto R, Pathak P, Maru D, et al. Durable complete responses in metastatic colorectal cancer treated with chemotherapy alone. Clin Colorectal Cancer. 2011;10(3):178–82.
50. Venook AP and Curley SA. Management of potentially resectable colorectal cancer liver metastases. In: UpToDate, Tanabe KK and Savarese D (Eds), UpToDate, Waltham, MA. (Accessed 2020).
51. Takamoto T, Sano K, Hashimoto T, et al. Practical contribution of virtual hepatectomy for colorectal liver metastases: a propensity-matched analysis of clinical outcome. J Gastrointest Surg. 2018;22(12):2037–44.
52. Ethun CG, Maithel SK. Determination of resectability. Surg Clin North Am. 2016;96(2):163–81.
53. Shindoh J, Vauthey JN, Zimmitti G, et al. Analysis of the efficacy of portal vein embolization for patients with extensive liver malignancy and very low future liver remnant volume, including a comparison with the associating liver partition with portal vein ligation for staged hepatectomy approach. J Am Coll Surg. 2013;217(1):126–33. discussion 133–124.
54. Shindoh J, Truty MJ, Aloia TA, et al. Kinetic growth rate after portal vein embolization predicts posthepatectomy outcomes: toward zero liver-related mortality in patients with colorectal liver metastases and small future liver remnant. J Am Coll Surg. 2013;216(2):201–9.
55. Capussotti L, Muratore A, Baracchi F, et al. Portal vein ligation as an efficient method of increasing the future liver remnant vol-

ume in the surgical treatment of colorectal metastases. Arch Surg. 2008;143(10):978–82. discussion 982
56. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg. 2012;255(3):405–14.
57. Hasselgren K, Rosok BI, Larsen PN, et al. ALPPS improves survival compared with TSH in patients affected of CRLM: survival analysis from the randomized controlled trial LIGRO. Ann Surg. 2019;
58. Olthof PB, Schnitzbauer AA, Schadde E. The HPB controversy of the decade: 2007–2017 – ten years of ALPPS. Eur J Surg Oncol. 2018;44(10):1624–7.
59. Di Martino M, Rompianesi G, Mora-Guzman I, Martin-Perez E, Montalti R, Troisi RI. Systematic review and meta-analysis of local ablative therapies for resectable colorectal liver metastases. Eur J Surg Oncol. 2019;
60. Tsitskari M, Filippiadis D, Kostantos C, et al. The role of interventional oncology in the treatment of colorectal cancer liver metastases. Ann Gastroenterol. 2019;32(2):147–55.
61. Wong SL, Mangu PB, Choti MA, et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. J Clin Oncol. 2010;28(3):493–508.
62. van Amerongen MJ, van der Stok EP, Futterer JJ, et al. Results after simultaneous surgery and RFA liver ablation for patients with colorectal carcinoma and synchronous liver metastases. Eur J Surg Oncol. 2019;45(12):2334–9.
63. Shady W, Petre EN, Gonen M, et al. Percutaneous radiofrequency ablation of colorectal cancer liver metastases: factors affecting outcomes – a 10-year experience at a single center. Radiology. 2016;278(2):601–11.
64. Solbiati L, Ahmed M, Cova L, Ierace T, Brioschi M, Goldberg SN. Small liver colorectal metastases treated with percutaneous radiofrequency ablation: local response rate and long-term survival with up to 10-year follow-up. Radiology. 2012;265(3):958–68.
65. Hildebrand P, Kleemann M, Roblick UJ, et al. Radiofrequency-ablation of unresectable primary and secondary liver tumors: results in 88 patients. Langenbeck's Arch Surg. 2006;391(2):118–23.
66. Ruers T, Van Coevorden F, Punt CJ, et al. Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. J Natl Cancer Inst. 2017;109(9)
67. Albert M, Kiefer MV, Sun W, et al. Chemoembolization of colorectal liver metastases with cisplatin, doxorubicin, mitomycin C, ethiodol, and polyvinyl alcohol. Cancer. 2011;117(2):343–52.
68. Vogl TJ, Zangos S, Eichler K, Yakoub D, Nabil M. Colorectal liver metastases: regional chemotherapy via transarterial chemoembolization (TACE) and hepatic chemoperfusion: an update. Eur Radiol. 2007;17(4):1025–34.
69. Akinwande O, Dendy M, Ludwig JM, Kim HS. Hepatic intra-arterial injection of irinotecan drug eluting beads (DEBIRI) for patients with unresectable colorectal liver metastases: a systematic review. Surg Oncol. 2017;26(3):268–75.
70. Martin RC 2nd, Scoggins CR, Schreeder M, et al. Randomized controlled trial of irinotecan drug-eluting beads with simultaneous FOLFOX and bevacizumab for patients with unresectable colorectal liver-limited metastasis. Cancer. 2015;121(20):3649–58.
71. Wasan HS, Gibbs P, Sharma NK, et al. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol. 2017;18(9):1159–71.
72. Scorsetti M, Comito T, Clerici E, et al. Phase II trial on SBRT for unresectable liver metastases: long-term outcome and prognostic factors of survival after 5 years of follow-up. Radiat Oncol. 2018;13(1):234.
73. Mahadevan A, Blanck O, Lanciano R, et al. Stereotactic Body Radiotherapy (SBRT) for liver metastasis – clinical outcomes from the international multi-institutional RSSearch(R) Patient Registry. Radiat Oncol. 2018;13(1):26.
74. Andratschke N, Alheid H, Allgauer M, et al. The SBRT database initiative of the German Society for Radiation Oncology (DEGRO): patterns of care and outcome analysis of stereotactic body radiotherapy (SBRT) for liver oligometastases in 474 patients with 623 metastases. BMC Cancer. 2018;18(1):283.
75. Okumura T, Boku N, Hishida T, et al. Surgical outcome and prognostic stratification for pulmonary metastasis from colorectal cancer. Ann Thorac Surg. 2017;104(3):979–87.
76. Handy JR, Bremner RM, Crocenzi TS, et al. Expert consensus document on pulmonary metastasectomy. Ann Thorac Surg. 2019;107(2):631–49.
77. Treasure T, Fallowfield L, Lees B. Pulmonary metastasectomy in colorectal cancer: the PulMiCC trial. J Thorac Oncol. 2010;5(6 Suppl 2):S203–6.
78. Menna C, Berardi G, Tierno SM, et al. Do repeated operations for recurrent colorectal lung metastases result in improved survival? Ann Thorac Surg. 2018;106(2):421–7.
79. Moghissi K, Dixon K. Image-guided surgery and therapy for lung cancer: a critical review. Future Oncol. 2017;13(26):2383–94.
80. Hamaji M, Cassivi SD, Shen KR, et al. Is lymph node dissection required in pulmonary metastasectomy for colorectal adenocarcinoma? Ann Thorac Surg. 2012;94(6):1796–800.
81. Blackmon SH, Stephens EH, Correa AM, et al. Predictors of recurrent pulmonary metastases and survival after pulmonary metastasectomy for colorectal cancer. Ann Thorac Surg. 2012;94(6):1802–9.
82. Lin AY, Kotova S, Yanagawa J, et al. Risk stratification of patients undergoing pulmonary metastasectomy for soft tissue and bone sarcomas. J Thorac Cardiovasc Surg. 2015;149(1):85–92.
83. Ganesh K, Shah RH, Vakiani E, et al. Clinical and genetic determinants of ovarian metastases from colorectal cancer. Cancer. 2017;123(7):1134–43.
84. Kiyokawa T, Young RH, Scully RE. Krukenberg tumors of the ovary: a clinicopathologic analysis of 120 cases with emphasis on their variable pathologic manifestations. Am J Surg Pathol. 2006;30(3):277–99.
85. Yamanishi Y, Koshiyama M, Ohnaka M, et al. Pathways of metastases from primary organs to the ovaries. Obstet Gynecol Int. 2011;2011:612817.
86. Tan DS, Agarwal R, Kaye SB. Mechanisms of transcoelomic metastasis in ovarian cancer. Lancet Oncol. 2006;7(11):925–34.
87. McCluggage WG, Wilkinson N. Metastatic neoplasms involving the ovary: a review with an emphasis on morphological and immunohistochemical features. Histopathology. 2005;47(3):231–47.
88. Ursem C, Zhou M, Paciorek A, et al. Clinicopathologic characteristics and impact of oophorectomy for ovarian metastases from colorectal cancer. Oncologist. 2020;36(4 suppl):779.
89. Mahajan A, Ahmed S, McAleer MF, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. Lancet Oncol. 2017;18(8):1040–8.
90. Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol. 2017;18(8):1049–60.
91. Tsao MN, Lloyd N, Wong RK, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Database Syst Rev. 2012;4:CD003869.
92. Mourra N, Hoeffel C, Duvillard P, Guettier C, Flejou JF, Tiret E. Adrenalectomy for clinically isolated metastasis from colorectal carcinoma: report of eight cases. Dis Colon Rectum. 2008;51(12):1846–9.

Locally Recurrent Rectal Cancer

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Key Concepts

- Local recurrence of rectal cancer is an extra-total mesorectal excision (TME) pathology and differs inherently to advanced primary rectal cancer with respect to treatment planning and management, as well as surgical training.
- Surgery for recurrent rectal cancer requires meticulous planning and is based on magnetic resonance imaging (MRI) and requires multidisciplinary team (MDT) interpretation and collaboration.
- Surgeons embarking on recurrent rectal cancer operations must be adept at resecting the anterior, lateral, and posterior pelvic compartments.
- Circumnavigate the involved pelvic compartment—operate in virgin planes.
- Gain proximal and distal control of organs, vessels, and nerves prior to final resection.
- If recurrence abuts an organ, vessel, nerve, or structure, then resect it, and avoid "close shaves," which risks an involved margin. R0 resection predicts both survival and quality of life.
- Posteriorly the pelvic floor is the site of recurrence. It arises from the sacrum (S3 down) and the sacrospinous ligament out to the ischial spine and abuts the piriformis muscle laterally and the obturator internus muscle anteriorly.
- When considering surgical anatomy, the ischial spine is the center of the lateral pelvic compartments, while the urethral orifice (as it passes through the pelvic floor) is the center of the anterior compartment.
- En bloc common and external iliac artery and vein excisions can be performed with R0 rates and survival comparable to more central recurrences and with good arterial graft patency but high rates of venous graft thrombosis. Consideration should be given to venous ligation without reconstruction after excision.

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Introduction

Dozois and Colibaseanu performed an excellent review of the management of locally recurrent rectal cancer (LRRC) in the previous edition of the *ASCRS Textbook of Colon and Rectal Surgery* (2016) [1]. The aim of this review is to provide an update on progress made in the past few years, discuss ongoing controversial issues, as well as provide a practical guide to the surgical approaches to LRRC to be used as a complement to the previous detailed review. Despite the worldwide adoption of the principles of total mesorectal excision (TME) and a more expanded usage of preoperative neoadjuvant therapy in lower and more advanced rectal cancers, the reported rate of local recurrence is still about 10% in most unselected series [2–5]. In the last decade, there has been an increasing experimentation with minimally invasive techniques for primary rectal cancer such as laparoscopic and robotic surgery and transanal TME (taTME), as well as organ-sparing techniques such as transanal endoscopic microsurgery (TEM), transanal minimally invasive surgery (TAMIS), and "watch-and-wait" nonoperative approaches to rectal cancer, which arguably may produce a significant increase in the need for radical salvage surgery in the immediate future [6–9]. While these various approaches are admirable, none have demonstrated benefit in randomized trials where small but clinically significant differences in local recurrence remain important.

Exenterative surgery is now well established as the treatment of choice for patients with LRRC and represents the only chance of cure for this group of patients. In patients who undergo radical surgery with clear resection margins, 40–50% overall survival at 5 years can be expected, which is comparable to the outcomes of patients with primary colorectal cancer who undergo excision of hepatic or pulmonary metastases [10–13]. Patients who do not undergo surgery may develop malignant fistulae and obstruction and neuropathic pain due to nerve, muscle, and bone infiltration. Palliative resectional surgery, including exenteration, has yet

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to be shown to actually palliate symptoms in terms of return to baseline quality of life despite modest survival advantages and should only be offered selectively [14].

General Considerations

The previous iteration of the ASCRS textbook proposed quite accurately that several centers around the world were achieving excellent results in situations that were previously believed to be absolute contraindications for curative surgery. They also put forward that lateral neurovascular resection and composite sacrectomy should only be undertaken at these higher-volume specialized centers. In 2020, we would argue that pelvic exenterative surgery for LRRC is fundamentally a different operation to exenteration for advanced primary rectal cancer and that all centers who embark on recurrent rectal cancer surgery should not only be competent but also expert in the lateral and posterior pelvic compartments.

Advanced primary rectal cancer sometimes breaches the mesorectal fascia, extending into the surrounding pelvic compartments and organs (T4). In contrast, almost by definition, local recurrence that develops following adequate proctectomy develops in the extra-mesorectal planes of the pelvic floor muscles, the presacral fascia, and the lateral compartment, including the iliac vessels and piriformis muscle, and deeper neurovascular structures posterolaterally including the sacrospinous and sacrotuberous ligaments. The pelvic floor continues anteriorly, and more laterally the obturator internus muscle and ischial and pubic bones become the important anatomical landmarks for dissection and resection for the recurrent rectal cancer surgeon. These are the most difficult surgical planes of the pelvis, and with the added complexity of redo surgery and post-radiotherapy fibrosis, pelvic exenteration for LRRC can be the most challenging of pelvic operations. Complete soft tissue pelvic exenteration for an advanced primary rectal cancer, while having obvious implications for the patient's quality of life with two stomas, remains a relatively straightforward procedure for an experienced exenteration surgeon and may be taken on by a colorectal surgeon trained in advanced rectal cancer surgery in combination with a urological colleague. These procedures, based on the central and anterior compartments, only become more challenging when a more radical perineal resection is required with complete vaginectomy, perineal urethrectomy with or without penectomy in males, or pubic bone resection.

While isolated iliac nodal and anastomotic recurrences are the simplest to excise, they are much less common in our experience and are perhaps still operated upon by the original "TME surgeon." The mindset of the "TME surgeon" exploring focally outside their realm in LRRC is fundamentally a flawed surgical plan in 2020. While this approach is often adequate in advanced primary rectal cancer, it will undoubtedly lead to low R0 resection rates in LRRC. This is contrasted by the increasingly radical approach by surgeons at specialized centers, where the R0 resection rates for LRRC have climbed from well below 50% in the mid-2000s to 70% as we approach the end of the current decade [13, 15–17]. In a recent review of well over 200 recurrent rectal cancer exenterations at our unit, 49% required total cystectomy, 58% required sacrectomy, and 73% involved the lateral compartment (defined as at least complete excision of the internal iliac vasculature) [17]. Major lumbosacral or complete sciatic nerve excision was performed in 38% of the cohort.

Patterns of Local Recurrence and Anatomical Considerations

Multiple classification systems have been proposed by various groups worldwide for exenteration, and these are often derived from the individual unit's current surgical expertise and opinions as to what is a contraindication to surgery, and none work truly well for LRRC [2, 18–22]. Confusion with the historical gynecological concept of exenteration, which was based on the uterus as the central component of the classification, leads to further disparity between what is considered the anterior and posterior pelvic compartments and indeed the definition of a pelvic exenteration. For the colorectal surgeon, an exenteration usually focuses on the rectum or previous rectal site (neorectum, anastomosis, or central pelvic floor scar post abdominoperineal excision) as the anatomical center of all classifications. None of these current systems have been universally adopted, and perhaps a different classification for advanced primary to recurrent rectal cancers should be considered. Classification systems for LRRC need to incorporate the important technical considerations in exenterative surgery: the extent of local invasion into adjacent organs and involvement of the neurovascular structures of the pelvic sidewall and the bony pelvis. These considerations influence the technical difficulty of achieving R0 resection and the functional consequences that will be envisaged for the patient, as well as the need for urological, perineal, vascular, and orthopedic reconstruction.

The pelvic floor and its bony attachments are the core determinants of our current classification system for LRRC and the extent of exenterative surgery [15, 23]. The five pelvic compartments can be subdivided into a supra- or infralevator section with reference to the pelvic floor. The anatomical compartments of the pelvis are illustrated in Fig. 32.1. Understanding, as most colorectal surgeons do well, the structures that abut the original TME plane of dissection allows the exenteration surgeon to conceptually plan the subsequent resection. Historically, 50% of recurrent

tumors operated upon are located in the center of the pelvis and are generally peri-anastomotic recurrences of the neorectum or arise from the rectal scar (after previous abdominoperineal resection) [10]. In our experience, true isolated anastomotic recurrences are unusual. Central tumors may involve the vagina and uterus in women or the prostate and seminal vesicles in men as well as the urinary bladder (i.e., extend into the anterior compartment) and are generally resectable by complete or total "soft tissue" exenteration. In the infralevator anterior compartment of the male, one must understand the anatomy of the membranous urethra as it exits the prostate and that this plane will be encroached upon when a routine cystectomy is performed. This should be considered when planning a soft tissue exenteration for LRRC, particularly after previous abdominoperineal excision [24, 25]. Where the tumor extends to the anterior boundary of the pelvis (the pubic rami and symphysis), radical anterior bone resection may be necessary (Fig. 32.2a) [24, 25]. Posterior recurrences sit on and usually infiltrate the presacral fascia, the sacrum, and its nerve roots and often necessitate en bloc sacrectomy in order to achieve clear resection margins (Fig. 32.2b). Lateral compartment recurrences require radical resection of the iliac vasculature, lumbosacral trunk, or sciatic nerve, sidewall muscles, and ligamentous structures (Fig. 32.3).

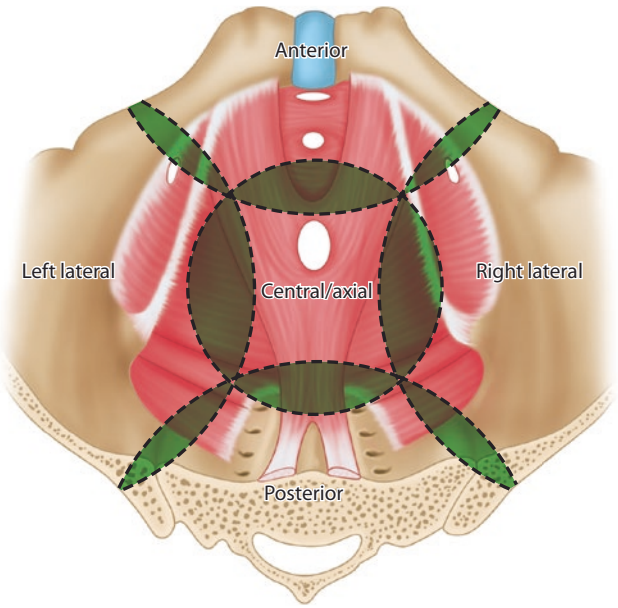

Fig. 32.1 The anatomical compartments of the pelvis

Patient Selection and Treatment Planning

The detection and confirmation of LRRC are often more difficult than expected, as in many patients, there is no luminal component of the recurrent tumor that would be readily identified at endoscopy and symptoms, if present, are often nonspecific. Confirmation is best done with biopsy of abnormal areas identified on radiographic imaging, but in some cases, it is difficult or potentially dangerous due to the biopsy path crossing vessels and bowel loops. In these cases, a combination of radiological changes with ^{18}F-fluorodeoxyglucose uptake on positron emission topography (PET) may be the best available evidence of recurrence and sufficient to initiate treatment. Once local recurrence is confirmed and the patient

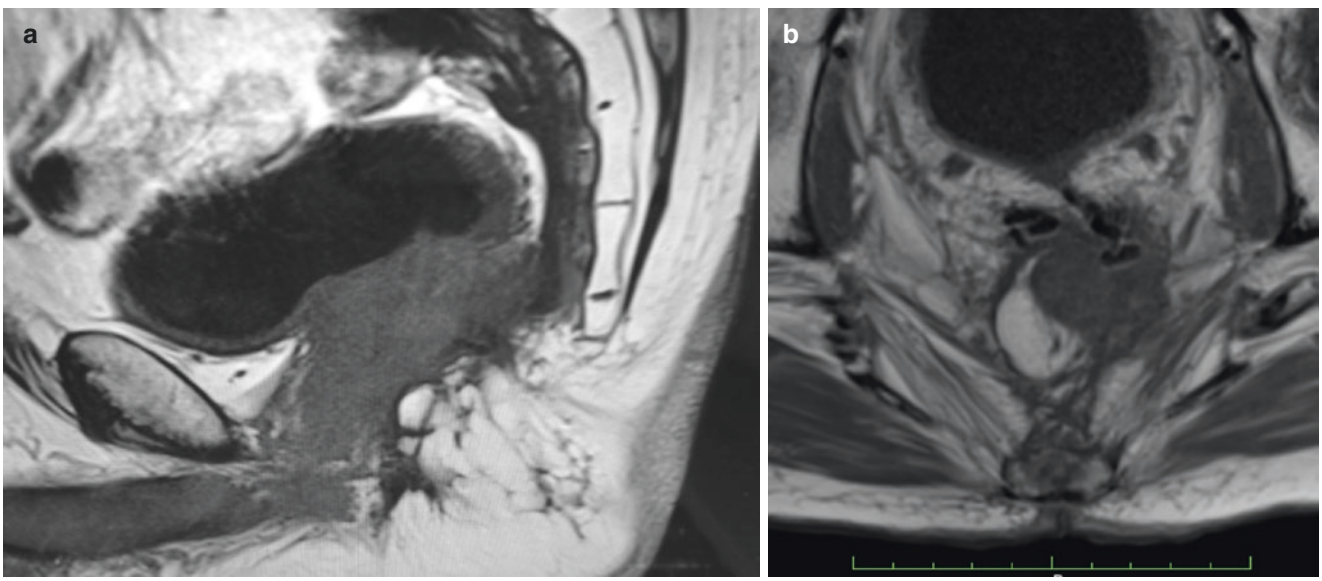

Fig. 32.2 (**a**) Recurrent rectal cancer after previous abdominoperineal resection, encasing membranous urethra extending to the base of the penis and posteriorly along pelvic floor to presacral fascia. (**b**) LRRC extending from the sacrum in posterior compartment along the left sacrospinous ligament approaching the ischial spine and invading the left seminal vesicle

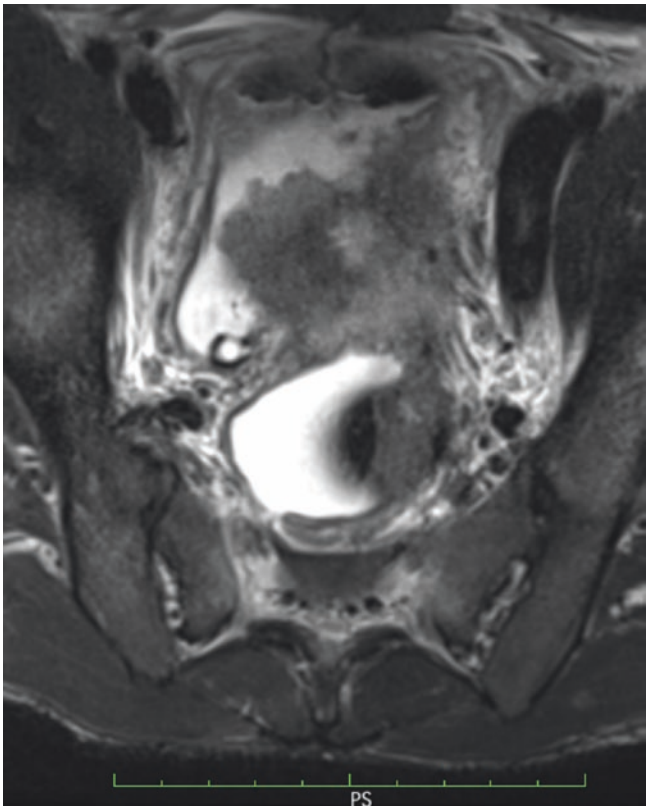

Fig. 32.3 Recurrent rectal cancer involving internal iliac vessels and left ureter with stent (identified with arrow), extending into the bladder and neorectum

is considered a potential candidate for exenteration and if metastatic disease is either absent or resectable, then discussions with the patient and family should commence in order to ensure their wishes for radical treatment are appropriately considered. In patients with true isolated pelvic recurrence referred for MDT assessment at our unit, about one in five patients will choose to pursue only palliative approaches despite being deemed suitable for attempt at curative exenteration.

Imaging

PET-CT combined with MRI is undoubtedly the mainstay of assessment of LRRC at the initial diagnosis, for excluding metastatic disease and for meticulous surgical planning [12, 26–28]. PET can be helpful in the identification of metastatic disease as it may detect small lesions not seen on CT [29], and it is also useful when post-radiation changes cannot be differentiated from tumor on MRI. MRI is important in not only confirming recurrence but in surgical planning. MRI has high positive (100%) and negative (89%) predictive values for the diagnosis of LRRC [30], and while it can accurately identify tumor invasion of major central pelvic organs, its accuracy declines when delineating infiltration of the smaller pelvic sidewall structures [31, 32]. In our recent review of preoperative MRI in patients with LRRC, predicted involvement of either the high sacrum or lateral compartment was associated with involved resection margins. On this basis, a more extensive resection should be planned when there is the possibility of posterior or lateral compartment involvement on MRI, rather than trying to "shave" a tumor off an involved structure which may result in R1 resection [33].

Multidisciplinary Team Assessment

Patient assessment for radical salvage surgery should be conducted by a dedicated multidisciplinary team (MDT). A major aim of any oncological MDT is to select appropriate patients for surgery. This exercise will hopefully minimize non-curative (R2) resections as well as operations which are aborted intraoperatively due to occult metastases or an unexpectedly unresectable tumor. Assessment of MDT decisions and referral patterns at our center have confirmed the determinant of resectability was about 70:30 in patients referred for consideration of exenteration and was not changed whether the exenteration surgeon had consulted with the patient before or after the MDT. This implies the MDT process is discriminatory and validates the importance of the multiple experts who have input at an exenteration MDT [34]. In a review of R1 resections for recurrent rectal cancer, we found perioperative miscommunication between the various involved physicians could negatively influence R0 resection rates [35].

A dedicated MDT is optimally attended by specialist colorectal, urological, orthopedic, vascular, and plastic surgeons, medical and radiation oncologists, a radiologist, psycho-oncologist, pain specialist, and palliative care and various allied health staff including care coordinators, stomal therapy nurses, dietitians, psychologists, physiotherapists, and research/audit officers. The availability of these personnel would depend on the number and extent of resections undertaken and local availability. Patient access to referral pathways and pelvic oncology MDTs remains a major issue, with recent data from Sweden indicating that fewer than one third of patients with LRRC nationally were discussed at an MDT prior to exenterative surgery [10]. These studies collectively confirm the importance of the MDT process in recurrent rectal cancer and the benefit of communication derived from the MDT.

Resectability

The definition of "resectable" LRRC has changed significantly in recent decades and continues to evolve [27, 36, 37]. In 2020, the indication for extended radical resection for

LRRC is a predicted R0 resection with acceptable anticipated morbidity in an appropriately consented and motivated patient.

LRRC infiltrating the lateral pelvic compartment and in particular the iliac vessels and major nerves of the pelvic sidewall had been considered unresectable until recently [20, 22, 27, 38, 39]. Development of a more radical approach to the lateral compartment in the last decade has led to significant improvements in R0 resection rates for tumors which invade the major neurovascular structures of the pelvic sidewall. By ligating and dividing the internal iliac vessels close to their origin, the surgeon can enter the undissected plane lateral to the vessels on top of piriformis fascia which allows the vessels to be readily excised en bloc with the recurrent tumor. Recent data from our unit shows an R0 resection rate of 69% in the lateral compartment (compared to 21% in 2008) [40, 41], and similar findings have been reported by the Karolinska Institute [42]. En bloc resection of the common and external iliac vessels is feasible in selected patients where deemed necessary due to tumor effacement or invasion, with R0 resection rates reported at 38–58%. Excellent long-term vascular arterial graft patency following vascular reconstruction can be achieved, but venous graft patency has been suboptimal [43, 44]. Consideration of ligation of the common or external iliac vein after resection without insertion of interposition grafts should be considered due to the high occlusion rate and risks of thrombosis and pulmonary embolism and is our current policy. In many cases of venous involvement with LRRC, there are established collaterals which both contribute to the resultant graft thrombosis and fortuitously limit the venous leg swelling when only ligation is performed.

En bloc resection of the sciatic nerve and/or lumbosacral trunk for tumors which extend more laterally into the piriformis muscle has R0 resection rates similar to central pelvic tumors and functional outcomes better than anticipated [45–48]. Radical resection of the sciatic nerve (partial or complete) with or without resection of the sciatic notch can be done either through the abdominal perineal access or transgluteal/prone access championed in London [45]. Partial or complete sciatic nerve resection can be more easily performed by these approaches. Almost all patients (96%) who require a complete sciatic nerve resection are able to mobilize postoperatively with intensive physiotherapy and orthotics input [45]. Patients mobilize by fixation of their resultant foot drop using ankle orthotics and raising of the ipsilateral hip followed by locking of the knee joint with the quadriceps (femoral nerve) on landing (the so-called rolling gait of sciatic nerve palsy). While an initial temporary reduction in the patient's physical quality of life can be expected after surgery for sciatic nerve involvement, this returns to preoperative baseline within 12 months.

Posterior pelvic compartment tumors generally involve or efface the sacrum and require en bloc sacrectomy for tumor clearance. Low sacrectomy (below S3) is now performed routinely by exenteration surgeons with relatively low complication rates, whether performed prone or in the abdominolithotomy position [49]. High sacrectomy (transection above S2/S3) remains controversial; however, several units have developed experience with this composite technique [50–53]. A recent international multicenter collaboration demonstrated that high sacrectomy can be performed without compromising rates of R0 resection and cancer-specific or overall survival [54]. High sacrectomy was, however, associated with higher blood loss, increased risk of complications, and obviously more sacral neurological impairment [55]. High sacrectomy should therefore no longer be considered a contraindicated procedure, although it does require consideration of the added morbidity during the consent process.

Metastatic Disease

Up to 40% of patients with LRRC will also have metastatic disease detected at the time of diagnosis [56, 57]. Salvage pelvic surgery is generally not pursued in the setting of unresectable metastases. Where isolated metastases are resectable, metastasectomy may be performed before or after local salvage surgery, but synchronous metastasectomy is generally avoided. Liver and/or lung surgery should typically occur before the exenteration due to the longer surgical recovery after pelvic exenteration. Delays prior to metastasectomy are associated with greater risk of cancer mortality.

Neoadjuvant and Intraoperative Treatment

Long-course neoadjuvant chemoradiotherapy is recommended prior to surgery for all patients with LRRC who did not undergo neoadjuvant therapy for treatment of their primary rectal cancer. Re-irradiation, intraoperative brachytherapy, and adjuvant chemotherapy remain contentious issues in recurrent rectal cancer and are the focus of international collaborative efforts and have been dealt with in the extensive review in the previous ASCRS textbook [1]. The appropriate balance between additional morbidity and improved local control has yet to be determined [58, 59].

Technical Considerations

While pelvic exenteration represents a heterogeneous and varied group of procedures, all salvage operations for LRRC can be considered in three phases: an initial *dissection phase* beginning with abdominal exploration to exclude metastatic disease, including extensive adhesiolysis of the small bowel with a meticulous "patience" to minimize the risk of

enterotomy and subsequent enteric fistulae, followed by ureterolysis and operative drainage of ureters with catheters if a conduit is planned, proximal and distal vascular control for planned resection of vessels, or just control of hemorrhage during lateral and posterior resections. Obliterated planes in the pelvis can be expected due to previous dissection of the mesorectal plane and fibrosis secondary to radiotherapy, so wider virginal planes to circumnavigate the most difficult compartment(s) are the safest approach to a hostile pelvis. Once the dissection has proceeded as far as possible, with proximal control of the bowel, ureters, and vessels, a *resection phase* begins where the tumor is excised with all contiguously involved structures. The final phase is the *reconstruction phase* which involves hemostasis, urinary and fecal conduit construction, or ureteric and/or bladder repair. Mesh reconstruction of soft tissue and bone defects as well as myocutaneous soft tissue reconstruction may be necessary in the reconstruction phase. The three-phase plan for exenteration involves a "6 C philosophy" coined by previous fellows in our unit: coherent plan, clear exposure, control (proximal and distal), circumnavigate the tumor, constantly reassess progress, and at all times be calm (additional latter "c" depending on surgeon personality!).

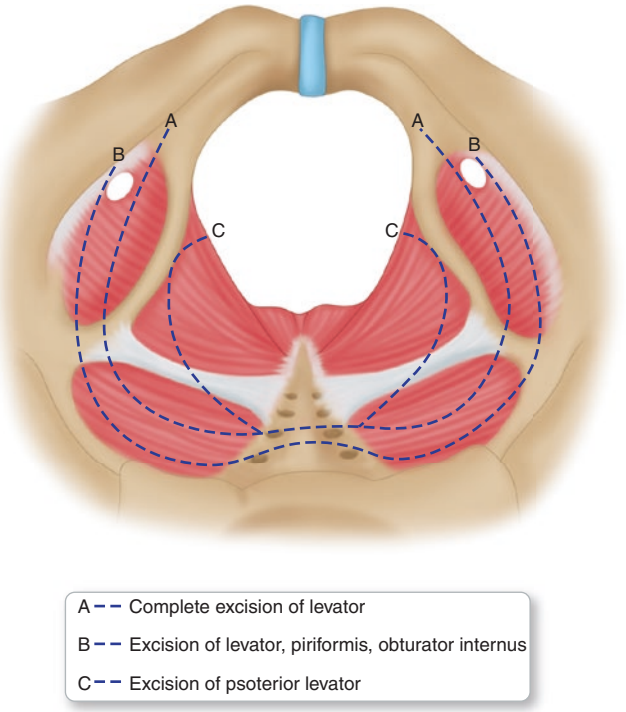

Fig. 32.4 Planned resection planes of the posterior and lateral compartments

Preparation

Safe and effective exenterative surgery relies on intra- and interdisciplinary teamwork. At our unit, two consultant colorectal surgeons are present for all cases where long procedures are expected and particularly for synchronous abdominal and perineal resection involving bone and/or lateral neurovascular structures. In 50% of recurrent rectal cancer, a urological surgeon is required for a conduit, and in a further 5–10%, the urologist is involved for reconstruction of the ureter with bladder re-implantation during the reconstruction phase. Support from orthopedic, plastic, and vascular surgeons is arranged in advance if their need is anticipated. Timing and planning are critical for surgical collegiality and anesthetic planning. Preoperatively the operative team reviews the imaging and revisits the operative plan developed at the MDT. This ensures there is a coherent plan which has been communicated to all members of the operative team (Fig. 32.4).

Positioning

The patient is placed on a nonslip gel mattress in the modified Lloyd-Davies position. The gel mattress distal end is rolled back over 10 cm, or a rolled towel is placed under the patient in the lumbar curve in order to raise the pelvis free of the operating table when an abdomino-lithotomy sacrectomy is planned [45]. The gel mattress provides security from slippage when in steeper Trendelenburg and allows for perineal reflection of the gluteus muscles free of the sacral bone posteriorly without compression of the skin on the sacrum ready for transection. This maneuver provides support of the lumbosacral curvature during operative anesthetic paralysis and limits low back pain postoperatively. In order to limit fecal contamination, any existing intestinal stomas are covered with gauze and a sterile occlusive dressing, and the anus, if present, is sutured closed. Stoma site markings by the stomal therapist are reinforced, and the skin is marked by a plastic surgeon for harvest of a vertical rectus abdominis myocutaneous (VRAM) flap if the need for perineal reconstruction is anticipated. The anticipated new stoma marked sites after VRAM harvest need to be marked accordingly (Fig. 32.5). The lower limbs are prepped down to the knees if vascular reconstruction may be required, to allow access to the groin and thigh for harvesting of autologous vein grafts.

Exploration and Preparing the Pelvis

A midline laparotomy and meticulous adhesiolysis are performed in order to avoid inadvertent enterotomies. After unanticipated peritoneal and hepatic metastases are excluded, the small bowel is excluded from the pelvis. If the tumor involves a small bowel loop(s), the bowel is transected

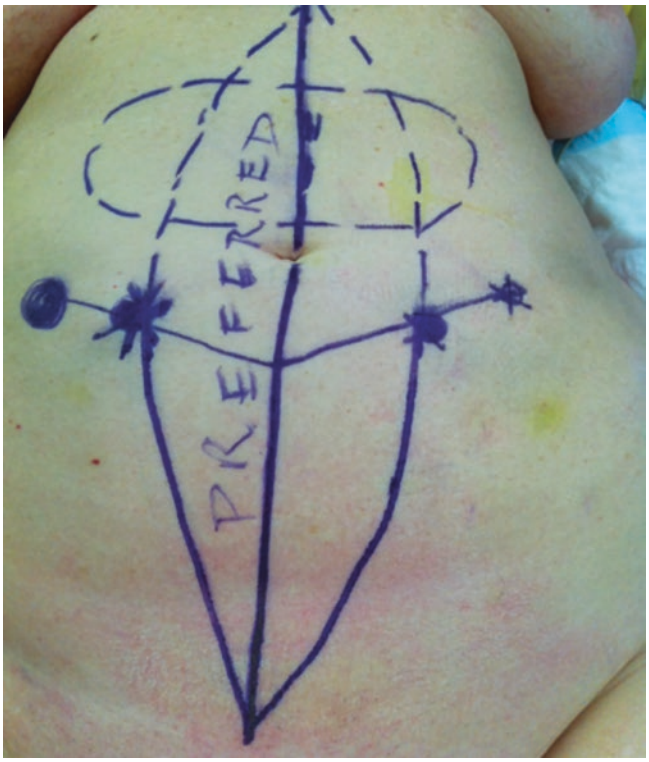

Fig. 32.5 Operative markings of potential vertical or horizontal rectus abdominis myocutaneous flaps and the expected repositioning of stoma sites after harvest of flaps

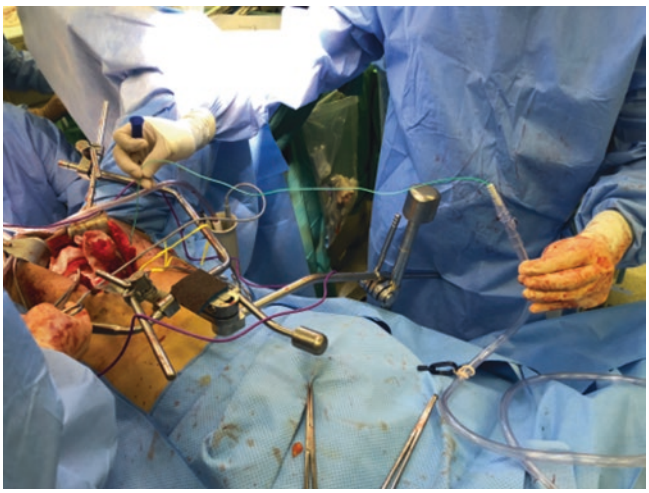

Fig. 32.6 Insertion of ureteric catheters during resection phase of exenteration prior to conduit fashioning in reconstruction phase

proximally and distally and excised en bloc. The ureters are identified proximally and dissected distally, over the pelvic brim, leaving a cuff of tissue surrounding each ureter to preserve their blood supply. If total cystectomy or ureterectomy is required, the ureters are divided as distal as possible, ensuring that only non-irradiated ureter is preserved for reconstruction. Infant feeding catheters are inserted into the proximal cut end of the ureter to allow monitoring of urine output during the resection phase and prevent back pressure on the kidney as acute tubular necrosis can occur during long operative times (Fig. 32.6).

Central Recurrences

Centrally located tumors, which do not involve the pubic bone anteriorly, lateral nerve or iliac vessels of the pelvic sidewall, or sacrum, may be completely excised by complete "soft tissue" exenteration. The posterior dissection commences first above the neorectum, if present, which is dissected free from the presacral fascia. Proceeding in an anterolateral direction, dissection continues in the extra-TME plane, and, after the peritoneum over the iliac vessels is incised, the vas deferens in males and round ligament in females need to be transected. The ureter is immediately deep to the peritoneum and can be retracted medially to give the surgeon access to the internal iliac vessels. The anterior division of the internal iliac artery gives rise to the named visceral branches (including the uterine artery and the superior and inferior vesical arteries) which are ligated and divided with their corresponding venous tributaries. After these vessels have been divided, the genitourinary organs can be retracted away from the pelvic sidewall to expose the obturator fossa including obturator internus muscle. Sidewall branches and tributaries of the internal iliac vessels are now accessible including the obturator vessels with the obturator nerve traversing the fossa to exit through the obturator canal. Care is taken if excising the obturator internus muscle with vessels and nerves, to ligate the vein carefully as the vein is friable post radiotherapy and retracts into the canal with potential venous oozing deep into the bony canal which can be difficult to access and control. The endopelvic fascia and the levator ani are exposed and are easier to resect abdominally under direct vision than the traditional approach from the perineum (Fig. 32.7). Anteriorly the bladder is mobilized by dissection in the prepubic plane, and the dorsal venous complex is ligated and divided. The dorsal venous complex and urethra may be transected during the abdominal phase if well clear of the recurrent tumor. Alternatively, this may be approached transperineally at the base of the penis (Fig. 32.2) [24]. Perineal urethrectomy allows a wider excision of the membranous urethra as well as minimizes bleeding from the dorsal venous complex which is always difficult in the abdominal radiated cave of Retzius (Figs. 32.1 and 32.7a, b).

Total cystectomy in the female with LRRC invariably coincides with extensive vaginal involvement. Preserving a functioning vagina that is radiated can be difficult once the anterior vaginal wall is resected with the urethra. An interlabial radical vaginectomy and cystectomy dissection plane

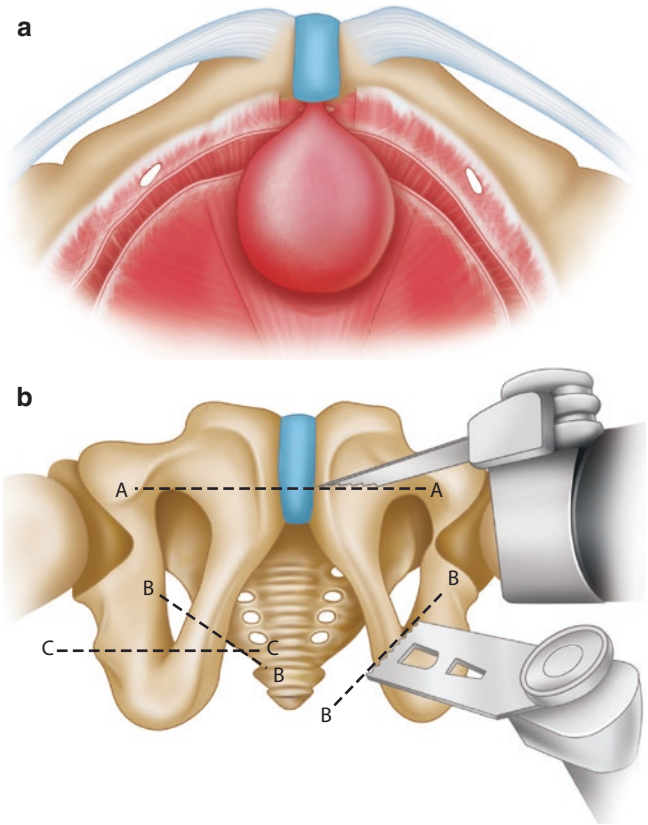

Fig. 32.7 (**a**) Incision of endopelvic fascia over levator and obturator internus muscle laterally. (**b**) Lines of transection of the pubic bone with oscillating saw

(Fig. 32.8a) provides a more radical margin and decreases the vaginal venous bleeding often encountered with subtotal radical vaginectomy. Preservation of the labia majora allows primary closure with no need for a myocutaneous flap (Fig. 32.8b) and arguably a much more cosmetic appearance than a flap (Fig. 32.8c). Neovaginal plastic surgical reconstruction (e.g., using the bowel) can be considered at the time of exenteration or in the future with utilization of the preserved labia majora. If the anterior vaginal wall remains with bladder preservation, then a myocutaneous flap is utilized to restore the posterior half of the vagina (Fig. 32.8d).

The perineal dissection is commenced by making an elliptical incision around the anus or old abdominoperineal resection perineal scar and extending the incision to the base of the scrotum or to include the introitus in females. Wide skin excision is not needed in tumors confined to the supralevator compartments and is usually only necessary if there is skin involvement by infralevator tumors. This is more commonly required in recurrent urogenital or anal SCC. After skin incision, however, a wide dissection through the ischiorectal fossae is carried toward the bony periphery of the pelvis. The bony landmarks of the coccyx, ischial tuberosities, and inferior pubic rami are the key to radical soft tissue planes. Soft tissue excision on the periosteum with high-powered diathermy in conjunction with assistance from the abdominal surgeon allows disconnection of the pelvic floor at the bony attachments of the levator plate defined by the preoperative MRI (Fig. 32.4). The perineal surgeon should approach this dissection anatomically rather than be guided by the abdominal surgeon to ensure predetermined MRI surgical margins are delivered. As a rule, the more pelvic floor, ligaments, and bone that can be disconnected and resected under direct vision by the abdominal surgeon, the clearer the margin is defined and improves the final combined resection. For tumors extending anterolaterally, the levator is released at its attachment to the inferior pubic rami with or without obturator internus more deeply. The abdominal and perineal surgeons continue dividing the pelvic floor until it is released circumferentially allowing delivery of the specimen. The extent of lateral and posterior resection, e.g., ischial bone, lateral neurovascular bundles, and sacrum, is defined by the preoperative plan and discussed below.

Composite Pubic Bone Resection

LRRC centered in the anterior compartment tends to be problematic following previous abdominoperineal excision for low rectal tumors in men and can involve the periosteum and fascia overlying and involving the pubic bone (Fig. 32.2b). Clear resection margins may only be achieved by radical pubic bone excision in this situation. This technique requires both en bloc pubic bone resection and perineal transection of the urethra at the base of the penis. In combination, these maneuvers allow an anterior margin beyond the pubic bone and membranous urethra [24, 25]. If pubic bone resection is not required, then dissection anterior to the bladder in the space of Retzius proceeds as usually but stops short of the inferior aspect of the pubic symphysis, without transection of the dorsal vein complex (Fig. 32.7a). Where pubic bone resection is required, the dissection stops above the point of tumor involvement (Fig. 32.4, line A). If total pubic bone resection is required, then the prepubic space is not entered but resected en bloc.

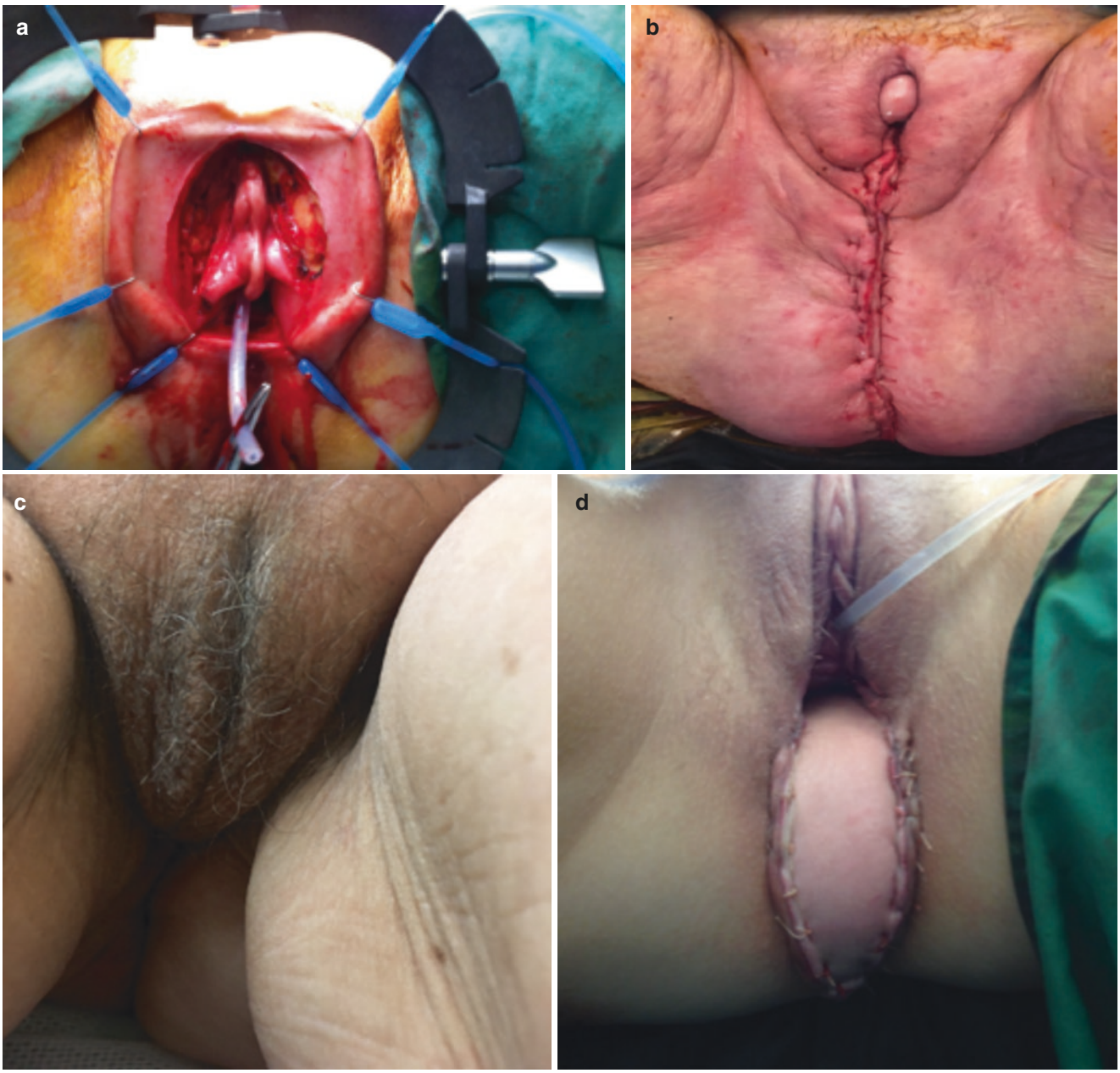

Fig. 32.8 Interlabial approach for radical vaginectomy with total cystectomy. (**a**) Incision between labia majora and minora. (**b**) Postoperative completed wound with clitoris preserved. (**c**) Long-term cosmetic appearance of healed wound. (**d**) VRAM flap posterior vaginal reconstruction

The perineal surgeon extends the skin incision toward the base of the scrotum, and the wide excision of the pelvic floor includes complete exposure of the inferior pubic rami out to the ischial tuberosities. With the base of the penis identified, the bulbospongiosus muscle, the dorsal venous complex, and the urethra (with the urinary catheter) are individually ligated and divided. This exposes the pubic symphysis, and, if required, a complete or partial pubic bone resection can be performed using an oscillating saw (Fig. 32.7b) [24].

Lateral Neurovascular Resection

En bloc internal iliac vascular resection is necessary for oncological clearance for laterally infiltrating tumors but is also required during high sacrectomy to "float" the common iliac vessels out of the pelvis and protect them during sacral transection from the prone approach and to minimize bleeding. For radiated and fibrosed vessels, starting the dissection of the common and external iliac vessels laterally in the

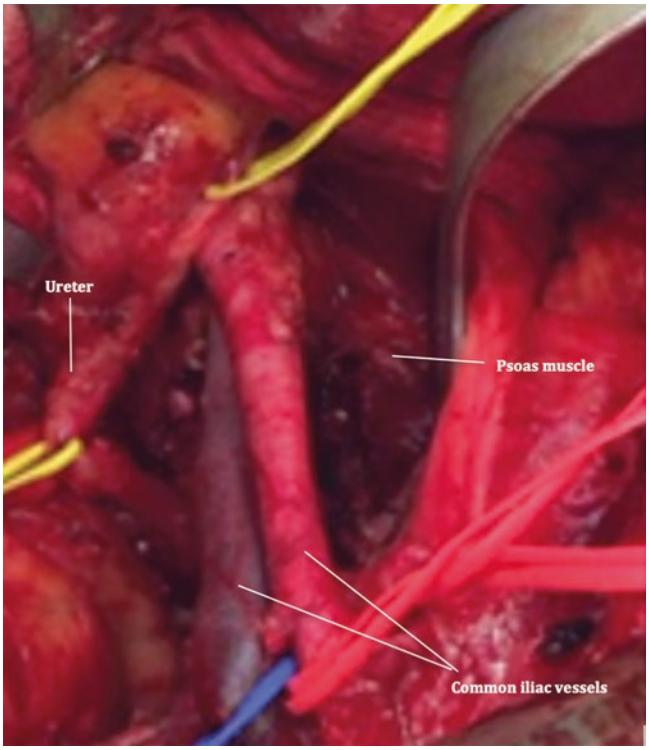

Fig. 32.9 The exposure of left lateral pelvic sidewall with left lateral compartment excision and common and external iliac vessels dissected free of psoas muscle laterally and ureter medially

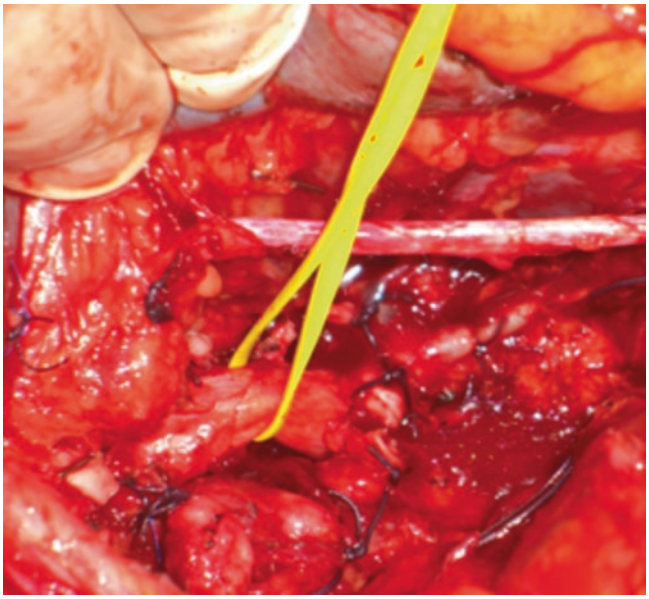

Fig. 32.10 A patient with locally recurrent rectal cancer: the left common and external iliac vessels have been "floated" out of the true pelvis (under surgeon's fingers), and the internal iliac vasculature has been excised en bloc with tumor. The piriformis muscle and fascia have been excised exposing the L5 nerve root with the exposed obturator nerve

plane medial to the psoas muscle on the bone similar to a lateral pelvic node dissection allows mobility in a virgin surgical plane (Fig. 32.9). Ligation and division of the internal iliac vessels close to their origin from the common iliac allows the lateral branches and tributaries (i.e., gluteal and ascending lumbar vessels) to be ligated and exposes the piriformis muscle, the lumbosacral trunk, and the sacral nerve roots which lie on the piriformis muscle. Care must be taken to identify and ligate these lateral internal iliac branches and tributaries, which can cause major bleeding which can be difficult to control if they retract back into the pelvic sidewall. The nerves lie deep to the piriformis fascia which needs to be incised to dissect the nerve roots and eventually leads down the ischial spine with the sciatic nerve exiting the pelvis posterolateral to this bone landmark. The obturator internus and piriformis muscles can be excised en bloc. If required to achieve a clear margin, the ischial spine can be excised en bloc using an osteotome with care taken not to go deeper into the sciatic nerve unnecessarily (this can also be performed using a Gigli saw). Once exposed, complete or partial sciatic nerve resection can be performed (Fig. 32.10) [45].

Extension of tumors outside the true lateral compartment can involve excision of the psoas muscle and dissection and/or resection of the femoral nerve. Identifying the femoral nerve is easiest just above the inguinal ligament lateral to where the external iliac artery becomes the common femoral artery. Incising the fascia overlying the iliopsoas muscle just above and parallel to the inguinal ligament will expose the femoral nerve. Superiorly at the origin of the psoas muscle at or above the L4–L5 vertebra level, the femoral nerve can be found between the larger anterior and smaller posterior muscle heads of the psoas muscle (Fig. 32.11).

Tumors that infiltrate or encase the common or external iliac vessels necessitate resection of the vessel with reconstruction [44]. Proximal vascular control must first be achieved by dissection at or just below the bifurcation of both the aorta and inferior vena cava as well as control of the distal external iliac vessels before transection (Fig. 32.9). Vessel reconstruction using autologous venous grafts is preferred due to concerns about graft infection after use of synthetic materials. Bovine pericardium is another alternative material used for interposition grafting.

Posterior Recurrences

LRRC involving the posterior compartment generally involves the presacral fascia, the sacrum, and its nerve roots, and composite distal sacrectomy is generally required to ensure a clear posterior resection margin. The nature of the previous posterior plane of the proctectomy dictates this close relationship to the sacrum above S3 and to the pelvic floor muscle as it originates from the S3 vertebra down. Abdomino-lithotomy sacrectomy is feasible if the level of sacral amputation is below S3 [49]. This allows the entire

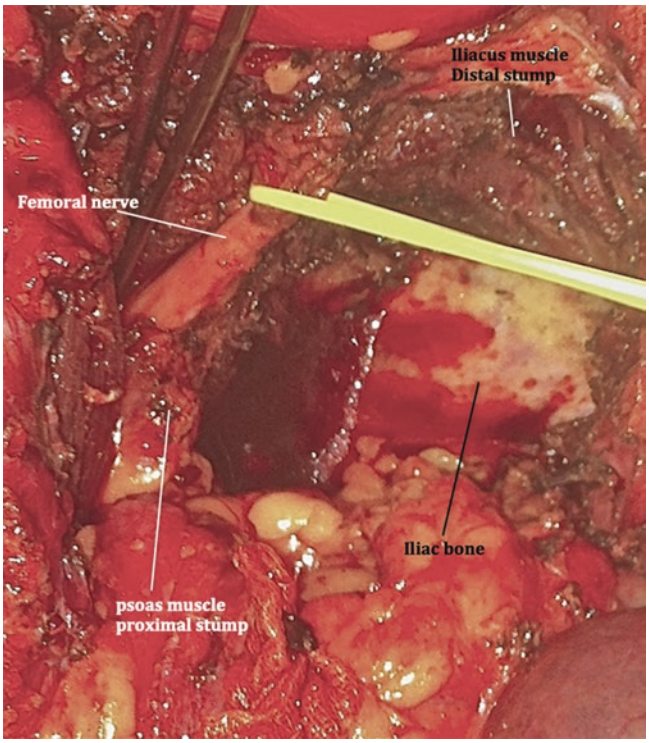

Fig. 32.11 Right femoral nerve identified in the psoas muscle after resection of iliopsoas muscle during extended lateral pelvic compartment resection

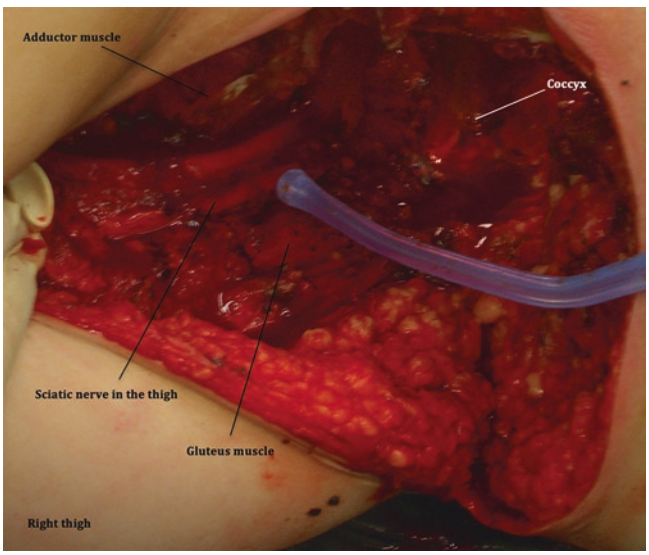

Fig. 32.12 Dissection of right sciatic nerve out from the pelvis into the thigh after excision of the ischial tuberosity in the abdomino-lithotomy position

operation to be performed in the abdomino-lithotomy position and does not require a prone phase. This preserves vascular control via access to the iliac vessels and allows better access to the sciatic nerve as it exits the pelvis more laterally than in the prone position (Fig. 32.12).

In preparation for sacrectomy, circumnavigation of the point of posterior bony fixation is required. This is achieved by circumferential dissection of the anterior and lateral compartment from the abdominal and perineal approaches, leaving the tumor attached only at the sacrum. For the abdominal surgeon, the posterior dissection between the neorectum or bladder after previous abdominoperineal resection and the presacral fascia stops above the level of tumor involvement according to the preoperative MRI. The level of sacral amputation is scored using high-powered diathermy and, if a prone sacrectomy is required, can be marked using a metallic sacral pin. Lateral dissection out to the ischial spine is necessary by following the sacrospinous ligament (Fig. 32.2) and transecting the ligament from the spine to free the sacrum prior to transection. Identification of the lumbosacral trunk, upper sacral nerve roots, and sciatic nerve as it starts in the thigh is critical at this stage. The perineal dissection is in the plane posterior to the coccyx and continues cephalad on the bone releasing the fibrous attachment of gluteus muscle to periosteum up to the level of S2. During this phase, all ligamentous and muscular attachments to the sacrum and coccyx are dissected free. The support of the lumbar groove on a rolled edge of a gel mattress or rolled towel allows the sacrum to be free posteriorly and is essential at this point; otherwise the gluteus muscle, sacral skin, and subcutaneous fat are compressed against and inseparable from the sacrum and coccyx due to the weight of the patient directly on the operating table [49]. After freeing the gluteus and overlying skin from the bone, the perineal surgeon places an osteotome posterior to the sacrum to protect the post-sacral skin, before the sacrum is transected transversely by the abdominal surgeon using an osteotome and mallet, allowing delivery of the specimen through the perineal wound.

Where high sacrectomy (i.e., sacral transection at or proximal to the S2/S3 junction) is required, the patient is turned prone in the jackknife position. With the assistance of an orthopedic spinal surgeon, a longitudinal incision is made over the sacrum which may be continuous with the perineal incision. The remaining attachments of the gluteal muscles are disconnected posteriorly, and after the level of sacral transection is confirmed by intraoperative fluoroscopy, a laminectomy is performed. Transverse osteotomies are made, and the sacrospinous and sacrotuberous ligaments are transected in order to allow delivery of the specimen. The sciatic nerve is preserved where possible although identifying the nerve roots is difficult in the prone position even with fluoroscopic confirmation of the vertebral level. Prior abdominal dissection of the lumbosacral trunk on the piriformis muscle and vessel looping the L5 and S1 nerve roots prior to the prone phase help confirm their identity prone and protect them from inadvertent injury or transection.

Where a central recurrence involves the presacral fascia and sacrum at a high level but centrally between the foram-

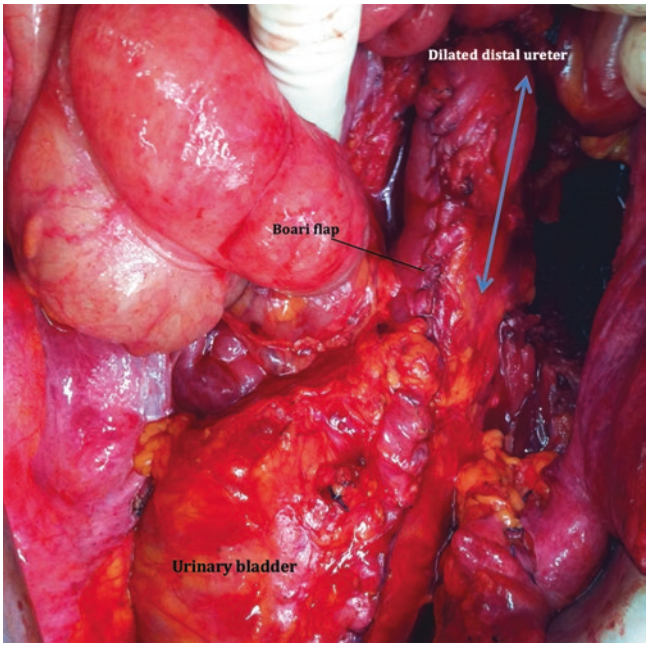

Fig. 32.13 Boari flap (arrow) ureterocystostomy reconstruction post left distal ureterectomy and partial cystectomy

ina (L5, S1, and S2) and without deep infiltration well into the vertebral body on MRI, anterior cortical sacrectomy is possible by making partial-thickness osteotomies around the point of involvement and allows the sacral nerve roots to be preserved [60, 61]. This central high cortical resection can be continued caudad with full-thickness bone transection en bloc below the level of the sacroiliac joint (S3) while remaining in the abdomino-lithotomy approach.

Reconstruction

The extent of reconstruction required depends on the organs, vessels, and soft tissues that require resection during the resection phase. Vascular surgery input may be required for interposition graft reconstruction if complete resection of the common or external iliac artery or vein was necessary [43, 44]. In an attempt to reduce limb ischemia time, vascular reconstruction is performed as soon as possible after vessel transection with a view to reduce the risk of thrombosis and compartment syndrome during long surgery time particularly with the legs elevated in lithotomy. Ureteric re-implantation with or without a Boari flap is necessary following partial cystectomy (Fig. 32.13). There are four options for urinary diversion following total cystectomy: the isolated ileal conduit, isolated colonic conduit, in-continuity colostomy and conduit ("wet colostomy"), and separated colonic colostomy and conduit with communal exit (Fig. 32.14a–d). The choice of conduit formation can depend on the radiation effects on the small bowel as well as previous bowel resections but usually follows local urological preferences. Colonic conduits have the advantage of avoidance of intestinal anastomosis and risk of subsequent anastomotic leak. Urinary reconstruction can be performed at the same time as primary perineal closure, or after a VRAM flap is harvested if required, while it is being inset.

Postoperative Management

Patients undergoing exenterative surgery at our center are routinely admitted to the intensive care unit postoperatively. All patients commence total parenteral nutrition on postoperative day 0 due to the high rate of malnutrition in patients with advanced pelvic malignancy and the risk of prolonged ileus in this patient population. Limb observations are necessary every 4 hours for the first three postoperative days in patients with arterial resection and reconstruction, and these patients also require compression stockings. In patients with urinary conduits, the creatinine level in the abdominal drain fluid is checked on days 1 and 5 in order to detect early urine leaks [62], and ureteric catheters through the conduit are removed on days 10–14 with or without a prior fluoroscopic contrast imaging to rule out subclinical urine leaks.

Outcomes

The PelvEx Collaborative is an international collaboration between specialist exenteration centers, and the most recent pooled data for patients undergoing surgery for LRRC included 1184 patients [16]. On average, the length of hospital stay was 15 days, and the rates of major postoperative complications and reintervention were 32% and 10%, respectively. The rate of R0 resection was 55% in the PelvEx study and 58% in a recent systemic review [16, 63]. Overall survival at 5 years after surgery between 40% and 50% can be expected, provided clear resection margins are achieved [10–13]. Recent data from our center demonstrated that, while a microscopically clear resection margin predicts lower rates of local recurrence and higher overall survival, margins wider than 0.1 mm did not convey an additional survival benefit [17]. This finding challenges the prevailing definition of R0 as a 1 mm margin, which is based on primary rectal cancer data.

Approximately 55% of patients who undergo radical salvage surgery for LRRC will develop disease recurrence. While a small number of patients (14–21%) will have locally re-recurrent tumor for which further radical surgery may be feasible, more will recur systemically with distant metastatic disease [12, 13, 64, 65]. There are no data reporting the outcomes of neoad-

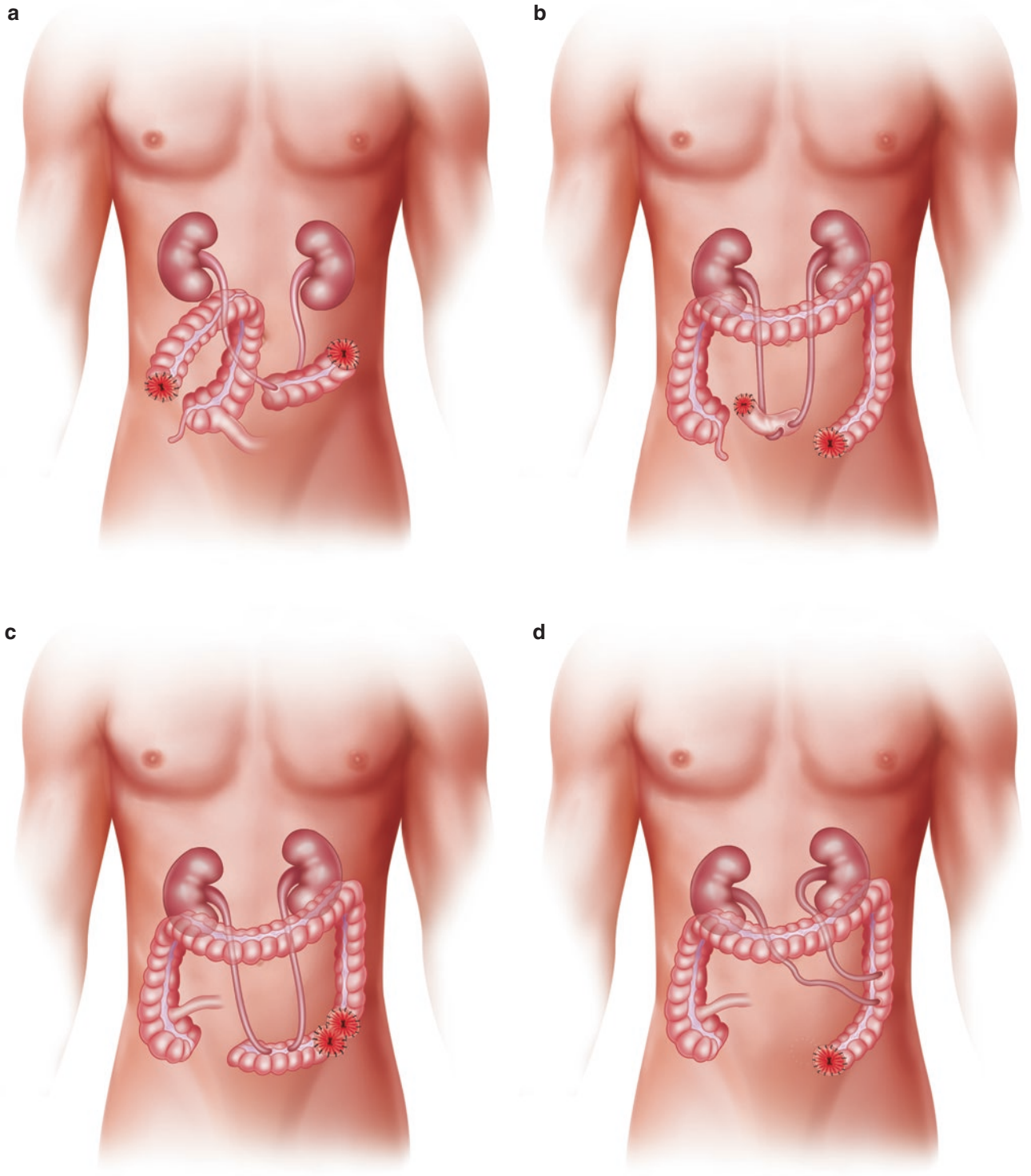

Fig. 32.14 Four options for urinary conduits. (**a**) Isolated colonic conduit + colostomy. (**b**) Isolated ileal conduit + colostomy. (**c**) Separated urine + fecal colostomy. (**d**) In-continuity urine and fecal colostomy

juvant chemotherapy in patients undergoing resection of LRRC; however, chemotherapy may be considered, with the intent of reducing the rate of systemic failure [12].

Conclusions

Exenterative surgery represents the only potentially curative option for patients with LRRC. Careful patient selection, meticulous planning, and interdisciplinary teamwork are required to provide patients with the best possible outcome. When approaching the previously dissected and irradiated pelvis, gain proximal and distal control of organs, vessels, and nerves before circumnavigating the most advanced and involved pelvic compartment. Where there is a question about tumor involvement, radically resect the structure in question in order to avoid a "close shave" and involved margin. Surgeons who operate on LRRC should be comfortable applying this concept to the lateral and posterior compartments of the pelvis. Systemic failure remains the most common form of recurrence after radical salvage surgery, and methods to reduce recurrence and lower morbidity require further investigation.

References

1. Dozois EJ, Colibaseanu DT. Colorectal cancer: management of local recurrence. In: The ASCRS textbook of colon and rectal surgery. New York: Springer Publishing Company; 2016.
2. Kusters M, Marijnen CAM, van de Velde CJH, et al. Patterns of local recurrence in rectal cancer; a study of the Dutch TME trial. Eur J Surg Oncol. 2010;36(5):470–6.
3. Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet. 2009;373(9666):811–20.
4. Rasanen M, Carpelan-Holmstrom M, Mustonen H, Renkonen-Sinisalo L, Lepisto A. Pattern of rectal cancer recurrence after curative surgery. Int J Color Dis. 2015;30(6):775–85.
5. Detering R, Karthaus EG, Borstlap WAA, et al. Treatment and survival of locally recurrent rectal cancer: a cross-sectional population study 15 years after the Dutch TME trial. Eur J Surg Oncol. 2019;45(11):2059–69.
6. Wasmuth HH, Faerden AE, Myklebust TA, et al. Transanal total mesorectal excision for rectal cancer has been suspended in Norway. Br J Surg. 2020;107(1):121–30.
7. Atallah S, Sylla P, Wexner SD. Norway versus The Netherlands: will taTME stand the test of time? Tech Coloproctol. 2019;23(9):803–6.
8. Warren OJ, Solomon MJ. The drive toward transanal total mesorectal excision - science or rhetoric? Dis Colon Rectum. 2015;58(9):909–10.
9. Brown KGM, Solomon MJ. Progress and future direction in the management of advanced colorectal cancer. Br J Surg. 2018;105(6):615–7.
10. Westberg K, Palmer G, Hjern F, Holm T, Martling A. Population-based study of surgical treatment with and without tumor resection in patients with locally recurrent rectal cancer. Br J Surg. 2019;106(6):790.
11. Nielsen M, Rasmussen P, Pedersen B, Hagemann-Madsen R, Lindegaard J, Laurberg S. Early and late outcomes of surgery for locally recurrent rectal cancer: a prospective 10-year study in the total mesorectal excision era. Ann Surg Oncol. 2015;22(8):2677–84.
12. You YN, Skibber JM, Hu CY, et al. Impact of multimodal therapy in locally recurrent rectal cancer. Br J Surg. 2016;103(6):753–62.
13. Harris CA, Solomon MJ, Heriot AG, et al. The outcomes and patterns of treatment failure after surgery for locally recurrent rectal cancer. Ann Surg. 2016;264:323–9.
14. Quyn AJ, Solomon MJ, Lee PM, et al. Palliative pelvic exenteration: clinical outcomes and quality of life. Dis Colon Rectum. 2016;59(11):1005–10.
15. Heriot AG, Byrne CM, Lee P, et al. Extended radical resection: the choice for locally recurrent rectal cancer. Dis Colon Rectum. 2008;51(3):284–91.
16. PelvEx Collaborative. Factors affecting outcomes following pelvic exenteration for locally recurrent rectal cancer. Br J Surg. 2018;105(6):650–7.
17. Koh CE, Brown KGM, Steffans D, Young JM, Salkeld G, Solomon MJ. What constitutes a clear margin in patients with locally recurrent rectal cancer undergoing pelvic exenteration. Ann Surg. 2020; in press.
18. Moore HG, Shoup M, Riedel E, et al. Colorectal cancer pelvic recurrences: determinants of resectability. Dis Colon Rectum. 2004;47(10):1599–606.
19. Boyle KM, Sagar PM, Chalmers AG, Sebag-Montefiore D, Cairns A, Eardley I. Surgery for locally recurrent rectal cancer. Dis Colon Rectum. 2005;48(5):929–37.
20. Suzuki K, Dozois RR, Devine RM, et al. Curative reoperations for locally recurrent rectal cancer. Dis Colon Rectum. 1996;39(7):730–6.
21. Wanebo HJ, Antoniuk P, Koness RJ, et al. Pelvic resection of recurrent rectal cancer: technical considerations and outcomes. Dis Colon Rectum. 1999;42(11):1438–48.
22. Yamada K, Ishizawa T, Niwa K, Chuman Y, Akiba S, Aikou T. Patterns of pelvic invasion are prognostic in the treatment of locally recurrent rectal cancer. Br J Surg. 2001;88(7):988–93.
23. Austin KKS, Solomon MJ. Operative technique for pelvic exenteration. In: O'Connell R, Madoff RD, Solomon MJ, editors. Operative surgery of the colon, rectum and anus. Boca Raton: CRC Press; 2016.
24. Solomon MJ, Austin KK, Masya L, Lee P. Pubic bone excision and perineal urethrectomy for radical anterior compartment excision during pelvic exenteration. Dis Colon Rectum. 2015;58(11):1114–9.
25. Austin KK, Herd AJ, Solomon MJ, Ly K, Lee PJ. Outcomes of pelvic exenteration with en bloc partial or complete pubic bone excision for locally advanced primary or recurrent pelvic cancer. Dis Colon Rectum. 2016;59(9):831–5.
26. Bird TG, Ngan SY, Chu J, Kroon R, Lynch AC, Heriot AG. Outcomes and prognostic factors of multimodality treatment for locally recurrent rectal cancer with curative intent. Int J Color Dis. 2018;33(4):393–401.
27. Mirnezami AH, Sagar PM, Kavanagh D, Witherspoon P, Lee P, Winter D. Clinical algorithms for the surgical management of locally recurrent rectal cancer. Dis Colon Rectum. 2010;53(9):1248–57.
28. Bhangu A, Ali SM, Cunningham D, Brown G, Tekkis P. Comparison of long-term survival outcome of operative vs nonoperative management of recurrent rectal cancer. Color Dis. 2013;15(2):156–63.
29. Watson AJ, Lolohea S, Robertson GM, Frizelle FA. The role of positron emission tomography in the management of recurrent colorectal cancer: a review. Dis Colon Rectum. 2007;50(1):102–14.
30. Ganeshan D, Nougaret S, Korngold E, Rauch GM, Moreno CC. Locally recurrent rectal cancer: what the radiologist should know. Abdom Radiol (NY). 2019;44(11):3709–25.
31. Dresen RC, Kusters M, Daniels-Gooszen AW, et al. Absence of tumor invasion into pelvic structures in locally recurrent rectal

cancer: prediction with preoperative MR imaging. Radiology. 2010;256(1):143–50.
32. Georgiou PA, Tekkis PP, Constantinides VA, et al. Diagnostic accuracy and value of magnetic resonance imaging (MRI) in planning exenterative pelvic surgery for advanced colorectal cancer. Eur J Cancer. 2013;49(1):72–81.
33. O'Shannassy SJ, Brown KGM, Steffens, Solomon MJ. Referral patterns and outcomes of a highly specialised pelvic exenteration multidisciplinary team meeting: A retrospective cohort study. European Journal of Surgical Oncology 2020;46(6): 1138–43
34. Denost Q, Solomon MS, Tuech JJT, Faucheron JLF, Mehrdad JM, Lefevre JL, Rullier ER, Heriot AH, Austin KA, Lee PL, Brown WB, Maillou-Martinaud HMM, Savel HS, Quintard BQ, Broc GB, Saillour-Glénisson FSG. International prospective benchmark pilot study in primary T4 and locally recurrent rectal cancer. British Journal of Surgery 2020; https://doi.org/10.1002/bjs.11854.
35. van Ramshorst GH, O'Shannassy S, Brown WE, Kench JG, Solomon MJ. A qualitative study of the development of a multidisciplinary case conference review methodology to reduce involved margins in pelvic exenteration surgery for recurrent rectal cancer. Color Dis. 2018;20(11):1004–13.
36. Zoucas E, Frederiksen S, Lydrup ML, Mansson W, Gustafson P, Alberius P. Pelvic exenteration for advanced and recurrent malignancy. World J Surg. 2010;34(9):2177–84.
37. Gannon CJ, Zager JS, Chang GJ, et al. Pelvic exenteration affords safe and durable treatment for locally advanced rectal carcinoma. Ann Surg Oncol. 2007;14(6):1870–7.
38. Lopez-Kostner F, Fazio VW, Vignali A, Rybicki LA, Lavery IC. Locally recurrent rectal cancer: predictors and success of salvage surgery. Dis Colon Rectum. 2001;44(2):173–8.
39. Pawlik TM, Skibber JM, Rodriguez-Bigas MA. Pelvic exenteration for advanced pelvic malignancies. Ann Surg Oncol. 2006;13(5):612–23.
40. Austin KK, Solomon MJ. Pelvic exenteration with en bloc iliac vessel resection for lateral pelvic wall involvement. Dis Colon Rectum. 2009;52(7):1223–33.
41. Solomon MJ, Brown KG, Koh CE, Lee P, Austin KK, Masya L. Lateral pelvic compartment excision during pelvic exenteration. Br J Surg. 2015;102(13):1710–7.
42. Iversen H, Martling A, Johansson H, Nilsson PJ, Holm T. Pelvic local recurrence from colorectal cancer: surgical challenge with changing preconditions. Color Dis. 2018;20(5):399–406.
43. Abdelsattar ZM, Mathis KL, Colibaseanu DT, et al. Surgery for locally advanced recurrent colorectal cancer involving the aortoiliac axis: can we achieve R0 resection and long-term survival? Dis Colon Rectum. 2013;56(6):711–6.
44. Brown KG, Koh CE, Solomon MJ, Qasabian R, Robinson D, Dubenec S. Outcomes after en bloc iliac vessel excision and reconstruction during pelvic exenteration. Dis Colon Rectum. 2015;58(9):850–6.
45. Brown KGM, Solomon M, Lau YC, Steffens D, Austin KKS, Lee PJ. Sciatic and femoral nerve resection during extended radical surgery for advanced pelvic tumors: long-term survival, functional, and quality-of-life outcomes. Ann Surg. 2021;273:982–8.
46. Shaikh I, Aston W, Hellawell G, et al. Extended lateral pelvic sidewall excision (ELSiE): an approach to optimize complete resection rates in locally advanced or recurrent anorectal cancer involving the pelvic sidewall. Tech Coloproctol. 2015;19(2):119–20.
47. Lee DJ, Waters PS, Larach JT, McCormick JJ, Heriot AG, Warrier SK. Pelvic sidewall excision with en bloc complete sciatic nerve resection in locally re-recurrent rectal cancer. ANZ J Surg. 2020;90(6):1202–4.
48. Kameyama M, Nakamori S, Imaoka S, et al. [Composite resection of sciatic nerve for local recurrence of rectal cancer]. Gan To Kagaku Ryoho. 1993;20(11):1689–91.
49. Solomon MJ, Tan KK, Bromilow RG, et al. Sacrectomy via the abdominal approach during pelvic exenteration. Dis Colon Rectum. 2014;57(2):272–7.
50. Milne T, Solomon MJ, Lee P, et al. Sacral resection with pelvic exenteration for advanced primary and recurrent pelvic cancer: a single-institution experience of 100 sacrectomies. Dis Colon Rectum. 2014;57(10):1153–61.
51. Colibaseanu DT, Dozois EJ, Mathis KL, et al. Extended sacropelvic resection for locally recurrent rectal cancer: can it be done safely and with good oncologic outcomes? Dis Colon Rectum. 2014;57(1):47–55.
52. Khaled F, Smith MJ, Moises C, Smith AJ, Yee AJ. Single-stage anterior high sacrectomy for locally recurrent rectal cancer. Spine. 2014;39(5):443–52.
53. Uehara K, Ito Z, Yoshino Y, et al. Aggressive surgical treatment with bony pelvic resection for locally recurrent rectal cancer. Eur J Surg Oncol. 2015;41(3):413–20.
54. Lau YC, Jongerius K, Wakeman C, et al. Influence of the level of sacrectomy on survival in patients with locally advanced and recurrent rectal cancer. Br J Surg. 2019;106(4):484–90.
55. Sasikumar A, Bhan C, Jenkins JT, Antoniou A, Murphy J. Systematic review of pelvic exenteration with en bloc sacrectomy for recurrent rectal adenocarcinoma: R0 resection predicts disease-free survival. Dis Colon Rectum. 2017;60(3):346–52.
56. Hagemans JAW, van Rees JM, Alberda WJ, et al. Locally recurrent rectal cancer; long-term outcome of curative surgical and non-surgical treatment of 447 consecutive patients in a tertiary referral centre. Eur J Surg Oncol. 2020;46(3):448–54.
57. Palmer G, Martling A, Cedermark B, Holm T. A population-based study on the management and outcome in patients with locally recurrent rectal cancer. Ann Surg Oncol. 2007;14(2):447–54.
58. Yu SK, Bhangu A, Tait DM, Tekkis P, Wotherspoon A, Brown G. Chemoradiotherapy response in recurrent rectal cancer. Cancer Med. 2014;3(1):111–7.
59. Mohiuddin M, Marks GM, Lingareddy V, Marks J. Curative surgical resection following reirradiation for recurrent rectal cancer. Int J Radiat Oncol Biol Phys. 1997;39(3):643–9.
60. Evans MD, Harji DP, Sagar PM, Wilson J, Koshy A, Timothy J, et al. Partial anterior sacrectomy with nerve preservation to treat locally advanced rectal cancer. Color Dis. 2013;15(6):e336–9.
61. Shaikh I, Holloway I, Aston W, et al. High subcortical sacrectomy: a novel approach to facilitate complete resection of locally advanced and recurrent rectal cancer with high (S1-S2) sacral extension. Color Dis. 2016;18(4):386–92.
62. Brown KG, Koh CE, Vasilaras A, Eisinger D, Solomon MJ. Clinical algorithms for the diagnosis and management of urological leaks following pelvic exenteration. Eur J Surg Oncol. 2014;40(6):775–81.
63. Platt E, Dovell G, Smolarek S. Systematic review of outcomes following pelvic exenteration for the treatment of primary and recurrent locally advanced rectal cancer. Tech Coloproctol. 2018;22(11):835–45.
64. Colibaseanu DT, Mathis KL, Abdelsattar ZM, Larson DW, Haddock MG, Dozois EJ. Is curative resection and long-term survival possible for locally re-recurrent colorectal cancer in the pelvis? Dis Colon Rectum. 2013;56(1):14–9.
65. Harji DP, Sagar PM, Boyle K, Maslekar S, Griffiths B, McArthur DR. Outcome of surgical resection of second-time locally recurrent rectal cancer. Br J Surg. 2013;100(3):403–9.

Appendiceal Neoplasms

33

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Key Concepts

- Appendiceal neoplasms are rare and typically present as incidental findings upon pathologic examination following appendectomy.
- Right colectomy should be considered for appendiceal adenocarcinoma, except for tumors limited to the submucosa.
- Benign mucinous neoplasms are adequately treated by appendectomy provided resection margins are clear.
- A perforated appendiceal tumor associated with peritoneal mucin should be treated with excision of the perforated lesion, peritoneal washings for cytology, and biopsy of any suspicious peritoneal lesions. Formal cytoreductive surgery should be delayed and performed by a specialized surgeon.
- Neuroendocrine tumors smaller than 2 cm are adequately treated with appendectomy alone.
- Neuroendocrine tumors larger than 2 cm, or those having high-risk features (incomplete resection, location at the base of the appendix, Ki 67 > 2%, lymphovascular or perineural invasion, mesoappendix invasion, grade 2 or greater) should be considered for right hemicolectomy.

Introduction

Appendiceal neoplasms are rare and most often present clinically as appendicitis [1]. Based on the histologic subtypes identified in a Surveillance, Epidemiology, and End Result (SEER) analysis, the individual incidence rates of appendiceal tumors between 1973 and 2001 ranged from 0.15 signet ring adenocarcinomas per 1,000,000 people per year to 1.3 mucinous tumors per 1,000,000 people per year. Appendiceal adenocarcinoma, "carcinoid" tumors, and goblet cell carcinoma were associated with intermediate incidence rates within this range [2]. While the definition of malignancy is often difficult to assess in administrative data, it has been reported as 0.12 age-adjusted cases per 1,000,000 people per year in an earlier review of SEER data [3].

The differential diagnosis of an appendiceal mass or thickening is quite extensive, and includes appendiceal mucinous neoplasms and adenocarcinoma subtypes, melanoma, leiomyoma, lipoma, fibroma, neuroma, lymphangioma, metastatic spread from other primary tumors (particularly ovarian) and cecal tumors involving the base of the appendix. Non-neoplastic causes of abnormalities of the appendix include Crohn's disease, neutropenic enterocolitis, tuberculosis, actinomycosis, mesenteric cystic disease, nonsteroidal anti-inflammatory drugs (NSAIDs)-induced damage, and, perhaps most importantly, appendicitis.

Appropriate diagnosis, and often times definitive treatment, requires appendectomy. A preoperative biopsy may be inconclusive and carries the risk of perforation, mucin extravasation, and increased risk of recurrence.

Epithelial Neoplasms

Epithelial neoplasms comprise different clinical entities, including invasive adenocarcinomas and benign mucinous neoplasms of variable histology, including low-grade appendiceal mucinous neoplasms (LAMNs) and high-grade appendiceal mucinous neoplasms (HAMNs). Goblet cell adenocarcinomas (GCAs), which were previously termed "goblet cell carcinoids" and "adenocarcinoids" and classified as neuroendocrine tumors, are now more appropriately classified as epithelial tumors [4].

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Adenocarcinoma

The histologic subtypes of this invasive malignancy include mucinous adenocarcinoma, non-mucinous adenocarcinoma, and, less commonly, signet ring cell adenocarcinoma. The latter is considered the most aggressive of the three subtypes. Adenocarcinomas of the appendix most commonly present as an incidental finding following appendectomy for suspected acute appendicitis. A recent SEER analysis of Medicare data indicated that 29% of patients older than 65 having an appendiceal cancer or neuroendocrine tumor first received an incorrect diagnosis of appendicitis between 2000 and 2014 [5].

Mucinous adenocarcinoma is associated with a propensity for local invasion and tumor perforation, leading to extravasation of mucin into the peritoneal cavity. This can lead to the development of pseudomyxoma peritonei, which will be covered in separately (see Chap. 35).

Staging of appendiceal adenocarcinoma is similar to staging for colorectal cancer. Computed tomography (CT) scan of the chest, abdomen, and pelvis is helpful to exclude distant metastases. In patients who cannot undergo CT, magnetic resonance imaging (MRI) of the abdomen and pelvis combined with chest radiograph is a reasonable alternative. Colonoscopy is recommended to rule out synchronous tumors. Carcinoembryonic antigen (CEA) should be measured, as it is useful in select cases to facilitate detection of recurrence. Measurement of other serum tumor markers such as cancer antigen 125 (CA-125) and carbohydrate antigen 19-9 (CA 19-9) is only indicated if the primary tumor site is unclear.

The prognosis of appendiceal adenocarcinoma is strongly affected by locoregional lymph node metastasis, distant metastatic disease, and tumor differentiation [6, 7]. Surprisingly, tumor perforation does not seem to be an obvious adverse prognosticator [8]. An additional determinant in the prognosis of appendiceal adenocarcinoma is the histologic subtype: signet ring type being associated with the worst prognosis; mucinous and intestinal type with an intermediate prognosis; and goblet cell with a more favorable prognosis [9]. A recent analysis of SEER data indicates that both overall survival and cancer-specific survival were comparable between mucinous and non-mucinous adenocarcinoma [10].

The treatment of appendiceal adenocarcinoma can be limited to simple appendectomy for tumors not extending beyond the submucosal layer; most of the remaining cases have been considered for right hemicolectomy. However, the recommendation for right hemicolectomy is controversial, as current data suggest comparable survival after appendectomy alone, and a relative rarity of nodal metastases in mucinous adenocarcinoma [11–13]. On the other hand, there are advocates of formal right hemicolectomy for all cases of appendiceal adenocarcinoma [14, 15]. We feel that the risks associated with right hemicolectomy are acceptable when balanced with the risks of lymph node metastasis. We therefore recommend right hemicolectomy except in cases of well-differentiated T1 tumors, or in patients with prohibitive co-morbidities. A particularly challenging scenario is the spontaneous perforation of an appendiceal tumor associated with the release of mucin into the peritoneal cavity. In the acute setting, the surgeon should remove the perforated lesion through either an appendectomy or right hemicolectomy, obtain peritoneal washings for cytology, and biopsy other suspicious peritoneal lesions. Formal cytoreductive surgery should be delayed to a later date and referred to specialized surgeons and/or centers. Prophylactic oophorectomy is not thought to be helpful.

Adjuvant therapy is largely modeled after colon cancer, as data specific for appendiceal adenocarcinoma are limited. Chemotherapy combinations include either infusional 5-fluorouracil, oxaliplatin, and leucovorin (FOLFOX) or oral capecitabine and oxaliplatin (CAPOX). Data from the National Cancer Database (NCDB) suggest that patients with either stage II or III adenocarcinoma benefit from adjuvant chemotherapy [7]. As overall survival is the only endpoint assessed in these datasets, it is unclear whether chemotherapy would have a similar effect when examining cancer-specific outcomes. In the absence of definitive data clarifying this issue, it is generally accepted that adjuvant chemotherapy should be considered for all patients with Stage III disease and select patients with Stage II disease, specifically those with T4 tumors, poor tumor differentiation, tumor perforation, or fewer than 12 evaluated lymph nodes in the surgical specimen. Patients suffering from metastatic disease (Stage IV) might also benefit from combination chemotherapy including irinotecan and bevacizumab. Second- and third-line treatment options similar to those available for colon cancer may also be attempted. The use of cytoreductive surgery for peritoneal carcinomatosis associated with advanced mucinous adenocarcinoma, with or without heated intraperitoneal chemotherapy (HIPEC), is reviewed in Chap. 35.

Surveillance following treatment of appendiceal adenocarcinoma mimics the recommendations and guidelines for resected colon adenocarcinoma.

Other Mucinous Lesions

The nomenclature of mucinous lesions has been clarified by the renewed classification proposed by the Peritoneal Surface Oncology Group International (PSOGI) [16, 17]. A *serrated polyp of the appendix* largely resembles its equivalent in the colon. A simple *mucocele* is the result of the distention of a mucin-filled appendix without evidence of mucosal hyperproliferation or neoplastic changes. Mucinous appendiceal

neoplasms are classified as *low-grade appendiceal mucinous neoplasms (LAMNs)* and *high-grade appendiceal mucinous neoplasms (HAMNs)*. Both are histologically dysplastic but lack an infiltrative growth pattern. LAMN and HAMN can be distinguished based on their degree of epithelial dysplasia. While HAMNs are staged using the same system as invasive adenocarcinoma because of its higher recurrence risk relative to LAMN, there is no conclusive evidence to support this designation [4]. It is widely accepted that HAMN is not associated with distant metastatic potential. When infiltration and invasion are present, the lesion is described as mucinous adenocarcinoma (see above). The term adenoma is not used to describe mucinous lesions and currently designates only those rare cases of appendiceal neoplasms having the same histology as their counterparts in the colon and rectum.

As mentioned in the Introduction, mucinous neoplasms are rare. They are frequently identified incidentally when performing diagnostic testing for unrelated reasons. This includes colonoscopy, where they may manifest as a raised, circumferential lesion with a central umbilication referred to as the "volcano sign" (Fig. 33.1). When symptoms are present, they can be limited to vague abdominal pain, bowel obstruction, or symptoms arising from tumor compression of an adjacent structure. A palpable mass indicates a larger neoplasm and is relatively uncommon. Mucinous neoplasms of the appendix are frequently identified as incidental findings on abdomino-pelvic CT. CT should also be considered as a diagnostic and staging test when an appendiceal tumor is suspected on colonoscopy. Sometimes, it is possible to identify peritoneal deposits of mucin or masses, which can be indicative of advanced and/or metastatic disease. Thickened or irregular appendiceal wall and concurrent calcifications are suggestive of a neoplasm and/or malignancy (Fig. 33.2). In general terms, a larger mass is more likely to be malignant than a smaller one, although there is no definitive size cutoff. Regardless, in most cases, it is difficult to accurately characterize the abnormal appendiceal mass as benign or malignant based on radiographic imaging. Abdominal ultrasound has been described as a useful imaging modality. In particular, the lesion's layered appearance has led to the term "onion skin sign," which has been described as pathognomonic for mucinous neoplasm [18]. However, ultrasound for this indication is rarely performed in the United States. Colonoscopy can also be used to assess the extent of the lesion in the cecum and can therefore be helpful in planning surgical intervention (appendectomy/cecectomy vs right colectomy). Colonoscopy is also indicated preoperatively to assess for synchronous colorectal neoplasia. The use of endoluminal ultrasound at the time of colonoscopy has been described, although this is not generally considered part of standard evaluation algorithms.

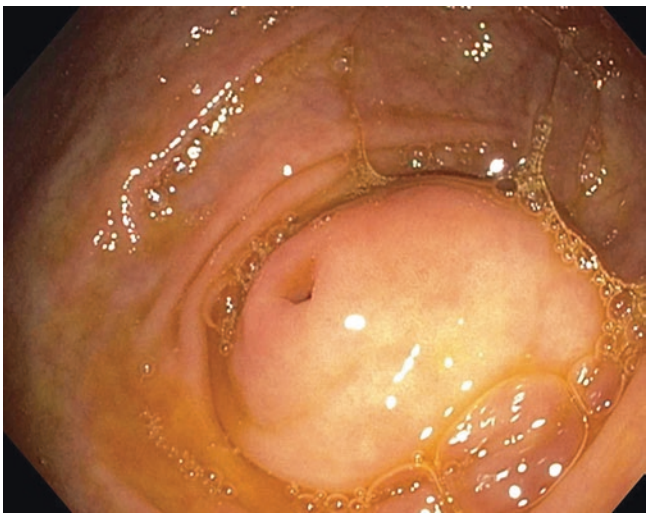

Fig. 33.1 Colonoscopy demonstrating a raised circumferential lesion with central umbilication referred to as the "volcano sign"

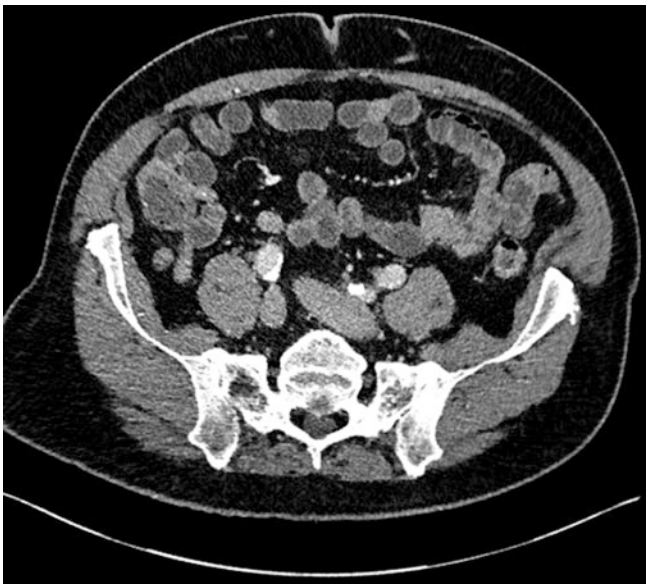

Fig. 33.2 Appendiceal dilatation with calcification suspicious for appendiceal neoplasm. The pathology after appendectomy revealed simple mucocele

Appropriate diagnosis, and often times definitive treatment, requires appendectomy. A preoperative biopsy may be inconclusive and carries the risk of perforation, mucin extravasation, and increased risk of recurrence. Depending on the specific location of the lesion within the appendix, it may be safer to excise in continuity the portion of the cecum surrounding the base of the appendix to ensure clear resection margins. In other cases, which may be possible to anticipate based on preoperative imaging, there can be direct involvement of the mesentery, mesocolon, and/or bowel.

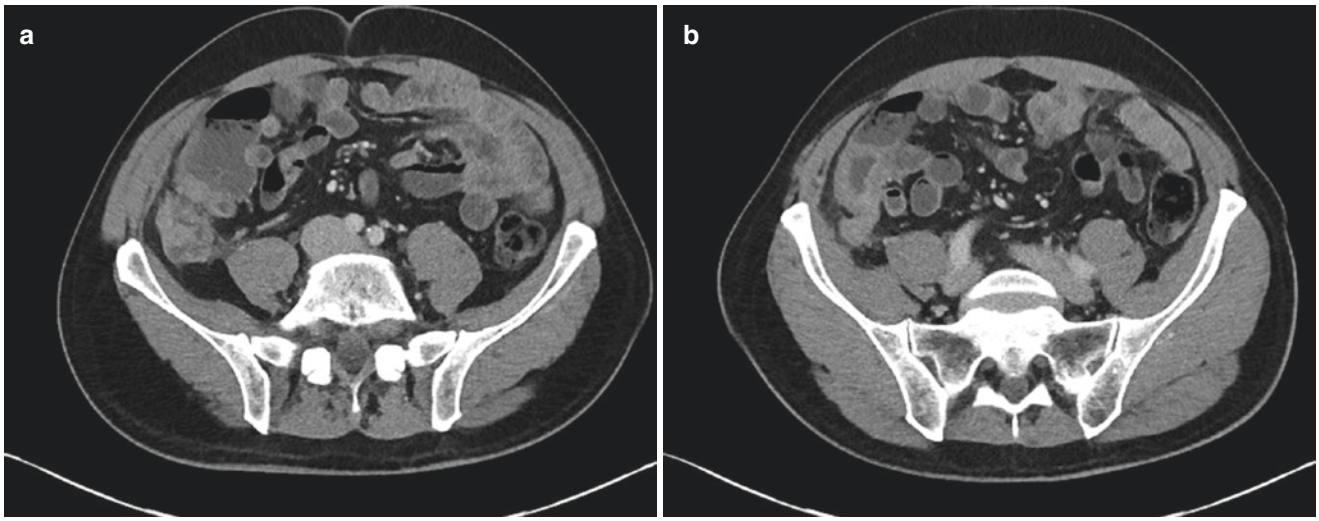

Fig. 33.3 Computed tomography scan showing replacement of the mid and distal portions of the appendix by a heterogeneous mass (**a**) associated with thickening of the adjacent cecal wall (**b**). This patient underwent right hemicolectomy. The pathology report indicated low-grade appendiceal mucinous neoplasm forming a 4 cm mass adherent to the cecum. Acellular mucin extended into the mesoappendix (T4a) and through the muscularis into the submucosa of the adjacent cecum

This finding typically prompts radical resection (Fig. 33.3a, b). An intraoperative frozen section has limited ability to accurately characterize mucinous tumors and will rarely lead to changes in operative treatment. More often, a pathologic diagnosis based on permanent specimen is necessary to dictate definitive management.

Patients having LAMN or HAMN limited to the appendix without perforation do not require any additional surgical treatment beyond appendectomy, provided there are clear resection margins. It is also questionable whether a completion right hemicolectomy is necessary when the appendectomy margins are histologically positive or have mucin on the resection margin [19]. There is agreement that the finding of mucin deposits on the serosal surface of the resected appendix (T4a) is a risk factor for peritoneal recurrence and subsequent pseudomyxoma peritonei (PMP). In particular, it is the identification of tumor cells outside of the appendix that is most closely associated with recurrence.[16] In two separate, comparative studies, the peritoneal recurrence rates associated with acellular mucin outside of the appendix were 4% and 7% at follow-up, compared with 33% and 75% in cases of cellular mucin, respectively [20, 21]. In this context, there is no evidence that a right hemicolectomy is associated with a reduction of PMP risk. Therefore, the general recommendation in these cases is surveillance with sequential imaging—generally performed with CT scans—although the specific intervals have not been established. Several authors have recommended CT intervals of 3–6 months during the initial 2 years of surveillance, and yearly afterward to 5 years [22, 23]. An alternative approach that may lead to earlier detection and optimized treatment is the use of diagnostic laparoscopy following index appendectomy in cases of either radiographically detected disease or empirically at 12 months postoperatively [24]. An even more aggressive, and controversial, approach for advanced stage neoplasms is what is referred to as "preemptive" cytoreductive surgery and HIPEC [25, 26]. Patients found to have peritoneal deposits of mucin should be referred to centers specializing in the treatment of peritoneal malignancies.

When LAMN is limited to the appendix, the prognosis is excellent. Even in cases of spread beyond the appendix, the prognosis remains relatively favorable with 5-year survival between 79% and 86% [27, 28]. The data regarding the prognostic implications of acellular mucin on the appendiceal surface are still limited but risk of recurrence is estimated to be between 5% and 20% [28, 29].

Neuroendocrine Tumors

Following the small bowel and rectum, the appendix is the third most frequent site for gastrointestinal neuroendocrine neoplasms (GI-NENs) [3, 30, 31]. The incidence of these tumors has been reported to be increasing in recent years, although it is unclear whether this is simply a reflection of changes in classification system, and/or increase in incidental detection at colonoscopy or operation for other pathology. Relatively speaking, appendiceal neuroendocrine neoplasms (aNENs) have a low prevalence in some cancer registries because they are often considered benign and cases are therefore not entered by all registrars [3]. In pediatric patients, aNEN is the second most common tumor of the bowel [32–34]. GI-NENs are frequently diagnosed during surgery for appendicitis or other abdominal treatments [35,

36]. In particular, aNEN discovered during appendectomy occurs at a rate of 0.3–2.3% [37–41]. The prevalence of aNEN among primary malignant tumors of the appendix ranges between 43% and 57% [1]. The most common histologic subtype of this tumor is giant cell carcinoma (GCC) at 59.6%, followed by malignant aNEN at 32.1%.

Many studies have shown a higher incidence of aNEN tumors among women as compared to men [42]. A review of the available studies also reveals that women predominantly present with initial tumor in the appendix, while men present initially with tumor in the small bowel. These findings may be the result of gynecological surgical intervention in female patients during which incidental appendectomy is performed [43]. aNEN displays an unusually early onset profile, with a maximum incidence in ages 15–19 years in women and 20–29 years in men [44]. In patients aged less than 35 years, the appendix represents the most frequent site for the tumor and there is some evidence indicating that patients with larger tumors and metastatic disease were younger than those with smaller and clinically benign tumors. The median age of patients with tumors greater than 2 cm was 31 years, and those with metastasis was 29 years, as compared to a median age of 42 years in patients with non-metastatic tumors [45].

The clinical presentation of aNEN is indistinguishable from that of appendicitis in over 54% of patients and obstructive features are present in 25% of cases [14, 46, 47]. The majority of aNEN occurs at the tip of the appendix, thus it is not surprising that obstruction of the lumen is relatively uncommon. However, non-appendicitis-like symptoms, such as intermittent abdominal pain in the right lower quadrant may be due to intermittent partial obstruction of the appendiceal lumen caused by the tumor. Because aNEN originates from neuroendocrine cells, one would think carcinoid syndrome is common. However, this is extremely rare as the hormones produced by the tumor are usually degraded in the liver. Symptoms of carcinoid syndrome are usually only present in the case of liver metastases.

Primary GI-NEN tumors typically evade standard radiographic detection until they are large enough to be evident on CT [48]. Cross-sectional radiographic studies (CT and MR) with both intravenous and luminal contrast have been reported to exhibit high sensitivity in identifying primary neoplasms of the small bowel [36]. However, luminal contrast is typically unhelpful in identifying tumors of the appendix, and therefore appendiceal tumors may be more difficult to detect until of relatively large size. Somatostatin receptor imaging (SRI) has been used successfully in staging GI-NEN [36, 49]. However, in a small retrospective study, it was not found to be reliable in pre-operative localization of aNENs [50]. SRI with Indium-111 pentetreotide imaging (octreotide) has been found similarly ineffective in identifying small tumors, especially aNEN <1 cm size [51]. However, this modality can be used to locate extra-hepatic and extra-abdominal tumor spread [52]. Octreotide studies with Ga-DOTATOC radiolabeling provide better spatial resolution and are now gaining support in staging of GI-NEN, but its usefulness in preoperative localization of small aNEN is not yet proven [49, 53].

Chromogranin A (CgA) is currently the most useful biomarker in the diagnostic algorithm for aNEN. CgA levels will not be elevated until the tumors are larger than 2 cm. Consequently, it is not a useful screening tool for aNEN [54, 55]. However, trending the levels of CgA regularly after initial treatment could help detecting recurrence or metastasis before these lesions can be detected radiographically [56]. Routine screening for 5-HIAA excretion is only recommended when the patient is suspected of having carcinoid syndrome [54].

Almost all primary endocrine tumors will exhibit CgA immunoreactivity [57]. While aNEN has some characteristics in common with tumors expressing cancer germline gene (CGG), it shows a stronger CgA and a weaker Ki67 marker [58, 59]. Additionally, a small proportion of aNEN tumors demonstrate abundant lipid accumulation and will need to be distinguished from giant cell carcinomas or signet ring adenocarcinomas [60].

Tumor size has traditionally been considered the most reliable indicator of malignant potential for aNEN. Tumor size greater than 2 cm in any dimension represents one of the most valuable predictive factors for lymph node metastases [36]. Over 95% of aNENs are less than 2 cm in size, with 60–85% being less than 1 cm in diameter and only 2–17% are greater than 2 cm [45, 46]. The risk of lymph node metastasis for tumors less than 1 cm is very low [61, 62].

The most reliable predictor for recurrence is location of the tumor. The majority of aNENs are located at the tip of the appendix, with 5–21% occurring in the body of the appendix and some 7–10% located at the base of the appendix [46, 47, 63]. Because incomplete resection is most likely to occur near the resection margin at the base of the appendix, such lesions are more likely to develop locoregional recurrence following a simple appendectomy compared to those located at the tip [55, 64]. Additionally, Grozinsky-Glasberg reported in 2013 that 33% of tumors located at the base of the appendix have metastases [54].

Mesoappendix invasion represents an extension of the tumor from the serosa into the pericolic fat. Despite the fact that serosal involvement alone is not usually considered an aggressive feature of the tumor, mesoappendix invasion is a strong predictor of worse prognosis and is considered an indication for right hemicolectomy. In 1979, Syracuse et al. reported that a small number of patients who had undergone right hemicolectomy for ≤1 cm aNEN had nodal metastasis when mesoappendix invasion was identified [65]. A study published in 2011 by Alexandraki found in 12 patients, 50% had mesoappendix invasion and 17% of those had one posi-

tive lymph node [55]. There is no correlation between mesoappendix invasion and tumor size or recurrence [35, 36].

Tumor proliferation markers may also predict potential metastases [36, 55]. A high Ki67 proliferation index or mitotic index has been demonstrated to predict aggressive biological behavior and decreased survival in aNEN [66, 67]. However, there is no correlation between high Ki67 index and tumor size or metastasis [68]. Vascular invasion is another indicator of potential aggressiveness. Sixty percent of patients with this invasion also exhibit lymph node metastases [54]. Similarly, patients with peritoneal invasion are also at increased risk for harboring lymph node metastases [54].

The American Joint Commission on Cancer (AJCC) staging system for aNEN is shown in Table 33.1. Stratification is primarily based on the size of the tumor and does not account for tumor grade or the other histologic features mentioned above which are associated with an increased risk of metastasis. The European Neuroendocrine Tumor Society (ENETS) staging does include tumor grade [36].

Treatment and prognosis are highly dependent on the size and degree of extension of the primary lesion. In the majority of cases, appendectomy is sufficient, as these tumors are usually small. No further staging or postoperative surveillance is necessary [36, 69]. Patients with Stage I tumors require only appendectomy, and while it is true that tumors at the base of the appendix are more likely to be insufficiently removed during appendectomy, this does not appear to be associated with a significantly worse prognosis [70]. For patients who have undergone an appendectomy when aNEN was present, it is recommended that the rest of the small bowel be examined prophylactically on a regular basis by visualization and palpation to ensure no other lesions are missed [36]. Right hemicolectomy is recommended for both stage II tumors of less than 2 cm diameter and for tumors up to 3 cm with serosal or mesoappendix invasion. For patients with aNEN greater than 2 cm but with no lymph node metastasis, there is no clear consensus regarding follow-up or surveillance recommendation. However, long-term follow-up is recommended for those with nodal, resected locoregional, or distant metastasis [71].

Table 33.1 American Joint Commission on Cancer (AJCC) staging system for aNEN

T Stage	TX	Primary tumor cannot be assessed
	Tis	Carcinoma in situ
	T1	Invades submucosa
	T2	Invades muscularis propria
	T3	Invades through muscularis propria
	T4a	Invades visceral peritoneum
	T4b	Invades all adjacent organs
Nodes	N0	No regional lymph node involvement
	N1	Metastasis to 1–3 regional nodes
	N2	Metastasis to ≥4 regional nodes
Metastasis	M0	No distant metastasis
	M1a	Intraperitoneal-only metastasis
	M1b	Extraperitoneal distant metastasis
Grade	GX	Cannot be determined
	G1	Well-differentiated
	G2	Moderately differentiated
	G3	Poorly differentiated
	G4	Undifferentiated
Stage	0	Tis, N0, M0
	I	T1/2, N0, M0
	IIA	T3, N0, M0
	IIB	T4a, N0, M0
	IIC	T4b, N0, M0
	IIIA	T1/2, N1, M0
	IIIB	T3/4, N1, M0
	IIIC	Any T, N2, M0
	IVA	Any T, N0, M1a, G1
	IVB	Any T, N0, M1a, any G
	IVC	Any T, any N, M1B, any G

In cases of incomplete resection of tumor at the base of the appendix, right hemicolectomy may be recommended. Patients should be informed about surgical complication rate and perioperative risk. No guidelines currently exist for the management of aNEN associated with perforated appendicitis. For those who present with distant metastasis at the time of presentation, it would seem reasonable to consider right hemicolectomy if the metastasis is considered resectable for cure. There are multiple systemic therapies that may be useful in treatment in combination with metastasectomy [55].

In conclusion, the appendix is the third most common location for neuroendocrine tumors of the GI tract. These tumors usually present as appendicitis and the majority are found after appendectomy on histologic review of the resected specimen. The prognosis of aNEN is significantly better than other neoplasms of the appendix [2]. For carcinoid tumors at the tip of the appendix and those tumors less than 2 cm in diameter, appendectomy is adequate treatment. Right hemicolectomy is recommended for larger tumors or when high-risk features are identified. However, there is little demonstrable difference in outcome between those offered only an appendectomy when compared to a right hemicolectomy and this may be due to the less aggressive nature of the tumor and a high 5-year survival rate [43, 72]. For the minority of patients who present with more extensive disease, or if surgery is not an option, treatment with somatostatin analogues has been shown to improve progression-free survival [36, 73]. There are scant reports of recurrence following a long postoperative interval in patients with tumors larger than 2 cm with local metastasis or with high risk features [63, 74]. Chromogranin A level can be used for surveillance, as these tumors are indolent. Yearly CgA level surveillance may be of benefit [54, 55]. Local recurrence or metastasis cannot easily be detected using

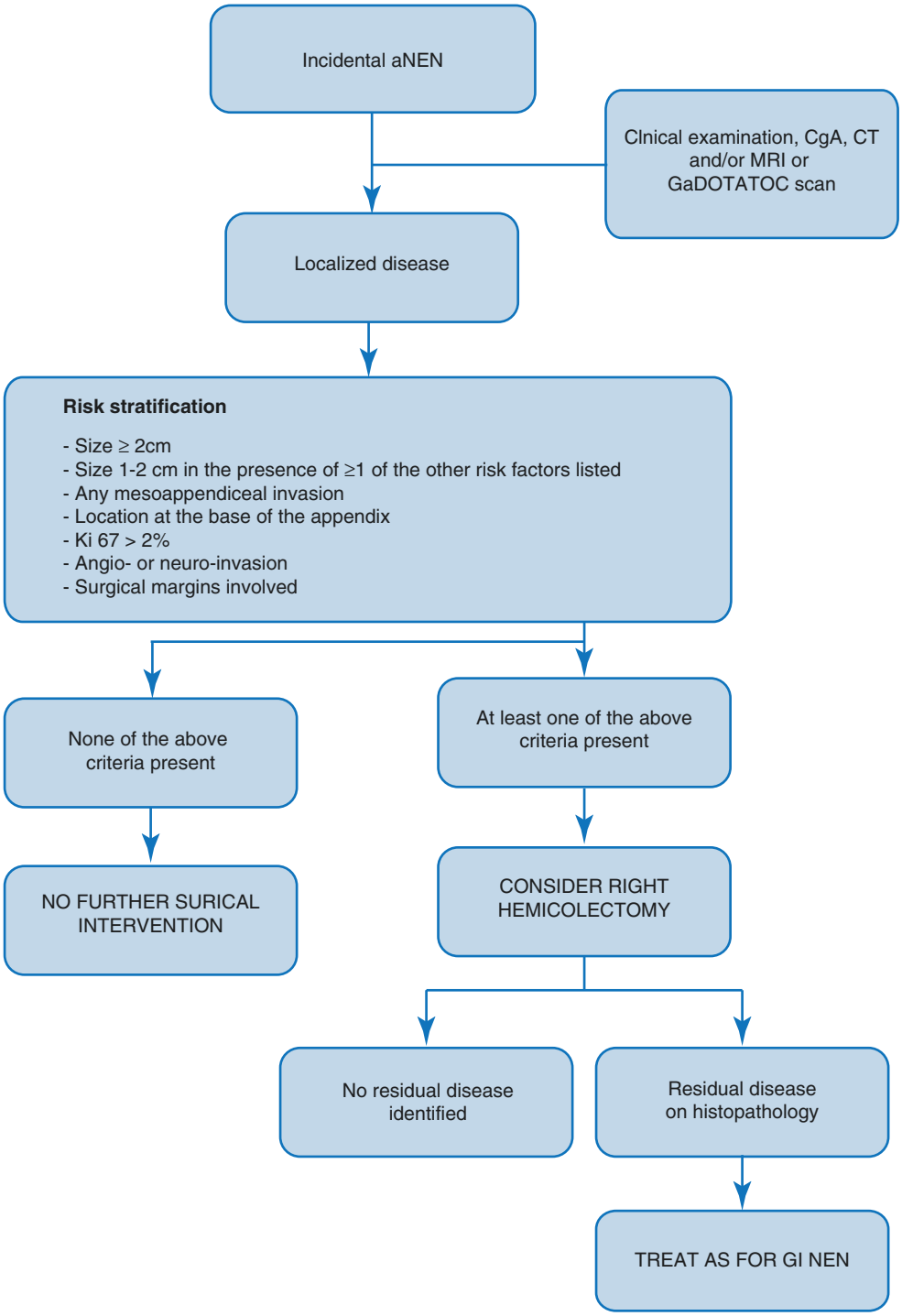

Fig. 33.4 Management of appendiceal neuroendocrine neoplasm. *aNEN* appendiceal neuroendocrine neoplasm, *CgA* Chromagranin A

current radiographic modalities. Usefulness of Ga-Octeotide PET studies needs to be evaluated in this regard. Yearly MRI and blood CgA may be useful in surveillance when there is residual disease after colectomy[68]. The algorithm in Fig. 33.4 shows the management of appendiceal neuroendocrine neoplasia.

Other Neoplasms

Goblet cell carcinoid tumors (GCC) are no longer considered aNENs but exhibit characteristics of both neuroendocrine tumors and appendiceal adenocarcinomas, differing in respect to their natural history, prognosis, and treatment [36].

They are composed of cells with secretory phenotypes including goblet cells, endocrine cells, and Paneth cells [75]. GCC can co-exist with high-grade adenocarcinoma, with the high-grade component dictating the treatment and prognosis.

Clear cell carcinoid tumors have been described only in case studies as they are exceedingly rare [76]. These tumors are filled with clear cells and abundant amounts of lipid. They may have a superficial resemblance to GCC or they may represent an appendiceal metastasis from clear cell carcinoma of non-appendiceal origin [60, 77].

References

1. Connor SJ, Hanna GB, Frizelle FA. Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. Dis Colon Rectum. 1998;41(1):75–80. https://doi.org/10.1007/bf02236899.
2. McGory ML, Maggard MA, Kang H, O'Connell JB, Ko CY. Malignancies of the appendix: beyond case series reports. Dis Colon Rectum. 2005;48(12):2264–71. https://doi.org/10.1007/s10350-005-0196-4.
3. McCusker ME, Coté TR, Clegg LX, Sobin LH. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973–1998. Cancer. 2002;94(12):3307–12. https://doi.org/10.1002/cncr.10589.
4. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020;76(2):182–8. https://doi.org/10.1111/his.13975.
5. Siddharthan RV, Byrne RM, Dewey E, Martindale RG, Gilbert EW, Tsikitis VL. Appendiceal cancer masked as inflammatory appendicitis in the elderly, not an uncommon presentation (Surveillance Epidemiology and End Results (SEER)-Medicare Analysis). J Surg Oncol. 2019;120(4):736–9. https://doi.org/10.1002/jso.25641.
6. Amin MB, Edge SB, Greene FL, et al. AJCC Cancer Staging Manual. 8th ed. 2017, Corr. 3rd printing 2018 edition. Chicago: Springer; 2018.
7. Asare EA, Compton CC, Hanna NN, et al. The impact of stage, grade, and mucinous histology on the efficacy of systemic chemotherapy in adenocarcinomas of the appendix: analysis of the National Cancer Data Base. Cancer. 2016;122(2):213–21. https://doi.org/10.1002/cncr.29744.
8. Nash GM, Smith JD, Tang L, et al. Lymph node metastasis predicts disease recurrence in a single-center experience of 70 stages 1-3 appendix cancers: a retrospective review. Ann Surg Oncol. 2015;22(11):3613–7. https://doi.org/10.1245/s10434-015-4415-5.
9. Turaga KK, Pappas SG, Gamblin TC. Importance of histologic subtype in the staging of appendiceal tumors. Ann Surg Oncol. 2012;19(5):1379–85. https://doi.org/10.1245/s10434-012-2238-1.
10. Widmann B, Warschkow R, Schmied BM, Marti L, Steffen T. Impact of mucinous histology on the prognosis of stage I-III adenocarcinomas of the appendix: a population-based, Propensity Score-Matched analysis. J Gastrointest Surg. 2016;20(8):1493–502. https://doi.org/10.1007/s11605-016-3148-5.
11. Hata K, Tanaka N, Nomura Y, Wada I, Nagawa H. Early appendiceal adenocarcinoma. A review of the literature with special reference to optimal surgical procedures. J Gastroenterol. 2002;37(3):210–4. https://doi.org/10.1007/s005350200023.
12. Turaga KK, Pappas S, Gamblin TC. Right hemicolectomy for mucinous adenocarcinoma of the appendix: just right or too much? Ann Surg Oncol. 2013;20(4):1063–7. https://doi.org/10.1245/s10434-012-2783-7.
13. Sugarbaker PH. When and when not to perform a right colon resection with mucinous appendiceal neoplasms. Ann Surg Oncol. 2017;24(3):729–32. https://doi.org/10.1245/s10434-016-5632-2.
14. O'Donnell ME, Badger SA, Beattie GC, Carson J, Garstin WIH. Malignant neoplasms of the appendix. Int J Color Dis. 2007;22(10):1239–48. https://doi.org/10.1007/s00384-007-0304-0.
15. Gahagan JV, Whealon MD, Phelan MJ, et al. Lymph node positivity in appendiceal adenocarcinoma: should size matter? J Am Coll Surg. 2017;225(1):69–75. https://doi.org/10.1016/j.jamcollsurg.2017.01.056.
16. Carr NJ, McCarthy WF, Sobin LH. Epithelial noncarcinoid tumors and tumor-like lesions of the appendix. A clinicopathologic study of 184 patients with a multivariate analysis of prognostic factors. Cancer. 1995;75(3):757–68. https://doi.org/10.1002/1097-0142(19950201)75:3<757::aid-cncr2820750303>3.0.co;2-f.
17. Carr NJ, Bibeau F, Bradley RF, et al. The histopathological classification, diagnosis and differential diagnosis of mucinous appendiceal neoplasms, appendiceal adenocarcinomas and pseudomyxoma peritonei. Histopathology. 2017;71(6):847–58. https://doi.org/10.1111/his.13324.
18. Degani S, Shapiro I, Leibovitz Z, Ohel G. Sonographic appearance of appendiceal mucocele. Ultrasound Obstet Gynecol. 2002;19(1):99–101. https://doi.org/10.1046/j.1469-0705.2002.00510.x.
19. Arnason T, Kamionek M, Yang M, Yantiss RK, Misdraji J. Significance of proximal margin involvement in low-grade appendiceal mucinous neoplasms. Arch Pathol Lab Med. 2015;139(4):518–21. https://doi.org/10.5858/arpa.2014-0246-OA.
20. Yantiss RK, Shia J, Klimstra DS, Hahn HP, Odze RD, Misdraji J. Prognostic significance of localized extra-appendiceal mucin deposition in appendiceal mucinous neoplasms. Am J Surg Pathol. 2009;33(2):248–55. https://doi.org/10.1097/PAS.0b013e31817ec31e.
21. Pai RK, Beck AH, Norton JA, Longacre TA. Appendiceal mucinous neoplasms: clinicopathologic study of 116 cases with analysis of factors predicting recurrence. Am J Surg Pathol. 2009;33(10):1425–39. https://doi.org/10.1097/PAS.0b013e3181af6067.
22. Choudry HA, Pai RK. Management of mucinous appendiceal tumors. Ann Surg Oncol. 2018;25(8):2135–44. https://doi.org/10.1245/s10434-018-6488-4.
23. Honoré C, Caruso F, Dartigues P, et al. Strategies for preventing Pseudomyxoma Peritonei after resection of a mucinous neoplasm of the appendix. Anticancer Res. 2015;35(9):4943–7.
24. Foster JM, Sleightholm RL, Wahlmeier S, Loggie B, Sharma P, Patel A. Early identification of DPAM in at-risk low-grade appendiceal mucinous neoplasm patients: a new approach to surveillance for peritoneal metastasis. World J Surg Oncol. 2016;14(1):243. https://doi.org/10.1186/s12957-016-0996-0.
25. Fish R, Selvasekar C, Crichton P, et al. Risk-reducing laparoscopic cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for low-grade appendiceal mucinous neoplasm: early outcomes and technique. Surg Endosc. 2014;28(1):341–5. https://doi.org/10.1007/s00464-013-3189-8.
26. McDonald JR, O'Dwyer ST, Rout S, et al. Classification of and cytoreductive surgery for low-grade appendiceal mucinous neoplasms. Br J Surg. 2012;99(7):987–92. https://doi.org/10.1002/bjs.8739.
27. Misdraji J, Yantiss RK, Graeme-Cook FM, Balis UJ, Young RH. Appendiceal mucinous neoplasms: a clinicopathologic analysis of 107 cases. Am J Surg Pathol. 2003;27(8):1089–103. https://doi.org/10.1097/00000478-200308000-00006.
28. Fournier K, Rafeeq S, Taggart M, et al. Low-grade Appendiceal Mucinous Neoplasm of Uncertain Malignant Potential (LAMN-

UMP): prognostic factors and implications for treatment and follow-up. Ann Surg Oncol. 2017;24(1):187–93. https://doi.org/10.1245/s10434-016-5588-2.
29. Guaglio M, Sinukumar S, Kusamura S, et al. Clinical surveillance after macroscopically complete surgery for Low-Grade Appendiceal Mucinous Neoplasms (LAMN) with or without limited peritoneal spread: long-term results in a prospective series. Ann Surg Oncol. 2018;25(4):878–84. https://doi.org/10.1245/s10434-018-6341-9.
30. Crocetti E. Gastrointestinal carcinoid tumours. A population-based study. Ital J Gastroenterol Hepatol. 1997;29(2):135–7.
31. Maggard MA, O'Connell JB, Ko CY. Updated population-based review of carcinoid tumors. Ann Surg. 2004;240(1):117–22. https://doi.org/10.1097/01.sla.0000129342.67174.67.
32. Parkes SE, Muir KR, al Sheyyab M, et al. Carcinoid tumours of the appendix in children 1957–1986: incidence, treatment and outcome. Br J Surg. 1993;80(4):502–4. https://doi.org/10.1002/bjs.1800800433.
33. Corpron CA, Black CT, Herzog CE, Sellin RV, Lally KP, Andrassy RJ. A half century of experience with carcinoid tumors in children. Am J Surg. 1995;170(6):606–8. https://doi.org/10.1016/s0002-9610(99)80025-7.
34. Scott A, Upadhyay V. Carcinoid tumours of the appendix in children in Auckland, New Zealand: 1965–2008. N Z Med J. 2011;124(1331):56–60.
35. Moertel CL, Weiland LH, Telander RL. Carcinoid tumor of the appendix in the first two decades of life. J Pediatr Surg. 1990;25(10):1073–5. https://doi.org/10.1016/0022-3468(90)90221-t.
36. Pape U-F, Perren A, Niederle B, et al. ENETS consensus guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. Neuroendocrinology. 2012;95(2):135–56. https://doi.org/10.1159/000335629.
37. Shapiro R, Eldar S, Sadot E, Venturero M, Papa MZ, Zippel DB. The significance of occult carcinoids in the era of laparoscopic appendectomies. Surg Endosc. 2010;24(9):2197–9. https://doi.org/10.1007/s00464-010-0926-0.
38. Yilmaz M, Akbulut S, Kutluturk K, et al. Unusual histopathological findings in appendectomy specimens from patients with suspected acute appendicitis. World J Gastroenterol. 2013;19(25):4015–22. https://doi.org/10.3748/wjg.v19.i25.4015.
39. Hatzipantelis E, Panagopoulou P, Sidi-Fragandrea V, Fragandrea I, Koliouskas DE. Carcinoid tumors of the appendix in children: experience from a tertiary center in northern Greece. J Pediatr Gastroenterol Nutr. 2010;51(5):622–5. https://doi.org/10.1097/MPG.0b013e3181e05358.
40. Ozer MT, Demirbas S, Celik E, et al. Natural behaviour and surgical treatment of appendiceal carcinoids: an analysis of 2,376 consecutive emergency appendectomies. Bratisl Lek Listy. 2011;112(11):619–22.
41. Doede T, Foss HD, Waldschmidt J. Carcinoid tumors of the appendix in children–epidemiology, clinical aspects and procedure. Eur J Pediatr Surg. 2000;10(6):372–7. https://doi.org/10.1055/s-2008-1072394.
42. Shaib W, Krishna K, Kim S, et al. Appendiceal neuroendocrine, goblet and signet-ring cell tumors: a spectrum of diseases with different patterns of presentation and outcome. Cancer Res Treat. 2016;48(2):596–604. https://doi.org/10.4143/crt.2015.029.
43. Carpenter SG, Chapital AB, Merritt MV, Johnson DJ. Increased risk of neoplasm in appendicitis treated with interval appendectomy: single-institution experience and literature review. Am Surg. 2012;78(3):339–43.
44. Hemminki K, Li X. Incidence trends and risk factors of carcinoid tumors: a nationwide epidemiologic study from Sweden. Cancer. 2001;92(8):2204–10. https://doi.org/10.1002/1097-0142(20011015)92:8<2204::aid-cncr1564>3.0.co;2-r.
45. Moertel CG, Weiland LH, Nagorney DM, Dockerty MB. Carcinoid tumor of the appendix: treatment and prognosis. N Engl J Med. 1987;317(27):1699–701. https://doi.org/10.1056/NEJM198712313172704.
46. Roggo A, Wood WC, Ottinger LW. Carcinoid tumors of the appendix. Ann Surg. 1993;217(4):385–90. https://doi.org/10.1097/00000658-199304000-00010.
47. Prommegger R, Obrist P, Ensinger C, Profanter C, Mittermair R, Hager J. Retrospective evaluation of carcinoid tumors of the appendix in children. World J Surg. 2002;26(12):1489–92. https://doi.org/10.1007/s00268-002-6440-3.
48. Wallace S, Ajani JA, Charnsangavej C, et al. Carcinoid tumors: imaging procedures and interventional radiology. World J Surg. 1996;20(2):147–56. https://doi.org/10.1007/s002689900023.
49. Sundin A, Vullierme M-P, Kaltsas G, Plöckinger U. Mallorca Consensus Conference participants, European Neuroendocrine Tumor Society. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological examinations. Neuroendocrinology. 2009;90(2):167–83. https://doi.org/10.1159/000184855.
50. Coursey CA, Nelson RC, Moreno RD, Dodd LG, Patel MB, Vaslef S. Carcinoid tumors of the appendix: are these tumors identifiable prospectively on preoperative CT? Am Surg. 2010;76(3):273–5.
51. Kwekkeboom DJ, Krenning EP, Scheidhauer K, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: somatostatin receptor imaging with (111)in-pentetreotide. Neuroendocrinology. 2009;90:184. https://doi.org/10.1159/000225946.
52. Kisker O, Weinel RJ, Geks J, Zacara F, Joseph K, Rothmund M. Value of somatostatin receptor scintigraphy for preoperative localization of carcinoids. World J Surg. 1996;20(2):162–7. https://doi.org/10.1007/s002689900025.
53. Gabriel M, Decristoforo C, Kendler D, et al. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. J Nucl Med. 2007;48(4):508–18. https://doi.org/10.2967/jnumed.106.035667.
54. Grozinsky-Glasberg S, Alexandraki KI, Barak D, et al. Current size criteria for the management of neuroendocrine tumors of the appendix: are they valid? Clinical experience and review of the literature. Neuroendocrinology. 2013;98(1):31–7. https://doi.org/10.1159/000343801.
55. Alexandraki KI, Griniatsos J, Bramis KI, et al. Clinical value of right hemicolectomy for appendiceal carcinoids using pathologic criteria. J Endocrinol Investig. 2011;34(4):255–9. https://doi.org/10.1007/BF03347081.
56. Kaltsas G, Rockall A, Papadogias D, Reznek R, Grossman AB. Recent advances in radiological and radionuclide imaging and therapy of neuroendocrine tumours. Eur J Endocrinol. 2004;151(1):15–27. https://doi.org/10.1530/eje.0.1510015.
57. Perez MA, Saul SH, Trojanowski JQ. Neurofilament and chromogranin expression in normal and neoplastic neuroendocrine cells of the human gastrointestinal tract and pancreas. Cancer. 1990;65(5):1219–27. https://doi.org/10.1002/1097-0142(19900301)65:5<1219::aid-cncr2820650531>3.0.co;2-w.
58. Alsaad KO, Serra S, Perren A, Hsieh E, Chetty R. CK19 and CD99 immunoexpression profile in goblet cell (mucin-producing neuroendocrine tumors) and classical carcinoids of the vermiform appendix. Int J Surg Pathol. 2007;15(3):252–7. https://doi.org/10.1177/1066896907302118.
59. Jiang Y, Long H, Wang W, Liu H, Tang Y, Zhang X. Clinicopathological features and immunoexpression profiles of goblet cell carcinoid and typical carcinoid of the appendix. Pathol Oncol Res. 2011;17(1):127–32. https://doi.org/10.1007/s12253-010-9291-5.

60. Chetty R, Serra S. Lipid-rich and clear cell neuroendocrine tumors ("carcinoids") of the appendix: potential confusion with goblet cell carcinoid. Am J Surg Pathol. 2010;34(3):401–4. https://doi.org/10.1097/PAS.0b013e3181ce9204.
61. Stinner B, Kisker O, Zielke A, Rothmund M. Surgical management for carcinoid tumors of small bowel, appendix, colon, and rectum. World J Surg. 1996;20(2):183–8. https://doi.org/10.1007/s002689900028.
62. Murray SE, Lloyd RV, Sippel RS, Chen H, Oltmann SC. Postoperative surveillance of small appendiceal carcinoid tumors. Am J Surg. 2014;207(3):342–5.; ; discussion 345. https://doi.org/10.1016/j.amjsurg.2013.08.038.
63. Fornaro R, Frascio M, Sticchi C, et al. Appendectomy or right hemicolectomy in the treatment of appendiceal carcinoid tumors? Tumori. 2007;93(6):587–90.
64. Sutton R, Doran HE, Williams EMI, et al. Surgery for midgut carcinoid. Endocr Relat Cancer. 2003;10(4):469–81. https://doi.org/10.1677/erc.0.0100469.
65. Syracuse DC, Perzin KH, Price JB, Wiedel PD, Mesa-Tejada R. Carcinoid tumors of the appendix. Mesoappendiceal extension and nodal metastases. Ann Surg. 1979;190(1):58–63. https://doi.org/10.1097/00000658-197907000-00013.
66. Van Eeden S, Quaedvlieg PFHJ, Taal BG, Offerhaus GJA, Lamers CBHW, Van Velthuysen M-LF. Classification of low-grade neuroendocrine tumors of midgut and unknown origin. Hum Pathol. 2002;33(11):1126–32. https://doi.org/10.1053/hupa.2002.129204.
67. Liu E, Telem DA, Hwang J, Warner RRP, Dikman A, Divino CM. The clinical utility of Ki-67 in assessing tumor biology and aggressiveness in patients with appendiceal carcinoids. J Surg Oncol. 2010;102(4):338–41. https://doi.org/10.1002/jso.21634.
68. Alexandraki KI, Kaltsas GA, Grozinsky-Glasberg S, Chatzellis E, Grossman AB. Appendiceal neuroendocrine neoplasms: diagnosis and management. Endocr Relat Cancer. 2016;23(1):R27–41. https://doi.org/10.1530/ERC-15-0310.
69. Boudreaux JP, Klimstra DS, Hassan MM, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. Pancreas. 2010;39(6):753–66. https://doi.org/10.1097/MPA.0b013e3181ebb2a5.
70. Bucher P, Mathe Z, Demirag A, Morel P. Appendix tumors in the era of laparoscopic appendectomy. Surg Endosc. 2004;18(7):1063–6. https://doi.org/10.1007/s00464-003-9255-x.
71. Kelly KJ. Management of appendix cancer. Clin Colon Rectal Surg. 2015;28(4):247–55. https://doi.org/10.1055/s-0035-1564433.
72. Groth SS, Virnig BA, Al-Refaie WB, Jarosek SL, Jensen EH, Tuttle TM. Appendiceal carcinoid tumors: predictors of lymph node metastasis and the impact of right hemicolectomy on survival. J Surg Oncol. 2011;103(1):39–45. https://doi.org/10.1002/jso.21764.
73. Arnold R. Endocrine tumours of the gastrointestinal tract. Introduction: definition, historical aspects, classification, staging, prognosis and therapeutic options. Best Pract Res Clin Gastroenterol. 2005;19(4):491–505. https://doi.org/10.1016/j.bpg.2005.03.006.
74. Svendsen LB, Bülow S. Carcinoid tumours of the appendix in young patients. Acta Chir Scand. 1980;146(2):137–9.
75. Yozu M, Johncilla ME, Srivastava A, et al. Histologic and outcome study supports reclassifying appendiceal goblet cell carcinoids as goblet cell adenocarcinomas, and grading and staging similarly to colonic adenocarcinomas. Am J Surg Pathol. 2018;42(7):898–910. https://doi.org/10.1097/PAS.0000000000001056.
76. Rossi G, Nannini N, Bertolini F, Mengoli MC, Fano R, Cavazza A. Clear cell carcinoid of the appendix: an uncommon variant of lipid-rich neuroendocrine tumor with a broad differential diagnosis. Endocr Pathol. 2010;21(4):258–62. https://doi.org/10.1007/s12022-010-9132-9.
77. Kang GH, Lee BS, Kang DY. Clear cell carcinoid of the appendix: report of two cases with literature review. Pathol Int. 2015;65(6):324–8. https://doi.org/10.1111/pin.12284.

Gastrointestinal Stromal Tumors, Neuroendocrine Tumors, and Lymphoma

34

Karim Alavi and Marylise Boutros

Key Concepts

- The majority of gastrointestinal stromal tumors (GISTs) stain positive for CD117 and have an alteration in *c-kit* proto-oncogene.
- Surgical excision with a 1–2 cm margin is the preferred treatment for GISTs located in the rectum.
- Treatment of midgut neuroendocrine tumors (NETs) is segmental resection with lymphadenectomy.
- Somatostatin analogs control the symptoms of carcinoid syndrome and help limit the progression of disease.
- Rectal NETs less than 1 cm in diameter may be treated by endoscopic or local excision, while tumors greater than 2 cm should be considered for radical resection.
- Patients with symptomatic colonic lymphomas are best treated with surgical resection prior to chemotherapy.

Gastrointestinal Stromal Tumors (GISTs)

Introduction

Gastrointestinal tumors (GISTs), originally thought to have originated from mesenchymal cells, actually arise from the interstitial cells of Cajal, the pacemaker cells of the gastrointestinal (GI) tract [1]. These cells are located within the muscular layer of the GI tract and coordinate autonomic movements [2]. GISTs comprise 20% of soft tissue sarcomas with an annual incidence of approximately 10 per million [3]. All GISTs are thought to have malignant potential, with 10–30% progressing to malignancy [4].

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Histology and Molecular Biology

The diagnosis of GIST is confirmed by both histopathology and immunochemistry. There are three different histologic subtypes, including spindle (70%), epithelioid (20%), or mixed type (10%). It is not uncommon for GISTs to be mischaracterized as leiomyoma or leiomyosarcomas prior to immunohistochemical analysis [5]. The majority of GISTs stain for CD117, a marker for type III receptor tyrosine kinase KIT (95%) [6] and anoctamin-1(DOG-1; 98%) [7]. Approximately 60–70% stain positive for CD34, a hematopoietic progenitor cell antigen. However, they do not stain for smooth muscle biomarkers such as desmin. These features help differentiate GISTs from leiomyomas which stain positive for desmin, S100, and smooth muscle actin [8].

The *c-kit* proto-oncogene encodes KIT. Alterations in the gene result from point mutations, deletions, and insertions in exons 11 and 9. KIT alterations are present in 70–80% of GISTs [9]. While mutations in exon 11 are responsible for the longest duration of response to imatinib and improved survival, mutations in exon 9 are responsible for a shorter duration of response to imatinib and overall poorer survival in advanced disease [9]. A mutation in platelet derived growth factor receptor A (PDGFRA), in exons 18, 12, and 14 on chromosome 4, is present in 10–20% of GISTs. With few exceptions, mutations in PDGFRA are associated with a similar response rate and overall outcome to medical therapy, as KIT mutations [10].

Previously, patients without a mutation in either KIT or PDGFRA were considered to harbor wild-type (WT) GISTs. More recent evidence suggests they may have a mutation in succinate dehydrogenase (SDH) complex gene, an enzyme involved in the Krebs' cycle, which leads to failed DNA methylation [11]. Mutation analysis of KIT and PDGFRA is mandatory for optimal care of GIST patients. In the absence of KIT or PDGFRA mutations, tumor immunostaining for SDH is recommended, as the absence of staining indicates a possible SDH mutation. These patients may subsequently

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need genetic counseling as the presence of SDH mutation suggests a heritable condition, in which patients present at a younger age and are prone to be afflicted with multifocal disease [8].

Incidence and Distribution

The majority (97%) of GISTs present sporadically at a median age of 65 (range, 10–100) with a 1:1 male to female ratio [5]. There are no known risk factors unless they present as part of tumor familial syndromes, including neurofibromatosis type 1, Carney–Stratakis syndrome, and Carney triad. Neurofibromatosis type 1 presents with multifocal intestinal GISTs that harbor mutated NF1 gene. The Carney–Stratakis syndrome harbors a germline mutation in the SDH complex genes. These patients present at a young age and have a high risk of gastric GIST and paragangliomas. The Carney triad, a possible variant of multiple endocrine neoplasia, consists of multiple gastric GISTs in young females, paraganglioma, and pulmonary chordoma. Esophageal leiomyomas, pheochromocytomas, and adrenocortical adenomas have also been described as part of this condition. Patients with Carney triad or Carney–Stratakis syndrome do not have KIT or PDGFRA mutations but may harbor a mutation in the SDH gene [12].

GISTs are most commonly found in the stomach (56%), followed by the small bowel (32%). Tumors of the colon and rectum account for 5–10% of GISTs with the majority arising in the rectum. GISTs may also arise in extragastrointestinal locations, principally in the mesentery, omentum, and retroperitoneum [13].

Clinical Presentation

GISTs are slow-growing tumors, which are often discovered incidentally during endoscopy, on abdominal cross-sectional imaging, or during surgery for other conditions. Presenting symptoms are variable and are largely dependent on location and behavior of the tumor. In the GI tract, GISTs can erode through the mucosa into the lumen, presenting with bleeding, or outward through the serosa, presenting with peritonitis. Symptomatic patients may present with nonspecific symptoms of nausea, vomiting, abdominal distension, early satiety, abdominal pain, and rarely as a palpable abdominal mass. Large tumors may cause intrinsic or extrinsic compression of the GI tract with presenting symptoms largely dependent on location, such as constipation or large bowel obstruction for distal colon or rectal GISTs [5, 14].

Approximately 20% of patients have overt metastases at diagnosis. The most common location is the liver followed by the peritoneal cavity. Metastases to the lungs, bone, and lymph nodes are rare. Increased likelihood of metastasis is associated with GISTs >5 cm and > 5 mitosis per 50 high power field (HPF), and GISTs >10 cm with any mitotic rate [15]. Studies have shown that tumor location is an important prognostic indicator. Miettinen and colleagues demonstrated that a non-gastric tumor of the same size and mitotic index has a higher risk of recurrence than a gastric tumor [4]. Joensuu and colleagues created the modified National Institutes of Health (NIH) classification, which determined that tumor rupture is a negative prognostic indicator. In sum, a GIST is considered high risk if the tumor is >10 cm with any mitotic index, the tumor is >5 cm with a mitotic count >5/50 HPF, or if it has ruptured. Following resection of a nonruptured GIST, the mitotic rate is the most important prognostic factor and determines the need for further adjuvant therapy [3].

Diagnosis

Definitive diagnosis of GIST is often made based on histopathologic evaluation of the excised tumor. However, the submucosal location of the lesion often makes pre-operative diagnosis challenging. Without mucosal ulceration, the diagnostic yield from mucosal biopsy is low. The diagnostic yield of endoscopy can be enhanced with the addition of endoscopic ultrasound (EUS) and fine needle aspiration (FNA) [16, 17]. Percutaneous biopsy is an option for tumors deemed inaccessible by endoscopy. CT-guided percutaneous biopsy of large GISTs is not without risk as these lesions are highly vascular and biopsy may be associated with hemorrhage [18]. Biopsy also risks tumor rupture and dissemination, and should generally only be performed in the setting of metastatic disease, unresectable tumor, or suspicion for lymphoma [19, 20].

Contrast-enhanced computed tomography (CT), specifically CT enterography, and magnetic resonance imaging (MRI) are often the initial imaging modalities and may aid in determining tumor location, perforation, invasion to nearby structures, and distant metastasis [17]. GISTs typically involve the muscularis propria and radiographically have the appearance of a well-circumscribed mass. MRI is preferred when evaluating rectal or duodenal GISTs, and can be performed serially without risk of radiation exposure, when evaluating tumor response to chemotherapy [21, 22]. Finally, positron emission tomography (PET) is not typically thought to be useful in the diagnosis of GIST but may have utility in evaluating response to treatment [5].

Treatment

Surgery

Surgical excision remains the gold standard for localized GIST. The goal is to completely excise the lesion with a 1–2 cm margin avoiding tumor rupture or violation of the accompanying pseudo-capsule, which leads to tumor seeding (Fig. 34.1). Given the absence of spread to draining lymph nodes, lymph node dissection is not necessary [23, 24]. Tumor location will dictate the extent of resection. Tumors of the small bowel or colon dictate a segmental resection using either a minimally invasive or open approach. Tumors of the rectosigmoid junction or upper rectum often necessitate an anterior resection. Management of GISTs of the mid to low rectum is largely dependent on size, distance to anal verge, rectal anatomy, and involvement of the sphincter complex. GISTs in this location can be managed by either a full thickness excision using any of a variety of available transanal platforms, such as transanal endoscopic microsurgery (TEM), transanal endoscopic operation (TEO), or transanal minimally invasive surgery (TAMIS). Regardless of the approach, several studies have shown that the local excision of rectal GIST is associated with higher recurrence rates as compared with radical resection. Changchien et al. reported outcomes on a series of patients who underwent local excision for rectal GISTs. Despite a smaller mean tumor size in the local excision group as compared to the radical resection group (4.5 cm vs. 7.2 cm), the local excision group experienced a higher local recurrence rate (77% vs. 31%) [25]. Low anterior resection or abdominoperineal resection may be necessary for large, bulky tumors of the lower rectum that are unresponsive or minimally responsive to neo-adjuvant therapy. However, many of these tumors are now treated with neo-adjuvant chemotherapy, which may limit the need for radical resection.

Medical Therapy

Imatinib mesylate (Gleevec; Novartis Pharmaceuticals, Basel, Switzerland) is a tyrosine kinase inhibitor (TKI) which works by binding Adenosine triphosphate (ATP) binding sites on CD117 and PDGFRA, blocking signal transduction. Since its introduction in 2000, imatinib has become the first-line agent for GIST therapy and is currently used in the neo-adjuvant, adjuvant, or palliative setting. Imatinib is currently recommended in the neo-adjuvant setting to shrink GISTs with the hope of limiting the extent of resection and associated morbidity. Cavnar et al. [26] reviewed their single-center experience of 47 patients with rectal GISTs, 17 patients in the pre-imatinib era and 30 patients in the imatinib era. In patients identified as high risk, organ preservation and negative margins were more common among the 13 patients treated with neo-adjuvant imatinib than among the 13 patients treated with surgery alone. An additional study reported on 19 patients with primary rectal GISTs. Imatinib used in the neoadjuvant setting in 15 patients significantly reduced tumor size from 7.6- to 4.1 cm ($p < 0.001$). Of the nine patients who underwent surgical resection, seven patients were able to undergo sphincter-preserving surgery who would have otherwise required a more radical approach [27].

Imatinib has been more extensively studied in the adjuvant setting following surgical excision to reduce the risk of recur-

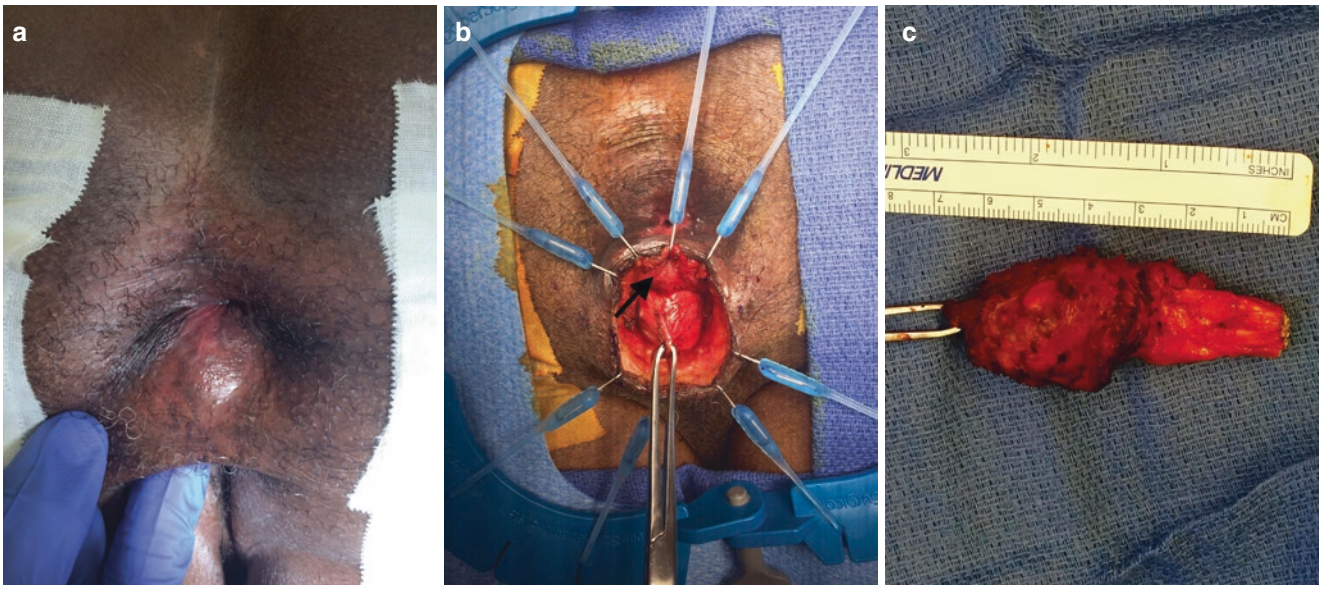

Fig. 34.1 Intraoperative photos of a perianal GIST (**a**), local excision with tumor in close proximity to sphincter mechanism (arrow) (**b**), and GIST completely excised with intact (**c**), Final specimen

rences. The American College of Surgeons Oncology Group (ACOSOG) Z9001 trial evaluated the impact of 1 year of adjuvant imatinib administration at 400 mg/day versus placebo and demonstrated an improved recurrence-free survival (RFS) compared to placebo (HR, 0.6; 95% CI 0.43–0.75) [28]. The European Organization for Research and Treatment of Cancer (EORTC) 62024 phase III trial also demonstrated an improved RFS following 2 years of administration of imatinib versus observation [29, 30]. The Scandinavian Sarcoma Group VVIII/German phase III trial randomized patients receiving imatinib at 400 mg/day between 1- and 3-year arms. With a median follow-up of 7.5 years, patients receiving 3 years of imatinib had a longer RFS and overall survival (OS) compared to those receiving Imatinib for 1 year [31]. The PERSIST-5 (Postresection Evaluation of Recurrence-free Survival for Gastrointestinal Stromal Tumors with 5 years of imatinib) prospective, single-arm, phase II clinical trial evaluated the impact of longer duration of therapy following macroscopically complete resection. This study estimated a 5-year RFS of 90% (95% CI, 80–95%) and an overall survival of 95% (95% CI, 86–99%). Of the 91 patients enrolled, there were 7 recurrences with the majority recurring after discontinuation of the drug. Approximately half of the patients discontinued treatment, mostly due to patient choice [32]. The optimal duration of treatment remains unknown. Patients with an elevated risk of recurrence should be treated for at least 3 years with imatinib and followed closely long term. A reasonable strategy may be to perform surveillance history and physical combined with cross-sectional imaging of the abdomen every 6–12 months for the first 10 years after surgery. More frequent imaging at 3–4 month intervals may be considered for 2 years following discontinuation of imatinib given the increased risk of recurrence during this time period [8].

In the setting of recurrent, progressive, or metastatic disease, the primary treatment modality remains imatinib. Sunitinib and regorafenib, both multitargeted tyrosine kinase inhibitors with activity against KIT, PDGFR, VEGFR, and FLT-1/KD, are alternative options approved for treatment of imatinib-resistant or intolerant GISTs [17]. The role of metastasectomy in the setting of stabilized disease while on imatinib is unclear. Du et al. [33] demonstrated in a small RCT that resection of residual disease on imatinib treatment improves overall survival (OS). In a small retrospective review, Bauer et al. demonstrated longer OS with debulking that achieved R0 or R1 status compared to those where surgery left gross tumor behind [34]. Finally, less invasive approaches may have a role in the management of GISTs. A small, single institution case series demonstrated tumor regression in all but seven patients following radiofrequency ablation of hepatic metastases. There were no GIST associated deaths and the OS was 85.7% at 30.6 months [35]. Gunter et al. reported on endoscopic ultrasound guided injection of 1.5 ml of 95% ethanol into 4 cm gastric GISTs in a patient with significant operative risks. Seven weeks following injection, a 1.5 cm ulcer was noted at the injection site with no evidence of residual tumor. Follow-up evaluation at 2 years demonstrated complete remission [36]..

Neuroendocrine Tumors (NETs)

Introduction

NETs of the GI tract were first described in 1888 in two patients with multiple small bowel tumors. In 1907, Siegfried Oberndorfer, a German pathologist, coined the term *karzinoide*, or "carcinoma-like," to describe the unique features of behaving like a benign tumor but having a malignant appearance microscopically [37]. While "carcinoid tumor," and other names reflecting the secretory nature of a specific tumor such as "insulinoma" or "glucagonoma," is a term used to describe tumors of neuroendocrine origin, "neuroendocrine tumor (NET)" more accurately represents the varied behavior of this family of tumors. NET is the preferred description by the North American Neuroendocrine Tumor Society (NANETS) and the European Neuroendocrine Tumor Society (ENETS) [38].

Histology and Biomarkers

Neuroendocrine cells are differentiated epithelial cells found throughout the GI tract which, depending on the organ of origin, secrete a variety of peptides and hormones. These cells are derived from adult GI stem cells and store peptides and proteins, such as Chromogranin A (CgA) and synaptophysin, in secretory vesicles within their cytoplasm [39].

Classification and terminology of GI NETs has evolved significantly over the past several decades. As noted above, classic terminology was based on the organ of origin or the specific peptide secreted. Two major categories of NETs of the GI tract have since emerged: well-differentiated NETs (WDNETs, which include carcinoids) and poorly differentiated neuroendocrine carcinoma (PDNETs) [40]. Grossly, WDNETs appear as smooth, round, polypoid lesions with normal overlying mucosa. Microscopically, WDNETs are characterized by proliferation of uniform, round to ovoid cells with enlarged nuclei and eosinophilic cytoplasm. Cells grow in a variety of patterns, including nested, solid, trabecular, pseudoglandular, and gyriform. The cytoplasm contains secretory vesicles that contain chromogranin and synaptophysin. PDNETs of the GI tract are high-grade carcinomas, which appear grossly as larger tumors with invasion into surrounding normal tissue. The tumor borders are infiltrative, with associated necrosis and hemorrhage. PDNETs are classified as small cell or large cell carcinomas. NANETS has published a "mini-

mum pathology dataset," which includes variables such as location, tumor/node/metastasis (TNM) staging, margin status, mitotic rate or Ki-67 index, and lymph node metastasis, and highlights the information that should be included on a pathology report for midgut and hindgut NETs [41]. The systems of nomenclature used to describe NETs have continued to evolve over time, although not all practitioners have adopted the new terminology, and thus confusion persists due to the continued use of traditional nomenclature.

NETS are further classified by grade. The grading system for NETs classifies tumors into three categories that are determined by the proliferative rate reflected by either mitotic rate or use of Ki-67 labeling. Grade 1 (G1), or low grade, tumors have fewer than 2 mitoses per 10 HPF, grade 2 (G2), or intermediate, tumors have 2 to 201 mitoses per HPF, and grade 3 (G3), high grade, have greater than 20 mitoses per HPF [38]. In virtually all systems of nomenclature, a sharp division is made between well-differentiated and poorly differentiated tumors. Well-differentiated NETs can include both low- and intermediate-grade groups. Poorly differentiated tumors are designated as "high grade" neuroendocrine carcinomas, which have a more aggressive biologic behavior compared to their well-differentiated counterpart [41].

Incidence and Distribution

NETS of both the midgut and hindgut are quite rare, accounting for ~1% of all new cancers diagnosed in the USA [42]. Overall, it is estimated that 52–58% of all NETs originate in the gastrointestinal tract and 21–32% originate in the bronchopulmonary tree. The most common primary sites for NETs are the rectum, lungs, bronchus, appendix, and small intestine followed by stomach, pancreas, and colon [43]. The true incidence of rectal NETs is unclear. In a retrospective study of 170 patients with GI carcinoids at the Oschner Clinic, Jetmore and colleagues demonstrated the rectum to be the most common location for GI NETs. However, this finding may not be representative of true disease distribution but a reflection of more vigorous screening measures [44]. The incidence of appendiceal/cecal NETs is similar between males and females, but slightly higher for males with respect to jejunal/ileal NETs. Hindgut NETs have a slight male preponderance, with a male-to-female ratio of approximately 1.1 [45]. Black patients are more likely to be diagnosed with NETs of the jejunum, ileum, and cecum than their white and Asian counterparts. White patients are more likely to be diagnosed with appendiceal NETs than their black counterparts [42]. In the hindgut, black patients are more likely to be diagnosed with rectal NETs than their white or Asian counterparts [45].

The median age of diagnosis of midgut NETs is 64 (SD 15.5) years with appendiceal NETs presenting at a younger age (median 47 years, SD 18). The true age at diagnosis of appendiceal lesions may actually be lower as most of the tumors found incidentally at appendectomy are benign and not reported to cancer registries. The mean age of diagnosis of colonic and rectal NETs is 65 and 56, respectively [46].

Clinical Presentation

Midgut NETs are usually small, slow growing tumors with symptoms that are vague and insidious in onset; leading to long delays in diagnosis. Patients may present with bloating, cramping, and mild episodic diarrhea; often being labeled with irritable bowel syndrome. Advanced locoregional disease may present as acute obstruction, caused by either the primary tumor or mesenteric fibrosis, or ischemia due to mesenteric vascular involvement. These tumors can metastasize to lymph nodes at the root of the mesentery triggering a significant desmoplastic reaction that shortens, distorts, and occasionally kinks the mesentery. In fact, occult NET should be considered in the differential diagnosis of patients with chronic bowel complaints or postprandial pain suggestive of ischemia. Systemic signs are rare and if present, are generally due to the presence of bioactive peptides that have bypassed metabolism in the liver. Serotonin, secreted by NETs, enters the portal circulation and is metabolized by the liver. In the setting of metastatic disease with heavy disease burden, specifically in the liver or outside the portal circulation, serotonin can bypass the liver and lead to symptoms of carcinoid syndrome (discussed in the next section) [38, 41].

The majority of appendiceal NETs are diagnosed on pathology after appendectomy for appendicitis and the majority are located at the tip of the appendix. A more detailed discussion of appendiceal carcinoids is presented in Chap. 32. Rectal NETs are often found incidentally on endoscopy in patients presenting for routine screening evaluations. These tumors rarely, if ever, present with the carcinoid syndrome. Colonic NETs generally have a worse prognosis as they typically present with more advanced locoregional disease and frequently with distant metastases [46]. Rectal NETs are indolent, slow-growing tumors with the majority being confined to the rectum. Symptomatic patients often present with hematochezia masquerading as hemorrhoids. Larger lesions with locoregional invasion can present with tenesmus and pain.

Carcinoid Syndrome

Primary colorectal NETs rarely exhibit symptoms of hormone secretion, as the liver is capable of metabolizing and inactivating most of the peptides secreted by these tumors. However, in the setting of advanced liver metastases (which

occurs in <10% of colorectal NETs) [47], secreted peptide hormones may enter the circulation, causing "carcinoid syndrome," with systemic consequences such as cutaneous flushing and gut hypermotility [47–49]. Carcinoid syndrome occurs most frequently (up to 90%) in patients with metastatic NETs, as it is these tumors that can produce high levels of serotonin [50]. However, it should be noted that hindgut NETs rarely produce serotonin, thus even when metastatic, these tumors rarely produce carcinoid syndrome [47].

The classic symptoms of carcinoid syndrome are flushing of the skin, watery diarrhea, abdominal pain, palpitations and wheezing. Patients usually experience intermittent symptoms with aggravating factors such as stress, ingestion of certain foods, caffeine, or alcohol. Flushing is the most common symptom, occurring in up to 85% of patients with the syndrome and may involve the face or the entire body. Secretion of a protease called kallikrein is thought to be responsible for these symptoms [51]. Abdominal symptoms are also common, occurring in up to 80% of patients, and include watery diarrhea and cramping. These symptoms are due to the excess serotonin secretion. Similarly, the surplus of serotonin causes accelerated fibroblast proliferation, increased vascular tone, bronchoconstriction, and platelet aggregation resulting in right-sided heart failure with pulmonary hypertension, tricuspid and pulmonary valve stenosis, and right ventricular hypertrophy and fibrosis [52]. Interestingly, the left side of the heart is spared from these effects as the lungs are capable of inactivating serotonin [52]. Many other symptoms, such as vague abdominal pain, weight loss, bleeding, obstruction, and constipation can occur. These may also be related to the mass effect of the primary tumor and mesenteric fibrosis.

Diagnostic Tests

Endoscopy and Imaging

Guidelines delineate the workup of NETs according to the site of origin [41]. Workup for all midgut NETs should include a complete colonoscopy to assess for any synchronous lesions. To assess for local invasion and distant spread, computed tomography (CT) scans of the thorax, abdomen, and pelvis with early and delayed phases should be performed [53]. Since NETs are hypervascular tumors, an early arterial phase (at 40 seconds) and washout during the delayed portal venous phase can be informative. To assess for indeterminate liver lesions identified on CT, magnetic resonance imaging (MRI) can be used, and would usually demonstrate a high signal on T2-weighted images for metastatic lesions [54]. NANETS recommends somatostatin receptor scintigraphy (SRS) or octreotide scans as part of the initial workup for midgut lesions in order to identify occult metastases. Since the majority of these NETs express receptors that have an affinity for somatostatin, SRS has an 80–90% sensitivity [55]. If metastases are identified on SRS, the patient is likely to respond to treatment with octreotide [56]. Positron emission tomography [^{18}F]-fluorodeoxyglucose (PET) imaging is generally not useful for WDNETs because of their low proliferative nature; however, PET can be used when SRS is equivocal and for PDNETs [41]. In cases where a midgut primary NET is suspected but not directly identified (e.g., a mesenteric fibrosis or mass in the ileal mesentery), a CT enterography, also performed in the arterial phase, can be used to locate the primary tumor. A newer PET modality using 68-Gallium-DOTA peptides (DOTATATE, DOTATOC, DOTANOC) combined with CT has been shown to be an accurate imaging modality for the detection of NETs. In a systematic review including 22 studies, ^{68}Ga-DOTA PET/CT was found to have excellent diagnostic accuracy, with a sensitivity and specificity of 93% and 96%, respectively [57]. Due to its sensitivity, authors suggest that ^{68}Ga-DOTA PET/CT may be used for WDNETs that are at higher risk of having occult metastases such as midgut NETs [58].

Although metabolic imaging tests may improve detection of occult tumor as compared to conventional imaging and clarify equivocal findings, it remains unclear whether any of the metabolic imaging tests would likely alter initial treatment if the patient has no evidence of metastatic disease on staging CT. If the patient would benefit from resection of the primary tumor irrespective of whether micrometastases were present, it may be preferable to proceed directly to operation.

Hindgut (distal colon and rectum) NETs are usually identified incidentally during colonoscopy. The endoscopic features of these neoplasms include a smooth, round, polypoid appearance, with a yellow color due to the presence of CgA and normal overlying mucosa (Fig. 34.2) [59–64]. The workup for hindgut NETs also begins with a complete colonoscopy. For lesions that are <1 cm that are completely resected during colonoscopy, no additional workup or follow-up is required as these tumors have a very good prognosis and low risk of regrowth or lymph node metastases [49]. For hindgut NETs that are 1–2 cm, an endoscopic ultrasound (EUS), endorectal ultrasound (ERUS), or rectal MRI is useful to assess tumor size, depth of invasion, and the presence or absence of lymph node metastases [65]. Using EUS or ERUS, very small tumors can be detected with excellent sensitivity [66]. For locally advanced tumors (T2 to T4), a CT of the abdomen and pelvis (as described above for midgut NETs) should be performed to rule out metastatic disease. SRS is not recommended in the initial workup of hindgut NETs; however, it can be used for investigation of metastatic NETs or rare PDNETs [67, 68]. Ga-DOTA PET/CT may be useful for the rare presentation of locally advanced hindgut NETs.

The TNM staging of NETs reflects depth of invasion, tumor size, and disease spread (Tables 34.1 and 34.2) [69].

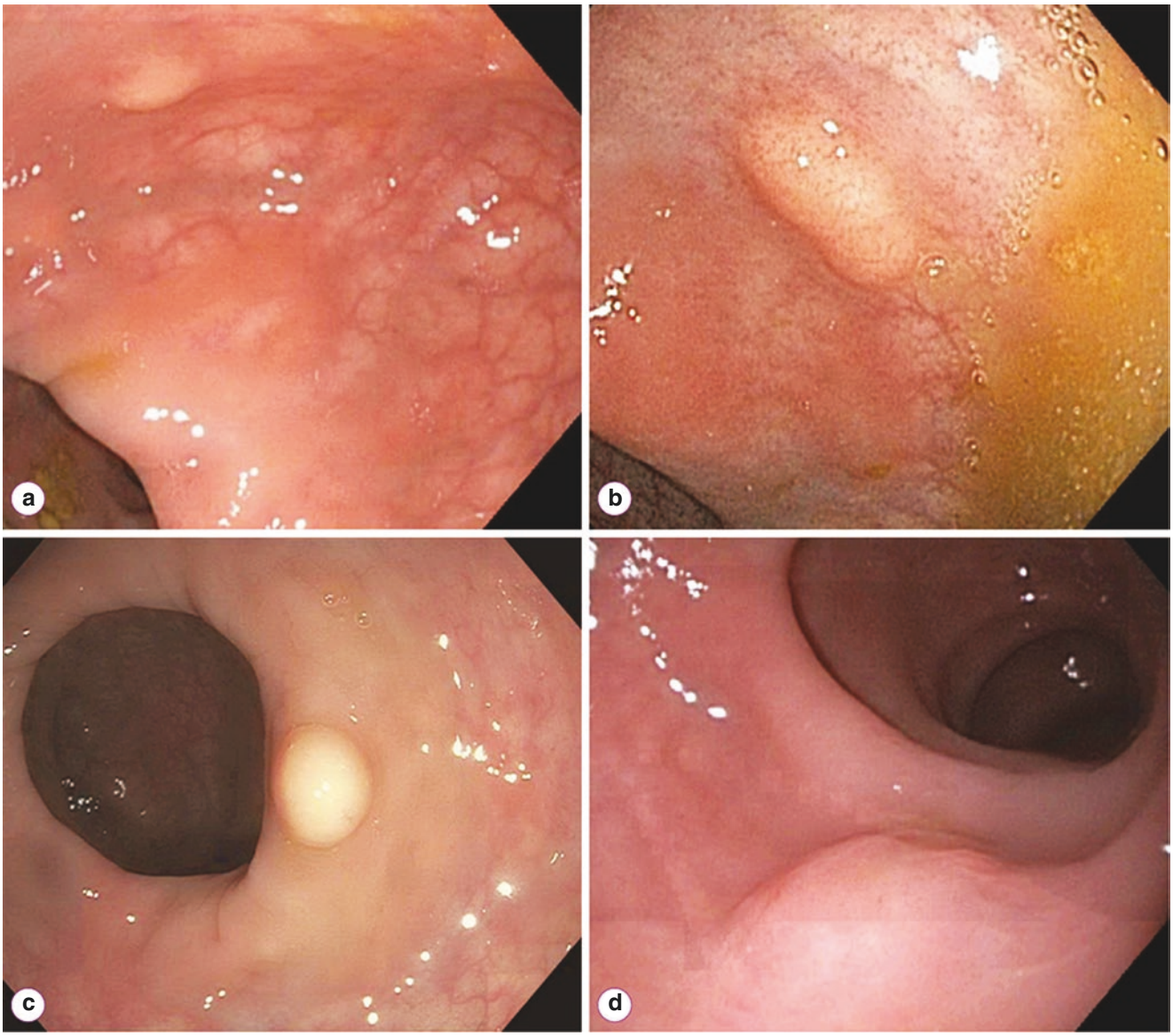

Fig. 34.2 Endoscopic views of various rectal NETs (**a**–**c**), and (**d**) their well-circumscribed, round appearance with normal overlying mucosa. (Reused with permission from Chablaney et al. [60]. Copyright © 2017 Korean Society of Gastroenterology)

Biochemical Workup

NETs have been linked to the production of multiple bioactive compounds. The most important of these biomarkers, CgA, is a 49-kd acidic polypeptide that is abundantly present in the secretory granules of neuroendocrine cells. Depending on the extent of disease, plasma CgA is elevated in 60–100% of patients with either functioning or nonfunctioning NETs. The sensitivity and specificities of CgA for detection of NETs ranges between 70% to 100% [70]. CgA may correlate to overall tumor volume; however, caution is necessary in the interpretation of the results as proton pump inhibitors, renal or liver failure, and chronic gastritis can spuriously elevate serum levels [41]. Urinary 5-hydroxy-indole-acetic-acid (5-HIAA) (24-hour collection) is a useful laboratory marker for well-differentiated NETs or carcinoids. It is a surrogate marker for serotonin metabolism that is tightly linked to the presence of carcinoid syndrome. Serotonin is derived from tryptophan and is stored and transported in platelets. Tryptophan is diverted away from protein (vitamin B_7 and B_3) synthesis in the presence of carcinoid tumors. Serotonin is first metabolized in the liver and then in the kidney to produce 5-hydroxy-indole-acetic-acid (5-HIAA), which is excreted in the urine. The specificity of urine 5-HIAA has been reported to be 88% [71, 72]. However, certain foods rich in serotonin and some medications can alter the metabolism and increase urinary levels of 5-HIAA and should be avoided for at least 24 hours prior to the testing (Table 34.3). Other biomarkers secreted by NETs include neuron-specific

Table 34.1 AJCC TNM staging of colon and rectal NETs

Stage	Primary tumor (T)
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades lamina propria or submucosa and size ≥ cm^2
T1a	Tumor size <1 cm in greatest dimension
T1b	Tumor size 1–2 cm in greatest dimension
T2	Tumor invades muscularis propria or size >2 cm with invasion of lamina propria or submucosa
T3	Tumor invades through muscularis propria into subserosa or into non-peritonealized pericolic or perirectal tissue
T4	Tumor invades peritoneum or other organs
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases
Distant metastases (M)	
M0	No distant metastases
M1	Distant metastases

Adapted from Edge et al. [69]

Table 34.2 AJCC staging of colon and rectal NETs

Stage	T	N	M
I	T1	N0	M0
IIA	T2	N0	M0
IIB	T3	N0	M0
IIIA	T4	N0	M0
IIIB	Any T	N1	M0
IV	Any T	Any T	M1
Stage	T	N	M
I	T1	N0	M0
IIA	T2	N0	M0
IIB	T3	N0	M0
IIIA	T4	N0	M0
IIIB	Any T	N1	M0
IV	Any T	Any T	M1

Adapted from Edge et al. [69]

enolase, substance P, neurotensin, and chromogranins B and C. Only a small fraction of hindgut NETs (<1%) produce and secrete serotonin or other biomarkers making routine measurement of urinary 5-HIAA not necessary. Serum CgA can be a useful marker for monitoring patients with metastatic disease or resected stage II or III disease.

Treatment

Once the diagnostic workup is complete, patients with midgut and hindgut NETs should be discussed at multidisciplinary tumor boards [41, 46, 49]. Surgical considerations differ for midgut and hindgut NETs due to differences in disease presentation and prognosis (Table 34.4).

Most midgut NETs remain asymptomatic and are only discovered when they become advanced, with the exception

Table 34.3 Foods, beverages, and medications that may falsely elevate urinary 5-HIAA levels

Foods and beverages	Medications
Alcoholic beverages	Cough and cold remedies containing expectorants
Banana	Muscle relaxants: methocarbamol
Butternuts	Phenothiazines
Kiwi	Chlorpromazine
Mockernut	Promethazine
Nuts	Methanamines
Pecans	Phenacetin
Pineapple	
Plantain	
Plums	
Tomatoes	
Walnuts	

Table 34.4 Surgical considerations by tumor site

Primary tumor	Factor	Extent of resection
Midgut	Limited disease	Resection of primary with lymphadenectomy and metastatic tumors
	Extensive disease	Resection with lymphadenectomy or bypass of primary tumor
		Debulking of metastasis
Colon		Colectomy with lymphadenectomy
Rectum	<1 cm	Endoscopic or local excision
	1–1.9 cm	Local excision or proctectomy
	>2 cm	Proctectomy

of small NETs of the appendix (covered in Chap. 33). NETs of the jejunum and ileum have greater malignant potential compared to other NETs, with even sub-centimeter NETs reported to present with advanced disease [41]. Of these small midgut NETS under 1 cm, 20–30% have been reported to have lymph node involvement [73]. Oncologic resection with wide lymphadenectomy is the preferred treatment. Since these NETs may be associated with bulky mesenteric nodes that can cause obstruction, ischemia, or fibrosis, oncologic resection should be considered even in the context of metastatic disease to prevent these complications (Fig. 34.3). During small bowel resection, the mesenteric resection should be performed or mapped out prior to resecting bowel, with the goal to preserve bowel length when possible. One-third of midgut NETs may be multicentric, thus it is important to examine the entire small bowel to rule out synchronous lesions [73]. NETs of the cecum and ascending colon often present as large bulky tumors that require a formal right hemicolectomy with adequate lymphadenectomy [41, 47]. Less commonly, right colon NETs may be small lesions that are discovered during pathological examination of a resected specimen for another indication.

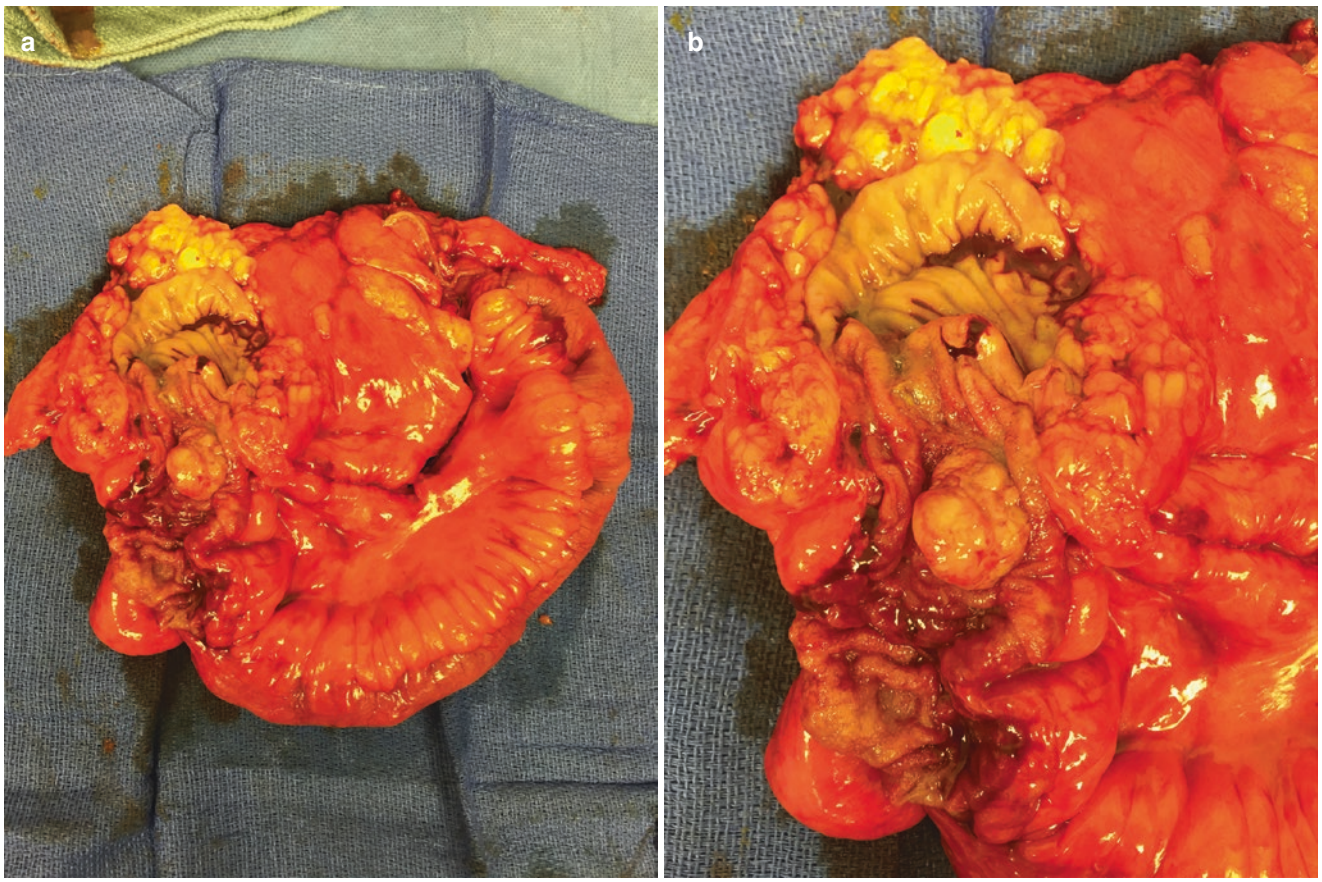

Fig. 34.3 (**a**) Surgical specimen demonstrating a NET of the terminal ileum. Note the desmoplastic response of the mesentery. (**b**) Close-up view of the lesion

Dissimilar to midgut NETs, most hindgut NETs are small submucosal neoplasms that follow an indolent disease course [47, 67]. Treatment is determined by size and depth of invasion (Fig. 34.4). Small (<1 cm) colorectal NETs that are confined to the submucosa (T1) can be managed with endoscopic resection during colonoscopy [46]. In several retrospective series, endoscopic resection was successful for these lesions, with positive resection margins being the sole predictor of recurrence (5–20%) [74–79]. Thus, when being removed endoscopically, the site should be tattooed to facilitate further management in the case of positive margins. To overcome the limitations of standard colonoscopy, two-channel endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) techniques have also been used for hindgut NETs [59, 60]. In a recent meta-analysis comparing conventional colonoscopy, EMR and ESD, complete resections were significantly less likely with conventional colonoscopy compared to advanced techniques (OR 0.42 95% CI 0.25–0.71), with no difference between different advanced techniques [80]. The relevance of positive margins for small WDNETS that are G1 and have no high-risk features is not known. National Comprehensive Cancer Network (NCCN) recommends that patients with these lesions be re-examined endoscopically at 6–12 months, and if there is no recurrence, they can continue to be surveyed [49]. However, for endoscopically resected lesions that are G2 with positive margins, further management is recommended [49].

The treatment of rectal NETs 1–2 cm in size is controversial. In a multicenter retrospective review of over 200 rectal NETs, size >1 cm and lymphovascular invasion were independent predictors of lymph node metastases, whereas the presence of lymph node metastases and lymphovascular invasion was associated with subsequent development of distant metastases [81]. Of note, most small NETs in this cohort were managed by colonoscopic removal or local excision, with only six patients managed by transanal endoscopic surgery (TES). Current guidelines recommend that rectal NETs between 1 and 2 cm that are confined to the submucosa (T1) or muscularis propria (T2) without any lymph node metastases or adverse histologic features (lymphovascular or perineural invasion), be managed by transanal excision [41]. TES is an excellent technique for these tumors as it offers good visualization, exposure, and access for performing a full-thickness excision with negative margins, even in the

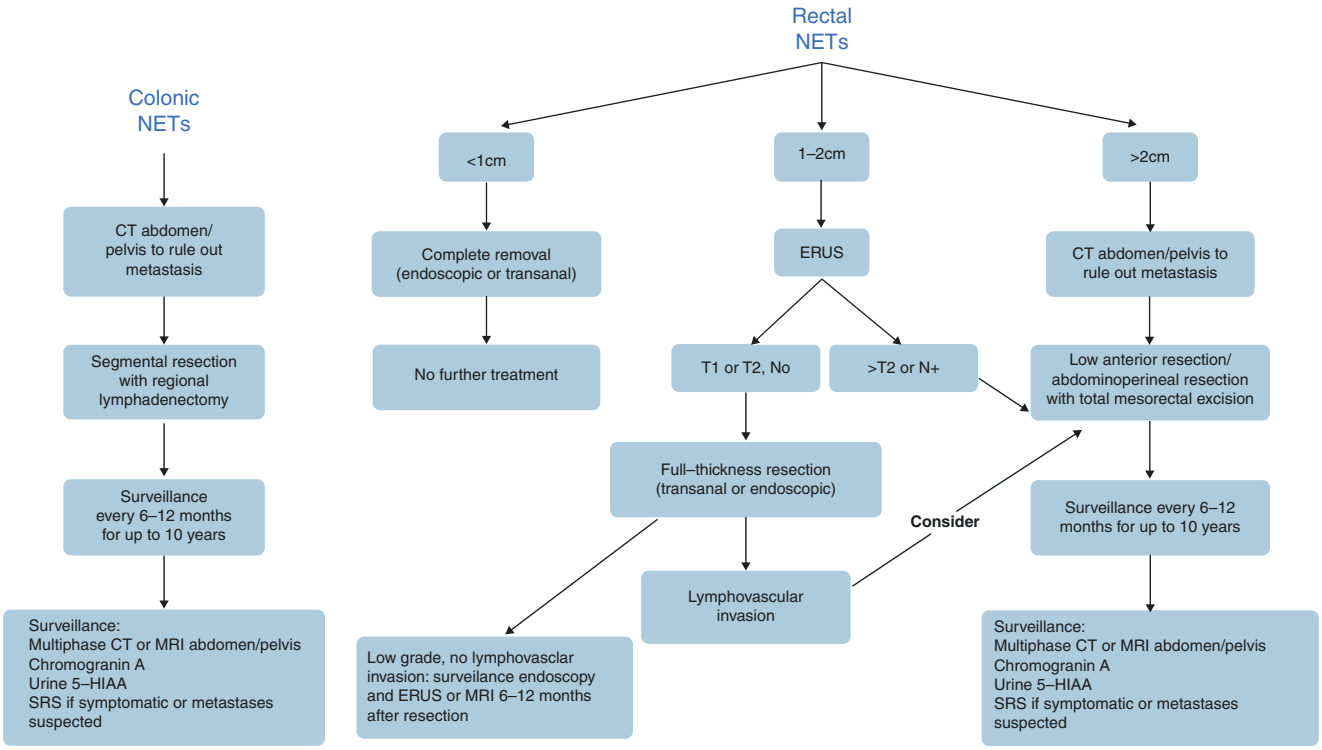

Fig. 34.4 Approach to the diagnosis, treatment, and surveillance of midgut and hindgut NETs. (Adapted from Ford [67])

proximal rectum (Fig. 34.5). In the case of endoscopically resected rectal NETs with a positive margin, TES can be used to re-excise the scar when indicated and obtain a negative margin [46, 49]. Small colonic NETs are less common than rectal NETs. When these tumors are small, they cannot be accurately evaluated for depth of invasion or presence of lymph node metastases. There are limited data showing a low rate (4%) of lymph node metastases with small colonic NETs, so it may be reasonable to remove them endoscopically, whenever possible [82]. Colonic and rectal NETs larger than 2 cm, invading the muscularis propria, with suspected lymph node involvement or adverse histologic features should generally be managed with radical resection and lymphadenectomy using the same oncologic principles of surgery for adenocarcinoma [67, 83]. Currently, there is no evidence for routine adjuvant medical therapy after surgery in any of these tumors [41, 49, 68, 84].

The management of metastatic NETs requires a multidisciplinary approach including surgery, hormonal therapy, chemotherapy, radiation, and interventional radiology [41, 68]. Somatostatin analogs (e.g., octreotide, lanreotide, and pasireotide) are the primary medical treatment for functioning and nonfunctioning metastatic NETs, as up to 80% of NETs have somatostatin receptors [85–88]. In cases of carcinoid syndrome, these drugs can control symptoms by inhibiting serotonin secretion. Interestingly, somatostatin analogs may also have antiproliferative properties and thus can be used for advanced disease control, regardless of symptoms [65]. Other medical treatment focuses on symptomatic treatment of the hormonal syndrome including the treatment of diarrhea with loperamide, diphenoxylate/atropine, and other antidiarrheal medications, and the use of antihistamines or H2 receptor antagonists for flushing.

Chemotherapy options for NETs remain limited. In the Eastern Cooperative Oncology Group randomized control trial, patients with metastatic NETs were randomized to 5-fluorouracil (5-FU) plus doxorubicin or 5-FU plus streptozocin. The median progression-free survival (PFS) was 4.5 and 5.3 months, respectively, and overall survival was 15 and 24 months, respectively. Thus, to date, there appears to be no dramatic survival benefit for chemotherapy, and its use can be reserved for patients who have exhausted all other options [89]. Interferon α has been used to induce disease stability in advanced cases. In a pooled analysis, only 37 (12%) of 309 patients treated with interferon α had a response [90]. Radiation therapy is mainly used in the palliation of NETs with bone metastases.

Debulking of liver metastases, if anatomically possible, has been shown to improve survival and aid in the palliation of hormone-related symptoms in patients with metastatic NETs [91]. As metastatic carcinoid tumors derive most of their blood supply from the hepatic artery, chemoembolization may play an important role in the treatment and pallia-

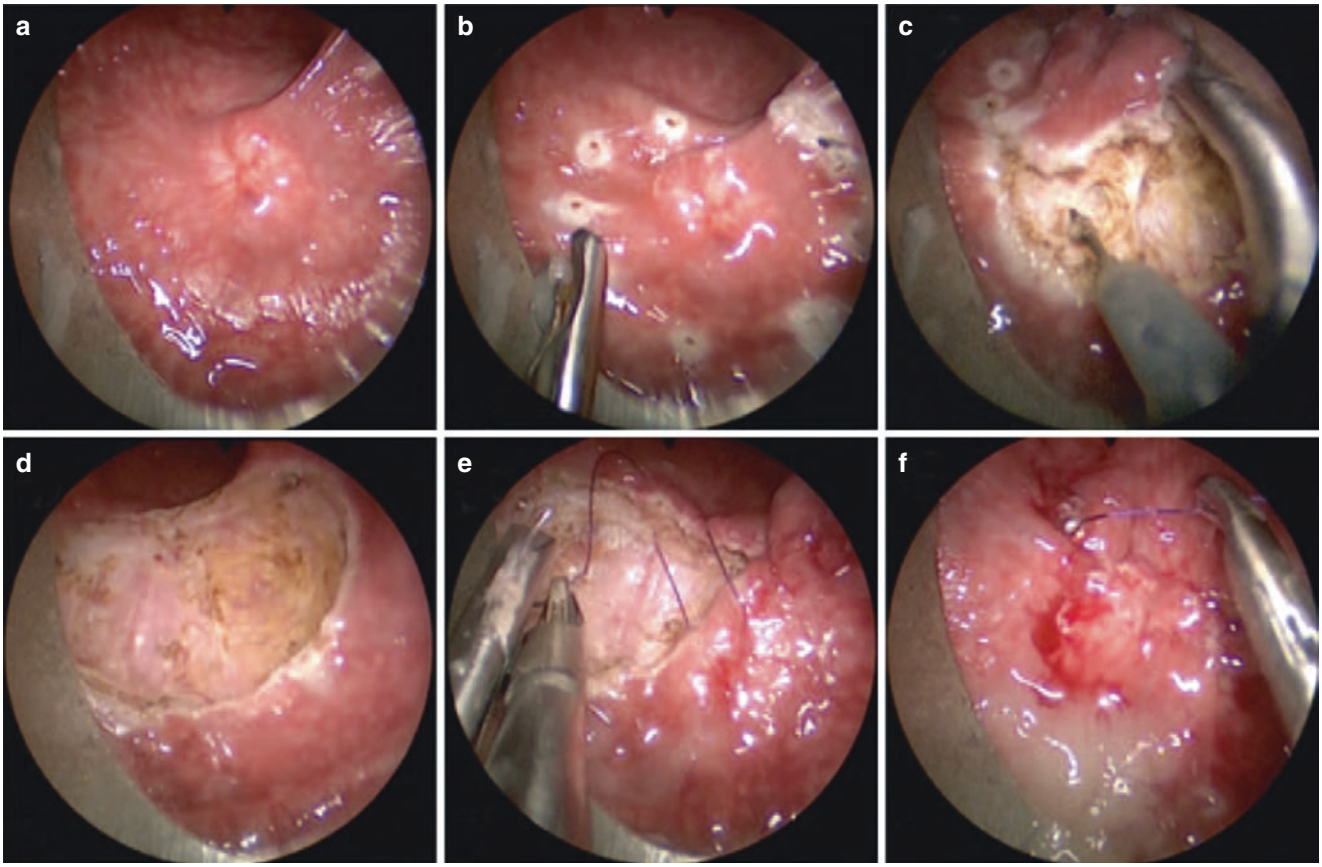

Fig. 34.5 Transanal endoscopic resection for rectal NET: (**a**) Rectoscopic view of hindgut NET; (**b**) A 1 cm resection margin was marked around the lesion before excision by point-needle diathermy; (**c**, **d**) Full-thickness excision was performed; (**e**, **f**) Rectal wall defect closed using running sutures of 3/0 absorbable suture. (Reused with permission from Xu et al. [125]. Copyright © 2017 Wolters Kluwer)

tion of systems. Patients with large tumors or those who are refractory to somatostatin frequently experience significant short-term improvement in their symptoms [91, 92]. Liver transplantation has also been reported in patients with metastatic NETs, with outcomes similar to transplantation for hepatocellular carcinoma [91, 93].

Surveillance

NETs can recur even many years after resection, but there is little consensus about the best surveillance strategy (Fig. 34.3)**.** For hindgut NETs <1 cm as per NCCN and NANETS, no follow-up is needed as these tumors have a very low risk of recurrence after complete removal [49, 68]. For 1–2 cm rectal NETs excised by endoscopic or transanal techniques, NANETS recommends no surveillance, while NCCN recommends ERUS or MRI at 6 and 12 months. For more advanced hindgut NETs, surveillance with an office visit and CT or MRI scans of the abdomen and pelvis are recommended on an annual basis. Since NETs may recur years after the initial diagnosis, surveillance for 7–10 years is recommended [68]. During surveillance after resection of advanced NETs, CgA and/or 5-HIAA may be considered.

Prognosis

Primary tumor site, tumor size, and stage are the strongest predictors of long-term survival [94]. Hindgut NETs have a much better survival rate than midgut NETs. The 5-year survival for rectal NETs <1 cm with no lymphovascular involvement is almost 100%, while node-positive rectal NETs and those with metastatic disease, have 5-year survival rates of 54–73% and 15–30%, respectively [47, 95]. Midgut NETs have the worst prognosis regardless whether they are localized or metastatic. For patients presenting with localized node-negative disease, 5-year survival can reach 80%, while those with node positive tumors have a < 40% 5-year survival [96]. Patients with metastatic midgut NETs are usually incurable with a reported median survival of 5 months [42, 47].

Lymphoma

Incidence and Distribution

Primary extranodal lymphoma is defined as lymphoma that is identified in a primary organ with no other clinical evidence of spread from distant lymph nodes or other organs, and accounts for 10–30% of all lymphoma. The gastrointestinal (GI) tract is the most common site to develop extranodal primary lymphoma; however, the colon and rectum are the least common GI location, accounting for only 10% of GI lymphomas and < 1% of all colorectal neoplasms [97, 98]. The most common colorectal site of involvement is the cecum, reported in 73% of patients, followed by the rectum [97]. Colorectal lymphoma occurs in about 3.5 in 2000 per million and is most commonly diagnosed between the ages of 50 and 70 years and among men (2:1) [99].

Risk factors for primary colorectal lymphoma remain largely unknown; however, established risk factors for primary extranodal non-Hodgkin's lymphoma (NHL) in general include a family history of lymphoma, personal history of radiation or chemotherapy, organ transplantation, immunosuppression, viral infections (e.g., HIV, hepatitis C), and exposures to toxins such as pesticides. Inflammatory bowel disease (IBD) has not been shown to be a risk factor for lymphoma; however, immunosuppressive medications for IBD including azathioprine, mercaptopurine, and infliximab have been associated with an increased risk of GI lymphoma [100–102].

Clinical Presentation

Unintentional weight loss, night sweats, fevers, and lethargy are the hallmark of colorectal lymphoma, in addition to a palpable abdominal mass (present in up to 80%) [103]. Other symptoms include those that mimic colorectal cancer, such as bleeding of the rectum, anemia, abdominal pain, diarrhea, or obstructive symptoms due to the large size of these lesions.

Histology

The vast majority of primary extranodal lymphomas are NHL. Similar to other primary extranodal lymphomas, colon and rectal lymphomas are usually NHL, with only case reports of primary colorectal Hodgkin lymphoma [104]. There are over 60 different subtypes of NHL as per the 2016 revision of the World Health Organization (WHO); however, the most common subtype of colorectal NHL is diffuse large B cell (DLBC) lymphoma (Table 34.5) [105]. Determining the specific histologic subtype of NHL is important, as it dictates the treatment options and expected outcomes.

Table 34.5 Most common subtypes of GI lymphoma based on the updated WHO classification

Subtype	Proportion (%)
Extranodal marginal zone B cell lymphoma	~45
Diffuse large B cell lymphoma	~45
Follicular lymphoma	<5
Mantle cell lymphoma	<5
Burkitt's lymphoma	<5
T cell lymphoma	<5

Adapted from Gay et al [105]

Diagnostic Tests

Diagnosis of primary extranodal NHL should be considered when lymphoma is identified in the colon or rectum with no other clinical evidence of spread from distant lymph nodes or other organs. Diagnostic criteria were first established by Dawson in 1961 as (1) a dominant colorectal lesion with only local lymphadenopathy, (2) no superficial palpable lymph nodes on clinical exam, (3) no radiologic evidence of chest lymphadenopathy, (3) a normal peripheral white blood cell smear and differential, (4) uninvolved liver, and (5) uninvolved spleen. More recently, these criteria have become more liberal to include any extranodal dominant site after clinical staging is complete, regardless of other lymph node involvement.

Diagnosis of lymphoma and the determination of the specific subtype are based on histologic, flow cytometric, and molecular evaluation of an adequate tissue specimen. In the case of a colorectal mass incidentally noted on radiographs, colonoscopy is typically performed as the next diagnostic maneuver. In cases of lymphoma, colonoscopy may show nonspecific abnormalities such as mucosal nodularity and induration, or an actual mass with or without ulceration (Fig. 34.6a, b) [106]. Colonoscopic biopsies are often too superficial and insufficient to confirm the diagnosis. At times, the diagnosis is only confirmed upon surgical resection. PET with computed tomography (PET/CT) scan of the chest, abdomen, and pelvis should be obtained to rule out extraintestinal disease. On imaging, primary lymphoma is more likely to demonstrate extension into the terminal ileum, have well-defined margins, preservation of fat planes, absence of invasion into adjacent structures, and perforation without a desmoplastic reaction, compared to colorectal adenocarcinoma. A bone marrow biopsy is also critical to assure accurate stage and confirm localized disease.

Several staging systems for primary GI lymphomas exist; however, the modified Ann Arbor staging system is most widely used (Table 34.6) [107–110]. Even though this staging system has been validated in colorectal lymphoma, it is not specific to primary GI lymphomas [111].

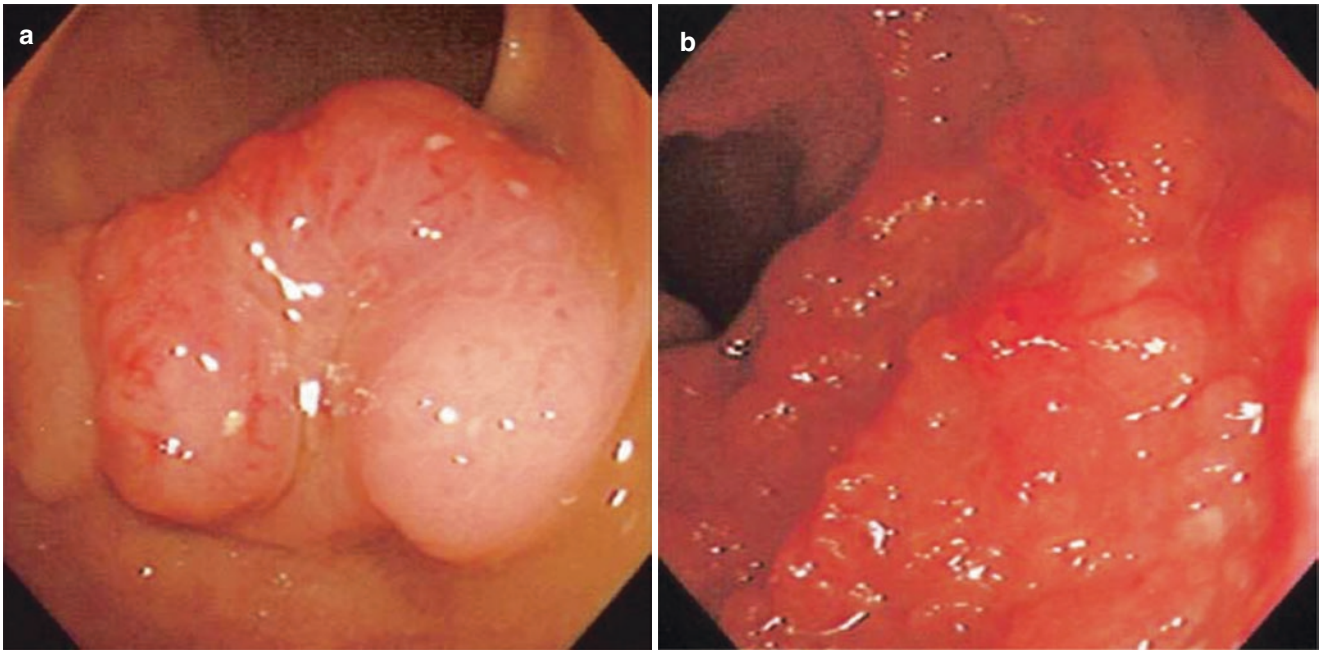

Fig. 34.6 (**a**) Lymphoma presenting as a fungating mass with a smooth, lobulated, non-ulcerated surface as seen on colonoscopy [106]. (**b**) Lymphoma presenting as a diffuse nodular lesion without a definite mass. (Reused with permission from Myung et al. [106]. Copyright © 2003 Elsevier)

Table 34.6 Ann Arbor staging

Stage	Description
I	Involvement of a single lymph node region or lymphoid structure
II	Involvement of two or more lymph node regions on the same side of the diagram
III	Involvement of lymph regions or structures on both sides of the diaphragm
IV	Involvement of extranodal site(s) beyond that designated E
A	No symptoms
B	Fever (38°), drenching sweats, weight loss (10% body weight over 6 mo)
E	Involvement of a single, extranodal site contiguous or proximal to known nodal site

Adapted from Rohatiner et al. [107]

Treatment

In contrast to nodal lymphoma, where chemotherapy and radiation are the mainstay of treatment, colorectal lymphoma presents a management challenge due to the high risk of complication when the bowel is irradiated. Given the limited availability of high-quality data to guide decision-making, the best approach to the management of colorectal lymphoma requires a multidisciplinary approach with early involvement of surgeons, radiation oncologists, and malignant hematologists. In general, treatment consists of surgery followed by chemotherapy alone, or chemotherapy with or without radiation therapy.

In the absence of disseminated disease, surgical resection is generally performed for colorectal lymphomas. The rationale for surgical treatment is twofold: cure and prevention of obstruction, perforation, or bleed. In a large retrospective cohort of 345 patients with colorectal DBCL from 16 hospitals in South Korea, patients with localized disease who underwent surgical resection followed by chemotherapy had lower relapse rates than with chemotherapy alone (15.3% vs. 36.7%, $p < 0.01$) [112]. Overall 3-year survival was significantly better with surgery followed by chemotherapy compared to chemotherapy alone (91% vs. 62%, $p < 0.001$). On multivariate cox regression, adjusting for age, performance status, lactate dehydrogenase level, number of extranodal involved sites, and stage, surgery followed by chemotherapy was a significant prognostic indicator of overall survival.

In the only available prospective cohort of 40 patients with DLBCL who received primary surgical resection with lymph node dissection and postoperative chemotherapy, the estimated 5-year overall and disease-free survival rates were 88.9% and 83.1% [111]. However, in earlier years, when operative series were less selective and included patients with more advanced disease, far worse outcomes were observed [113, 114]. Thus, in early-stage disease, definitive local control by surgical resection is a good strategy.

Based on the data available in the literature, the proportion of patients with no regional lymph node involvement (stage IE) ranges from 14% to 24%, while the majority of patients have regional lymph node involvement (stage IIE) in

addition to their primary tumor at the time of surgery (62–86%). Thus, an extended lymph node dissection (i.e., not limited to grossly abnormal nodes) similar to colon adenocarcinoma is advocated [115]. Following surgical resection, chemotherapy with three to six cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP), with or without rituximab is recommended.

For unresectable DLBCL of the colon or rectum, or for patients with localized disease who are unfit for surgery, treatment with a full six cycles of CHOP chemotherapy is generally recommended. In nodal lymphoma, radiation is considered for incomplete positron emission tomography (PET) response after completion of systemic chemotherapy. However, the small and large bowel are particularly susceptible to complications of radiation, thus external beam radiation is not a preferred adjuvant option in the treatment of colorectal lymphoma. Radiation has been used as part of the treatment for rectal lymphomas, as this region can be irradiated with limited damage to the small bowel [116].

Two other scenarios warrant mention, both of which are managed operatively. Occasionally, colonic lymphoma will present with acute perforation, in which case resection is warranted. Rarely, chemotherapy will induce necrosis of the tumor that has replaced the bowel wall, resulting in subacute perforation with abscess and/or fistula. Resection may be necessary in this case, typically after percutaneous drainage of abscess, antibiotic therapy, and optimization of blood counts.

In general, treatment of the less common subtypes of primary colorectal lymphoma is also centered on surgical resection and chemotherapy for early disease, and chemotherapy for more advanced disease. An important feature of lymphomas is their variable susceptibility to chemotherapy regimens. Generally, rapidly proliferating tumors are more susceptible to cytotoxic chemotherapy than indolent tumors.

Mucosa-associated lymphoid tissue (MALT) lymphoma most commonly occurs in the stomach and small bowel, with colorectal primaries only accounting for a minority of cases [117, 118]. *Helicobacter pylori* infection contributes to 90% of gastric MALT lymphoma; however, its role in colorectal MALT is unclear. There is a paucity of data on the ideal treatment of colorectal MALT lymphoma with case reports describing successful treatment with radiation alone, surgical resection, or endoscopic mucosal resection [119, 120]. Size determines the surgical approach (local excision vs. radical resection). Given the indolent nature of this tumor, systemic chemotherapy is reserved for the adjuvant setting (in the case of residual disease) or for disseminated disease. Successful use of a variety of agents, including alkylators, purine analogs, and anthracyclines has been reported [121].

Primary colorectal follicular lymphoma is an uncommon and poorly defined disease. Follicular colorectal lymphoma can be managed with aggressive upfront local therapy, including surgery and/or radiation [122]. However, given the toxicity of potential bowel radiation, upfront surgery may be the best option for localized disease. Adjuvant chemotherapy in the treatment of primary colorectal follicular lymphoma is of unclear additional benefit. There are case series that report long-term disease-free survival with surgery with or without adjuvant chemo-immunotherapy [122].

Primary T-cell lymphoma accounted for 18% of primary GI lymphomas in a series of 95 patients [123]. These tumors are characterized by multifocal ulcerative lesions in relatively young patients, a high rate of hematochezia, fever, or perforation, and have a poor prognosis even in cases of localized disease [123]. Mantle cell lymphoma is often discovered in the GI tract, as a secondary site of involvement rather than a primary tumor [124]. It usually is found in patients who present with abdominal symptoms at the time of their lymphoma diagnosis, which then prompted a GI evaluation.

References

1. Mazur MT, Clark HB. Gastric stromal tumors reappraisal of histogenesis. Am J Surg Pathol. 1983;7(6):507–20. https://doi.org/10.1097/00000478-198309000-00001.
2. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol. 1998;152(5):1259–69.
3. Joensuu H, Reichardt P, Eriksson M, Hall KS, Vehtari A. Gastrointestinal stromal tumor: a method for optimizing the timing of CT scans in the follow-up of cancer patients. Radiology. 2014;271(1):96–106. https://doi.org/10.1148/radiol.13131040.
4. Fletcher CDM, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol. 2002;33(5):459–65. https://doi.org/10.1053/hupa.2002.123545.
5. Parab TM, DeRogatis MJ, Boaz AM, et al. Gastrointestinal stromal tumors: a comprehensive review. J Gastrointest Oncol. 2018;10(1):144–54. https://doi.org/10.21037/jgo.2018.08.20.
6. Medeiros F, Corless CL, Duensing A, et al. KIT-negative gastrointestinal stromal tumors. Am J Surg Pathol. 2004;28(7):889–94. https://doi.org/10.1097/00000478-200407000-00007.
7. West RB, Corless CL, Chen X, et al. The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of KIT or PDGFRA mutation status. Am J Pathol. 2004;165(1):107–13. https://doi.org/10.1016/S0002-9440(10)63279-8.
8. von Mehren M, Joensuu H. Gastrointestinal stromal tumors. J Clin Oncol. 2018;36(2):136–43. https://doi.org/10.1200/JCO.2017.74.9705.
9. Reichardt P, Hogendoorn PCW, Tamborini E, et al. Gastrointestinal stromal tumors I: pathology, pathobiology, primary therapy, and surgical issues. Semin Oncol. 2009;36(4):290–301. https://doi.org/10.1053/j.seminoncol.2009.06.002.
10. Heinrich MC. PDGFRA activating mutations in gastrointestinal stromal tumors. Science (80). 2003;299(5607):708–10. https://doi.org/10.1126/science.1079666.
11. Mason EF, Hornick JL. Succinate dehydrogenase deficiency is associated with decreased 5-hydroxymethylcytosine production in gastrointestinal stromal tumors: implications for mechanisms of tumorigenesis. Mod Pathol. 2013;26(11):1492–7. https://doi.org/10.1038/modpathol.2013.86.

12. Ricci R. Syndromic gastrointestinal stromal tumors. Hered Cancer Clin Pract. 2016;14(1):15. https://doi.org/10.1186/s13053-016-0055-4.
13. Søreide K, Sandvik OM, Søreide JA, Giljaca V, Jureckova A, Bulusu VR. Global epidemiology of gastrointestinal stromal tumours (GIST): a systematic review of population-based cohort studies. Cancer Epidemiol. 2016;40:39–46. https://doi.org/10.1016/j.canep.2015.10.031.
14. Scherübl H. Management of early asymptomatic gastrointestinal stromal tumors of the stomach. World J Gastrointest Endosc. 2014;6(7):266. https://doi.org/10.4253/wjge.v6.i7.266.
15. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med. 2006;130(10):1455–78.
16. Scarpa M, Bertin M, Ruffolo C, Polese L, D'Amico DF, Angriman I. A systematic review on the clinical diagnosis of gastrointestinal stromal tumors. J Surg Oncol. 2008;98(5):384–92. https://doi.org/10.1002/jso.21120.
17. Kelley K, Byrne R, Lu K. Gastrointestinal stromal tumors of the distal gastrointestinal tract. Clin Colon Rectal Surg. 2018;31(05):295–300. https://doi.org/10.1055/s-0038-1642053.
18. Stelow EB, Stanley MW, Lai R, Mallery S. Endoscopic ultrasound-guided fine-needle aspiration findings of gastrointestinal leiomyomas and gastrointestinal stromal tumors. Am J Clin Pathol. 2003;119(5):703–8. https://doi.org/10.1309/UWUV-Q001-0D9W-0HPN.
19. Eriksson M, Reichardt P, Sundby Hall K, et al. Needle biopsy through the abdominal wall for the diagnosis of gastrointestinal stromal tumour – does it increase the risk for tumour cell seeding and recurrence? Eur J Cancer. 2016;59:128–33. https://doi.org/10.1016/j.ejca.2016.02.021.
20. Hølmebakk T, Bjerkehagen B, Boye K, Bruland Ø, Stoldt S, Sundby HK. Definition and clinical significance of tumour rupture in gastrointestinal stromal tumours of the small intestine. Br J Surg. 2016;103(6):684–91. https://doi.org/10.1002/bjs.10104.
21. Vernuccio F, Taibbi A, Picone D, et al. Imaging of gastrointestinal stromal tumors: from diagnosis to evaluation of therapeutic response. Anticancer Res. 2016;36(6):2639–48.
22. Stroszczynski C, Jost D, Reichardt P, et al. Follow-up of gastrointestinal stromal tumours (GIST) during treatment with imatinib mesylate by abdominal MRI. Eur Radiol. 2005;15(12):2448–56. https://doi.org/10.1007/s00330-005-2867-x.
23. Joensuu H, Vehtari A, Riihimäki J, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol. 2012;13(3):265–74. https://doi.org/10.1016/S1470-2045(11)70299-6.
24. Joensuu H, Hohenberger P, Corless CL. Gastrointestinal stromal tumour. Lancet. 2013;382(9896):973–83. https://doi.org/10.1016/S0140-6736(13)60106-3.
25. Changchien CR, Wu M-C, Tasi W-S, et al. Evaluation of prognosis for malignant rectal gastrointestinal stromal tumor by clinical parameters and Immunohistochemical staining. Dis Colon Rectum. 2004;47(11):1922–9. https://doi.org/10.1007/s10350-004-0687-8.
26. Cavnar MJ, Wang L, Balachandran VP, et al. Rectal Gastrointestinal Stromal Tumor (GIST) in the era of Imatinib: organ preservation and improved oncologic outcome. Ann Surg Oncol. 2017;24(13):3972–80. https://doi.org/10.1245/s10434-017-6087-9.
27. Wilkinson MJ, Fitzgerald JEF, Strauss DC, et al. Surgical treatment of gastrointestinal stromal tumour of the rectum in the era of imatinib. Br J Surg. 2015;102(8):965–71. https://doi.org/10.1002/bjs.9818.
28. Corless CL, Ballman KV, Antonescu CR, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. J Clin Oncol. 2014;32(15):1563–70. https://doi.org/10.1200/JCO.2013.51.2046.
29. Benjamin RS, Casali PG. Adjuvant Imatinib for GI stromal tumors: when and for how long? J Clin Oncol. 2016;34(3):215–8. https://doi.org/10.1200/JCO.2015.64.0102.
30. Casali PG, Le Cesne A, Poveda Velasco A, et al. Time to definitive failure to the first tyrosine kinase inhibitor in localized GI stromal tumors treated with Imatinib as an adjuvant: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Intergroup Randomized Tr. J Clin Oncol. 2015;33(36):4276–83. https://doi.org/10.1200/JCO.2015.62.4304.
31. Joensuu H, Eriksson M, Sundby Hall K, et al. Adjuvant Imatinib for high-risk GI stromal tumor: analysis of a randomized trial. J Clin Oncol. 2016;34(3):244–50. https://doi.org/10.1200/JCO.2015.62.9170.
32. Raut CP, Espat NJ, Maki RG, et al. Efficacy and tolerability of 5-year adjuvant Imatinib treatment for patients with resected intermediate- or high-risk primary gastrointestinal stromal tumor. JAMA Oncol. 2018;4(12):e184060. https://doi.org/10.1001/jamaoncol.2018.4060.
33. Du C-Y, Zhou Y, Song C, et al. Is there a role of surgery in patients with recurrent or metastatic gastrointestinal stromal tumours responding to imatinib: a prospective randomised trial in China. Eur J Cancer. 2014;50(10):1772–8. https://doi.org/10.1016/j.ejca.2014.03.280.
34. Bauer S, Rutkowski P, Hohenberger P, et al. Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib – analysis of prognostic factors (EORTC-STBSG collaborative study). Eur J Surg Oncol. 2014;40(4):412–9. https://doi.org/10.1016/j.ejso.2013.12.020.
35. Yamanaka T, Takaki H, Nakatsuka A, et al. Radiofrequency ablation for liver metastasis from gastrointestinal stromal tumor. J Vasc Interv Radiol. 2013;24(3):341–6. https://doi.org/10.1016/j.jvir.2012.11.021.
36. Günter E, Lingenfelser T, Eitelbach F, Müller H, Ell C. EUS-guided ethanol injection for treatment of a GI stromal tumor. Gastrointest Endosc. 2003;57(1):113–5. https://doi.org/10.1067/mge.2003.39.
37. Oberndorfer S. Karzinoide tumoren des dunndarms. Frankf Z Pathol. 1907;1(7):426.
38. Byrne R, Pommier R. Small bowel and colorectal carcinoids. Clin Colon Rectal Surg. 2018;31(05):301–8. https://doi.org/10.1055/s-0038-1642054.
39. Wiedenmann B, John M, Ahnert-Hilger G, Riecken E-O. Molecular and cell biological aspects of neuroendocrine tumors of the gastroenteropancreatic system. J Mol Med. 1998;76(9):637–47. https://doi.org/10.1007/s001090050261.
40. Patel N, Barbieri A, Gibson J. Neuroendocrine tumors of the gastrointestinal tract and pancreas. Surg Pathol Clin. 2019;12(4):1021–44. https://doi.org/10.1016/j.path.2019.08.007.
41. Boudreaux JP, Klimstra DS, Hassan MM, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. Pancreas. 2010;39(6):753–66. https://doi.org/10.1097/MPA.0b013e3181ebb2a5.
42. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26(18):3063–72. https://doi.org/10.1200/JCO.2007.15.4377.
43. Korse CM, Taal BG, van Velthuysen M-LF, Visser O. Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: experience of two decades of cancer registry. Eur J Cancer. 2013;49(8):1975–83. https://doi.org/10.1016/j.ejca.2012.12.022.

44. Jetmore AB, Ray JE, Gathright BJ, McMullen KM, Hicks TC, Timmcke AE. Rectal carcinoids. Dis Colon Rectum. 1992;35(8):717–25. https://doi.org/10.1007/BF02050318.
45. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer. 2003;97(4):934–59. https://doi.org/10.1002/cncr.11105.
46. Anthony LB, Strosberg JR, Klimstra DS, et al. The NANETS consensus guidelines for the diagnosis and management of gastrointestinal Neuroendocrine Tumors (NETs). Pancreas. 2010;39(6):767–74. https://doi.org/10.1097/MPA.0b013e3181ec1261.
47. Chung TP, Hunt SR. Carcinoid and neuroendocrine tumors of the colon and rectum. Clin Colon Rectal Surg. 2006;19(2):45–8. https://doi.org/10.1055/s-2006-942343.
48. Ganim RB, Norton JA. Recent advances in carcinoid pathogenesis, diagnosis and management. Surg Oncol. 2000;9(4):173–9. https://doi.org/10.1016/S0960-7404(01)00007-X.
49. NCCN. Neuroendocrine tumors. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed February 4, 2020.
50. Barclay THC, Schapira DV. Malignant tumors of the small intestine. Cancer. 1983;51(5):878–81. https://doi.org/10.1002/1097-0142(19830301)51:5<878::AID-CNCR2820510521>3.0.CO;2-V.
51. Lucas KJ, Feldman JM. Flushing in the carcinoid syndrome and plasma kallikrein. Cancer. 1986;58(10):2290–3. https://doi.org/10.1002/1097-0142(19861115)58:10<2290::AID-CNCR2820581022>3.0.CO;2-4.
52. Lips CJ, Lentjes EG, Hoppener JW. The spectrum of carcinoid tumours and carcinoid syndromes. Ann Clin Biochem. 2003;40(6):612–27. https://doi.org/10.1258/000456303770367207.
53. Fujimura Y, Mizuno M, Takeda M, et al. A carcinoid tumor of the rectum removed by strip biopsy. Endoscopy. 1993;25(06):428–30. https://doi.org/10.1055/s-2007-1010353.
54. Semelka RC, Custodio CM, Balci NC, Woosley JT. Neuroendocrine tumors of the pancreas: spectrum of appearances on MRI. J Magn Reson Imaging. 2000;11(2):141–8. https://doi.org/10.1002/(SICI)1522-2586(200002)11:2<141::AID-JMRI10>3.0.CO;2-U.
55. Krenning EP, Kooij PPM, Bakker WH, et al. Radiotherapy with a radiolabeled somatostatin analogue, [111 In-DTPA-d-Phe 1]-Octreotide. Ann N Y Acad Sci. 1994;733(1 Molecular and):496–506. https://doi.org/10.1111/j.1749-6632.1994.tb17300.x
56. Reubi J, Laissue J, Waser B, Horisberger U, Schaer J. Expression of somatostatin receptors in normal, inflamed, and neoplastic human gastrointestinal tissues. Ann N Y Acad Sci. 1994;733(1 Molecular and):122–137. https://doi.org/10.1111/j.1749-6632.1994.tb17262.x
57. Geijer H, Breimer LH. Somatostatin receptor PET/CT in neuroendocrine tumours: update on systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2013;40(11):1770–80. https://doi.org/10.1007/s00259-013-2482-z.
58. Tirosh A, Kebebew E. The utility of 68Ga-DOTATATE positron-emission tomography/computed tomography in the diagnosis, management, follow-up and prognosis of neuroendocrine tumors. Future Oncol. 2018;14(2):111–22. https://doi.org/10.2217/fon-2017-0393.
59. Onozato Y, Kakizaki S, Iizuka H, Sohara N, Mori M, Itoh H. Endoscopic treatment of rectal carcinoid tumors. Dis Colon Rectum. 2010;53(2):169–76. https://doi.org/10.1007/DCR.0b013e3181b9db7b.
60. Chablaney S, Zator ZA, Kumta NA. Diagnosis and management of rectal neuroendocrine tumors. Clin Endosc. 2017;50(6):530–6. https://doi.org/10.5946/ce.2017.134.
61. Hay DJ, Curt JR. Carcinoid tumour as a complication of ulcerative colitis. Postgrad Med J. 1979;55(644):430–2. https://doi.org/10.1136/pgmj.55.644.430.
62. Dodd SM. Chronic ulcerative colitis complicated by atypical carcinoid tumour. J Clin Pathol. 1986;39(8):913–6. https://doi.org/10.1136/jcp.39.8.913.
63. Owen DA, Hwang WS, Thorlakson RH, Walli E. Malignant carcinoid tumor complicating chronic ulcerative colitis. Am J Clin Pathol. 1981;76(3):333–8. https://doi.org/10.1093/ajcp/76.3.333.
64. Breen EM, Misdraji J. Case 28-2000. Cabot RC, Scully RE, Mark EJ, et al., eds. N Engl J Med 2000;343(11):794–800. doi:https://doi.org/10.1056/NEJM200009143431108.
65. Rodrigues Â, Castro-Poças F, Pedroto I. Neuroendocrine rectal tumors: main features and management. GE Port J Gastroenterol. 2015;22(5):213–20. https://doi.org/10.1016/j.jpge.2015.04.008.
66. Kobayashi K, Katsumata T, Yoshizawa S, et al. Indications of endoscopic polypectomy for rectal carcinoid tumors and clinical usefulness of endoscopic ultrasonography. Dis Colon Rectum. 2005;48(2):285–91. https://doi.org/10.1007/s10350-004-0765-y.
67. Ford MM. Neuroendocrine tumors of the colon and rectum. Dis Colon Rectum. 2017;60(10):1018–21. https://doi.org/10.1097/DCR.0000000000000917.
68. Strosberg JR, Coppola D, Klimstra DS, et al. The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas. Pancreas. 2010;39(6):799–800. https://doi.org/10.1097/MPA.0b013e3181ebb56f.
69. Edge S, Byrd D, Compton C, Fritz A, Greene F, Trotti A. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.
70. Nehar D, Lombard-Bohas C, Olivieri S, et al. Interest of chromogranin a for diagnosis and follow-up of endocrine tumours. Clin Endocrinol. 2004;60(5):644–52. https://doi.org/10.1111/j.1365-2265.2004.02030.x.
71. Tormey WP, FitzGerald RJ. The clinical and laboratory correlates of an increased urinary 5-hydroxyindoleacetic acid. Postgrad Med J. 1995;71(839):542–5. https://doi.org/10.1136/pgmj.71.839.542.
72. Bajetta E, Ferrari L, Martinetti A, et al. Chromogranin A, neuron specific enolase, carcinoembryonic antigen, and hydroxyindole acetic acid evaluation in patients with neuroendocrine tumors. Cancer. 1999;86(5):858–65. https://doi.org/10.1002/(SICI)1097-0142(19990901)86:5<858::AID-CNCR23>3.0.CO;2-8.
73. Stinner B, Kisker O, Zielke A, Rothmund M. Surgical management for carcinoid tumors of small bowel, appendix, colon, and rectum. World J Surg. 1996;20(2):183–8. https://doi.org/10.1007/s002689900028.
74. Rösch T, Sarbia M, Schumacher B, et al. Attempted endoscopic en bloc resection of mucosal and submucosal tumors using insulated-tip knives: a pilot series. Endoscopy. 2004;36(9):788–801. https://doi.org/10.1055/s-2004-825838.
75. Yamamoto H. Endoscopic submucosal dissection of early cancers and large flat adenomas. Clin Gastroenterol Hepatol. 2005;3(7):S74–6. https://doi.org/10.1016/S1542-3565(05)00254-5.
76. Kajiyama T, Hajiro K, Sakai M, et al. Endoscopic resection of gastrointestinal submucosal lesions: a comparison between strip biopsy and aspiration lumpectomy. Gastrointest Endosc. 1996;44(4):404–10. https://doi.org/10.1016/S0016-5107(96)70089-5.
77. Berkelhammer C, Jasper I, Kirvaitis E, Schreiber S, Hamilton J, Walloch J. "Band-snare" resection of small rectal carcinoid tumors. Gastrointest Endosc. 1999;50(4):582–5. https://doi.org/10.1016/S0016-5107(99)70092-1.
78. Fujishiro M, Yahagi N, Nakamura M, et al. Successful outcomes of a novel endoscopic treatment for GI tumors: endoscopic submucosal dissection with a mixture of high-molecular-weight hyaluronic acid, glycerin, and sugar. Gastrointest Endosc. 2006;63(2):243–9. https://doi.org/10.1016/j.gie.2005.08.002.

79. Ono A, Fujii T, Saito Y, et al. Endoscopic submucosal resection of rectal carcinoid tumors with a ligation device. Gastrointest Endosc. 2003;57(4):583–7. https://doi.org/10.1067/mge.2003.142.
80. He L, Deng T, Luo H. Efficacy and safety of endoscopic resection therapies for rectal carcinoid tumors: a meta-analysis. Yonsei Med J. 2015;56(1):72. https://doi.org/10.3349/ymj.2015.56.1.72.
81. Shields CJ, Tiret E, Winter DC. Carcinoid tumors of the rectum: a multi-institutional international collaboration. Ann Surg. 2010;252(5):750–5. https://doi.org/10.1097/SLA.0b013e3181fb8df6.
82. Al Natour RH, Saund MS, Sanchez VM, et al. Tumor size and depth predict rate of lymph node metastasis in colon carcinoids and can be used to select patients for endoscopic resection. J Gastrointest Surg. 2012;16(3):595–602. https://doi.org/10.1007/s11605-011-1786-1.
83. Schindl M, Niederle B, Häfner M, et al. Stage-dependent therapy of rectal carcinoid tumors. World J Surg. 1998;22(6):628–34. https://doi.org/10.1007/s002689900445.
84. Cestaro G, Amato B, De Rosa M, Bianco T, Compagna R, Massa G, Vigliotti G, MSGM. Neuroendocrine tumors of the rectum: an updated review. Minerva Chir. 2014;69(April):67–71.
85. Eriksson B, Arnberg H, Öberg K, et al. A polyclonal antiserum against chromogranin A and B – a new sensitive marker for neuroendocrine tumours. Acta Endocrinol. 1990;122(2):145–55. https://doi.org/10.1530/acta.0.1220145.
86. Rinke A, Müller H-H, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. J Clin Oncol. 2009;27(28):4656–63. https://doi.org/10.1200/JCO.2009.22.8510.
87. Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371(3):224–33. https://doi.org/10.1056/NEJMoa1316158.
88. Wolin E, Jarzab B, Eriksson B, et al. Phase III study of pasireotide long-acting release in patients with metastatic neuroendocrine tumors and carcinoid symptoms refractory to available somatostatin analogues. Drug Des Devel Ther. September 2015;5075 https://doi.org/10.2147/DDDT.S84177.
89. Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG. Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: eastern cooperative oncology group study E1281. J Clin Oncol. 2005;23(22):4897–904. https://doi.org/10.1200/JCO.2005.03.616.
90. Schnirer II, Yao JC, Ajani JA. Carcinoid a comprehensive review. Acta Oncol (Madr). 2003;42(7):672–92. https://doi.org/10.1080/02841860310010547.
91. Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG. Surgical treatment of neuroendocrine metastases to the liver. J Am Coll Surg. 2003;197(1):29–37. https://doi.org/10.1016/S1072-7515(03)00230-8.
92. Christante D, Pommier S, Givi B, Pommier R. Hepatic artery chemoinfusion with chemoembolization for neuroendocrine cancer with progressive hepatic metastases despite octreotide therapy. Surgery. 2008;144(6):885–94. https://doi.org/10.1016/j.surg.2008.08.037.
93. Gedaly R. Liver transplantation for the treatment of liver metastases from neuroendocrine tumors. Arch Surg. 2011;146(8):953. https://doi.org/10.1001/archsurg.2011.186.
94. Shen C, Yin Y, Chen H, et al. Neuroendocrine tumors of colon and rectum: validation of clinical and prognostic values of the World Health Organization 2010 grading classifications and European Neuroendocrine Tumor Society staging systems. Oncotarget. 2017;8(13):22123–34. https://doi.org/10.18632/oncotarget.13641.
95. Scherübl H, Klöppel G. Neuroendokrine Neoplasien des Rektums auf dem Vormarsch – ein Update. Z Gastroenterol. 2009;47(04):365–71. https://doi.org/10.1055/s-2008-1027930.
96. Surveillance, Epidemiology, and End Results Program. National Cancer Institute. https://seer.cancer.gov. Published 2006. Accessed February 4, 2020.
97. Zighelboim J, Larson MV. Primary colonic lymphoma: clinical presentation, histopathologic features, and outcome with combination chemotherapy. J Clin Gastroenterol. 1994;18(4):291–7. https://doi.org/10.1097/00004836-199406000-00007.
98. Doolabh N, Anthony T, Simmang C, et al. Primary colonic lymphoma. J Surg Oncol. 2000;74(4):257–62. https://doi.org/10.1002/1096-9098(200008)74:4<257::AID-JSO3>3.0.CO;2-U.
99. Kang H, O'Connell JB, Leonardi MJ, Maggard MA, McGory ML, Ko CY. Rare tumors of the colon and rectum: a national review. Int J Color Dis. 2007;22(2):183–9. https://doi.org/10.1007/s00384-006-0145-2.
100. Papamichael K, Lin S, Moore M, Papaioannou G, Sattler L, Cheifetz AS. Infliximab in inflammatory bowel disease. Ther Adv Chronic Dis. 2019;10(Table 2):204062231983844. https://doi.org/10.1177/2040622319838443
101. Kotlyar DS, Lewis JD, Beaugerie L, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. Clin Gastroenterol Hepatol. 2015;13(5):847–858.e4. https://doi.org/10.1016/j.cgh.2014.05.015.
102. Kandiel A, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. Gut. 2005;54(8):1121–5. https://doi.org/10.1136/gut.2004.049460.
103. Henry CBR. Primary lymphoma of the large intestine. Am Surg. 1988;54(5):262–6.
104. Devaney K, Jaffe ES. The surgical pathology of gastrointestinal Hodgkin's disease. Am J Clin Pathol. 1991;95(6):794–801. https://doi.org/10.1093/ajcp/95.6.794.
105. Gay ND, Chen A, Okada CY. Colorectal lymphoma: a review. Clin Colon Rectal Surg. 2018;31(5):309–16. https://doi.org/10.1055/s-0038-1642048.
106. Myung SJ, Joo KR, Yang SK, et al. Clinicopathologic features of ileocolonic malignant lymphoma: analysis according to colonoscopic classification. Gastrointest Endosc. 2003;57(3):343–7. https://doi.org/10.1067/mge.2003.135.
107. Rohatiner A, d'Amore F, Coiffier B, et al. Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. Ann Oncol. 1994;5(5):397–400. https://doi.org/10.1093/oxfordjournals.annonc.a058869.
108. Rosenberg S. Validity of the Ann Arbor staging classification for the non-Hodgkin's lymphomas. Cancer Treat Rep. 1977;61(6):1023–7.
109. Moormeier JA, Williams SF, Golomb H. The staging of non-Hodgkin's lymphomas. Semin Oncol. 1990;17(01):43–50.
110. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the committee on Hodgkin's disease staging classification. Cancer Res. 1971;31:1860–1.
111. Lee J, Kim WS, Kim K, et al. Prospective clinical study of surgical resection followed by CHOP in localized intestinal diffuse large B cell lymphoma. Leuk Res. 2007;31(3):359–64. https://doi.org/10.1016/j.leukres.2006.06.018.
112. Kim SJ, Kang HJ, Kim JS, et al. Comparison of treatment strategies for patients with intestinal diffuse large B-cell lymphoma:

surgical resection followed by chemotherapy versus chemotherapy alone. Blood. 2011;117(6):1958–65. https://doi.org/10.1182/blood-2010-06-288480.
113. Jinnai D, Iwasa Z, Watanuki T. Malignant lymphoma of the large intestine —operative results in Japan. Jpn J Surg. 1983;13(4):331–6. https://doi.org/10.1007/BF02469515.
114. Lai Y-L, Lin J-K, Liang W-Y, Huang Y-C, Chang S-C. Surgical resection combined with chemotherapy can help achieve better outcomes in patients with primary colonic lymphoma. J Surg Oncol. 2011;104(3):265–8. https://doi.org/10.1002/jso.21927.
115. Quayle FJ, Lowney JK. Colorectal lymphoma. Clin Colon Rectal Surg. 2006;19(2):49–53. https://doi.org/10.1055/s-2006-942344.
116. Devine RM, Beart RW, Wolff BG. Malignant lymphoma of the rectum. Dis Colon Rectum. 1986;29(12):821–4. https://doi.org/10.1007/BF02555355.
117. Takenaka R, Tomoda J, Sakata T, et al. Mucosa-associated lymphoid tissue lymphoma of the rectum that regressed spontaneously. J Gastroenterol Hepatol. 2000;15(3):331–5. https://doi.org/10.1046/j.1440-1746.2000.02086.x.
118. Tsang RW, Gospodarowicz MK, Pintilie M, et al. Stage I and II malt lymphoma: results of treatment with radiotherapy. Int J Radiat Oncol Biol Phys. 2001;50(5):1258–64. https://doi.org/10.1016/S0360-3016(01)01549-8.
119. Okamura T, Suga T, Iwaya Y, et al. Helicobacter pylori-negative primary rectal MALT lymphoma: complete remission after radiotherapy. Case Rep Gastroenterol. 2012;6(2):319–27. https://doi.org/10.1159/000339461.
120. Orita M, Yamashita K, Okino M, Enoki T, Noshima S, Morita N, Esato K. A case of MALT (mucosa-associated lymphoid tissue) lymphoma occurring in the rectum. Hepato-Gastroenterology. 1999;46(28):2352–4.
121. Kiesewetter B, Ferreri AJM, Raderer M. Chemoimmunotherapy for mucosa-associated lymphoid tissue-type lymphoma: a review of the literature. Oncologist. 2015;20(8):915–25. https://doi.org/10.1634/theoncologist.2015-0109.
122. Shia J, Teruya-Feldstein J, Pan D, et al. Primary follicular lymphoma of the gastrointestinal tract: a clinical and pathologic study of 26 cases. Am J Surg Pathol. 2002;26(2):216–24. https://doi.org/10.1097/00000478-200202000-00008.
123. Kim YH, Lee JH, Yang SK, et al. Primary colon lymphoma in Korea: a KASID (Korean Association for the Study of Intestinal Diseases) study. Dig Dis Sci. 2005;50(12):2243–7. https://doi.org/10.1007/s10620-005-3041-7.
124. Romaguera J, Hagemeister FB. Lymphoma of the colon. Curr Opin Gastroenterol. 2005;21(1):80–4.
125. Xu G, Wang P, Xiao Y, Wu X, Lin G. Local resection of rectal neuroendocrine tumor with first clinical manifestation of giant liver metastasis by transanal endoscopic microsurgery: a case report. Med (United States). 2017;96(50). https://doi.org/10.1097/MD.0000000000009153

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

35

Michael A. Valente and Brendan John Moran

Key Concepts

- Peritoneal dissemination is a frequent occurrence in the natural history of colorectal cancer, which may be synchronous or metachronous.
- The clinical benefit of systemic chemotherapy in patients with colorectal peritoneal metastases is less than in patients with other metastatic sites.
- A substantial survival benefit, with some patients cured, can be achieved in selected patients undergoing CRS and HIPEC.
- Outcome of CRS and HIPEC for colorectal peritoneal metastases is best in patients with low disease burden and complete cytoreduction.
- Currently, a shift in focus is taking place from treatment of established colorectal peritoneal metastases to prevention and early detection, by identification of patients at high risk for developing colorectal peritoneal metastases.
- Combining CRS and HIPEC with limited resection of liver metastases is feasible and achieves good oncological outcomes in a highly selected group of patients.

Introduction

Peritoneal malignancy is a neoplastic condition affecting the peritoneum and may be primary or secondary. Primary peritoneal malignancy, such as peritoneal mesothelioma, is rare and much less frequent compared with secondary peritoneal malignancy, with the commonest primaries being advanced gastrointestinal tract cancers including colorectal, appendiceal, gastric, and nongastrointestinal causes, namely ovarian. In many patients, the disease diffusely involves the peritoneal cavity, including both the parietal and visceral peritoneum. This is termed carcinomatosis. Carcinomatosis is common in end stage gastrointestinal tract cancers and is a terminal event in many patients, often leading to inoperable gastrointestinal tract obstruction.

The visceral peritoneum covers all intraperitoneal organs, including the small and large bowel. Diffuse disease of the peritoneum, of the small bowel in particular, traditionally has precluded attempts at surgical cure. Palliative treatment by best supportive care, systemic drug treatments, and optimal pain relief provides best outcomes. Select patients with malignant intestinal obstruction may benefit from venting gastrostomy, palliative endoluminal stenting, or rarely surgical bypass.

In the past three decades a novel strategy has been proposed, and popularized, for select patients with peritoneal malignancy – cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). The technique arose from seminal work by Paul Sugarbaker and colleagues at the National Institute of Health in the 1980s. The anti-cancer drug 5-fluorouracil (5-FU), developed in 1957 and still in use today as a key component of practically all colorectal cancer chemotherapeutic regimens, was evaluated in a randomized controlled trial, administered by either intravenous or intraperitoneal administration in patients with advanced colon or rectal cancer [1]. A unique feature of this study was a per protocol second look laparotomy at 6 months postoperatively. The number of patients recruited was low and the route of administration did not improve survival, or time to recurrence. However, intraperitoneal 5-FU significantly reduced peritoneal implants at second look laparotomy with 2 out of 10 having peritoneal carcinomatosis in the intraperitoneal 5-FU group compared with 10 out of 11 in the systemic 5-FU group. The concept of peritoneal disease control by intraperitoneal chemotherapy was a stimulus to pursue

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this strategy for patients with pseudomyxoma peritonei (PMP) where, despite low-grade histological features, disease progresses within the peritoneal cavity, usually without other metastatic disease, and surgery alone generally fails to control the disease. Sugarbaker proposed, and popularized, this treatment for PMP. The indications gradually expanded to include other visceral malignancies. CRS and HIPEC have evolved into an effective oncological treatment strategy in select patients, and one of the fastest growing novel surgical cancer strategies of the past two decades.

Pseudomyxoma Peritonei (PMP): The Pathophysiology of Peritoneal Disease and the Re-distribution Phenomenon

Pseudomyxoma peritonei (PMP) is an uncommon condition and until recently was reported to have an incidence of one per million per year. This figure of one per million arose not from hard data, but rather was a relatively crude estimate made by one of the authors of this chapter (BJM) in an application to the English National Institute of Health Commissioning Service to establish a treatment center in 2000. Interestingly this figure, which was based merely on guesswork, was adopted globally as the widely accepted incidence of the condition, partly due to a publication by the English National Institute for Clinical Effectiveness (NICE) in 2004 entitled "Complete cytoreduction for Pseudomyxoma (Sugarbaker technique)" [2].

However, the true incidence of PMP is now considered two to four operable cases, per million, per year. PMP is characterized by diffuse mucinous ascites secondary to peritoneal implants and colloquially PMP is also known as "jelly belly" [3]. PMP was traditionally considered a benign condition, but its behavior over time suggests that it should always be considered, at best, a "borderline malignant" condition with inevitable disease persistence and progression [3]. While traditionally diagnosed at laparotomy, increasingly the diagnosis is considered prior to laparotomy, due to increased awareness of the condition and advances in cross-sectional imaging and percutaneous biopsy techniques.

The term "pseudomyxoma peritonei" was coined by Werth in 1884 in a woman with a mucinous carcinoma of the ovary, and Frankel went on to describe a case of PMP in association with a cyst of the appendix in 1901 [3]. While there has been ongoing discussion as to the origin of PMP, particularly in females, most authorities, and recent reviews, now accept that, in the majority of patients with PMP, the primary is a perforated mucinous epithelial tumor of the appendix [4].

Recently, a consensus agreement was published on the pathological classification of primary tumors of the appendix and peritoneal implants, by Carr and colleagues on behalf of the Peritoneal Surface Oncology Group International (PSOGI) group [5]. Appendiceal tumors are characterized as low-grade appendiceal mucinous neoplasms (LAMNs), high-grade appendiceal mucinous neoplasms (HAMNs), and appendiceal adenocarcinomas with, or without, signet ring cell morphology. Peritoneal implants are classified as either mucinous carcinoma peritonei-low grade or mucinous carcinoma peritonei-high grade (see Chap. 41, *Appendiceal Neoplasms)* [6]. All types of mucinous appendiceal tumors (from low grade to signet ring cell) can result in mucinous ascites, manifesting as the clinical syndrome of PMP. Compared with colorectal cancers, appendiceal mucinous neoplasms usually stay confined to the peritoneal cavity and rarely metastasize to lymph nodes or other distant sites, and thus, systemic chemotherapy is generally not effective in these patients. These facts make these patients candidates for aggressive locoregional therapy, namely CRS and HIPEC.

Despite the rarity of PMP, there are now a number of publications reporting long-term outcomes, in large series from both single and multiple centers [7, 8]. Current intraperitoneal treatment strategies of other peritoneal malignancies have evolved mainly from experience with PMP.

The Peritoneal Cavity

The anatomy and pathophysiology of the peritoneal cavity are poorly understood. The peritoneum is a serous membrane that lines the abdominal cavity and envelops most of the abdominal organs. The peritoneum originates from the mesoderm and is composed of a layer of mesothelium, supported by a thin layer of connective tissue. The peritoneal lining of the abdominal cavity supports many of the abdominal organs and serves as a conduit for blood vessels, lymphatics, and nerves to the abdominal organs. The peritoneum is one continuous sheet, forming into two layers with a potential space, the peritoneal cavity, in between. The outer layer (parietal peritoneum) is attached to the inside of the abdominal wall and the walls of the pelvis. The inner layer (visceral peritoneum) is thinner than the parietal peritoneum and envelops the intraperitoneal organs. The mesentery is a double layer of visceral peritoneum, attached to the gastrointestinal tract, enveloping the blood supply, lymphatics, and nerves to the gastrointestinal tract organs.

The peritoneal cavity contains approximately 50 milliliters of serous fluid which acts as a lubricant allowing gastrointestinal peristalsis and motility. The peritoneal cavity is subdivided into the greater sac (the main peritoneal cavity) and the lesser sac, enveloped by the lesser and greater omentum (Fig. 35.1). The lesser (gastro-hepatic) omentum is attached to the lesser curve of the stomach and the liver. The greater omentum (gastrocolic) is attached to the greater curve of the stomach, forms the anterior border of the lesser

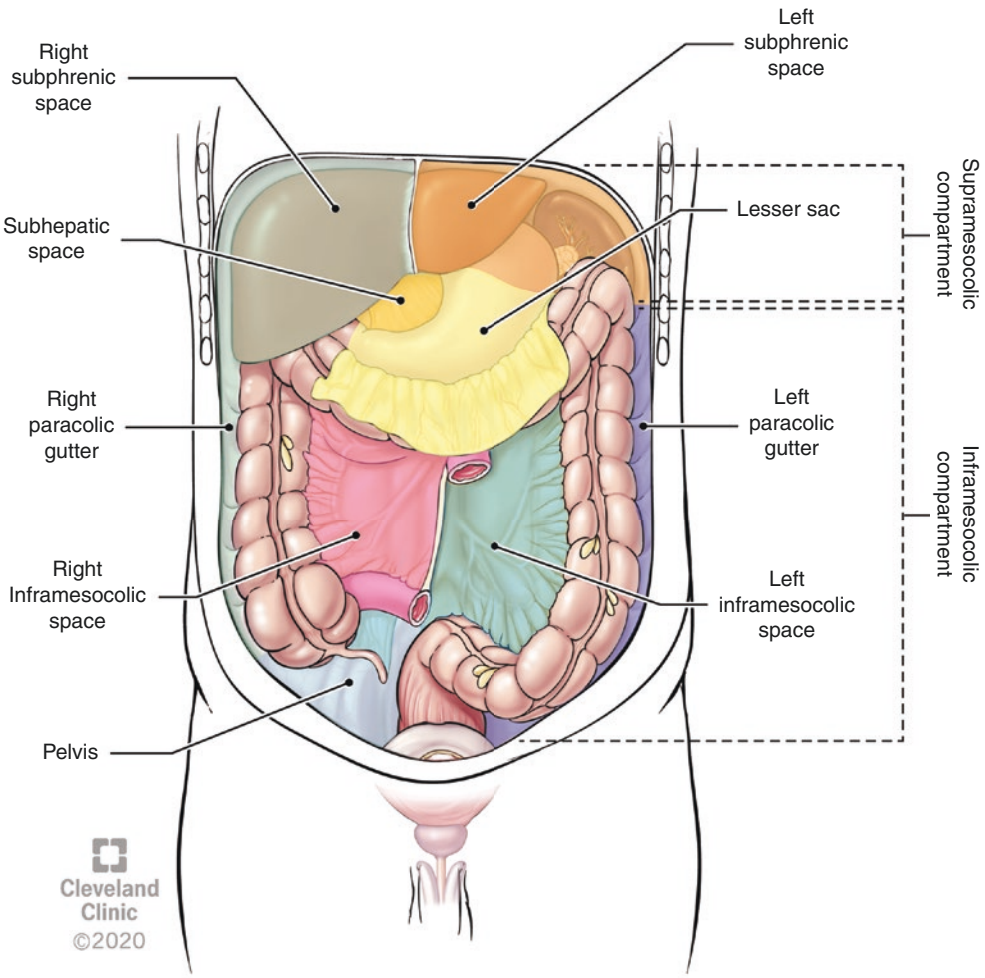

Fig. 35.1 The peritoneal cavity and spaces. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2020. All Rights Reserved)

sac, then extends inferiorly for a variable distance anterior to the intestines, and then curves superiorly to attach to the transverse colon and acts as an insulating and protective layer. The omentum has often been called "the policeman" of the abdomen as it moves toward, and tries to contain, intraperitoneal inflammatory pathology.

The fluid in the peritoneal cavity originates from serous glands and is constantly being produced, renewed, and absorbed to maintain homeostasis. The main purpose of this fluid is as a lubricant, similar to oil in an internal combustion engine in a motorcar. As in a combustion engine, where an oil filter is required to remove particles from the combustion process, the peritoneal cavity has absorption and filtration systems that both remove fluid and filter out abnormal contents, such as bacteria or free-floating cells. The main sites of fluid absorption are the under-surfaces of the diaphragm (particularly the right side) and the greater and lesser omentum.

The distribution and spread of PMP within the peritoneal cavity have been described as the "*re-distribution phenomenon*" (Fig. 35.2) [9]. Redistribution involves three main mechanisms, namely normal peritoneal fluid circulation and absorption, an effect of gravity in the standing and lying position, and relative (indeed often total) sparing of motile organs, particularly the small bowel. Figure 35.2 outlines an appendix tumor with peritoneal spread, but the concept is similar for any motile cells within the peritoneal cavity. Fluid, containing tumor cells, is absorbed and filtered in two main areas, namely the omentum (particularly the greater omentum) and via lacunae on the under-surface of the diaphragm (particularly on the right side). This accounts for the concentration of disease in the greater omentum (the so-called omental cake) as the omentum functions to absorb fluid and concentrate malignant cells.

Gravitational effects result in disease concentration in the pelvis and paracolic gutters. Constant peristaltic movement of the intestinal organs, particularly the small bowel, offers relative protection from tumor involvement, although more invasive tumor cells (colorectal adenocarcinoma, for example), surgical adhesions, and advanced disease often overcome this protective effect, ultimately resulting in small bowel involvement.

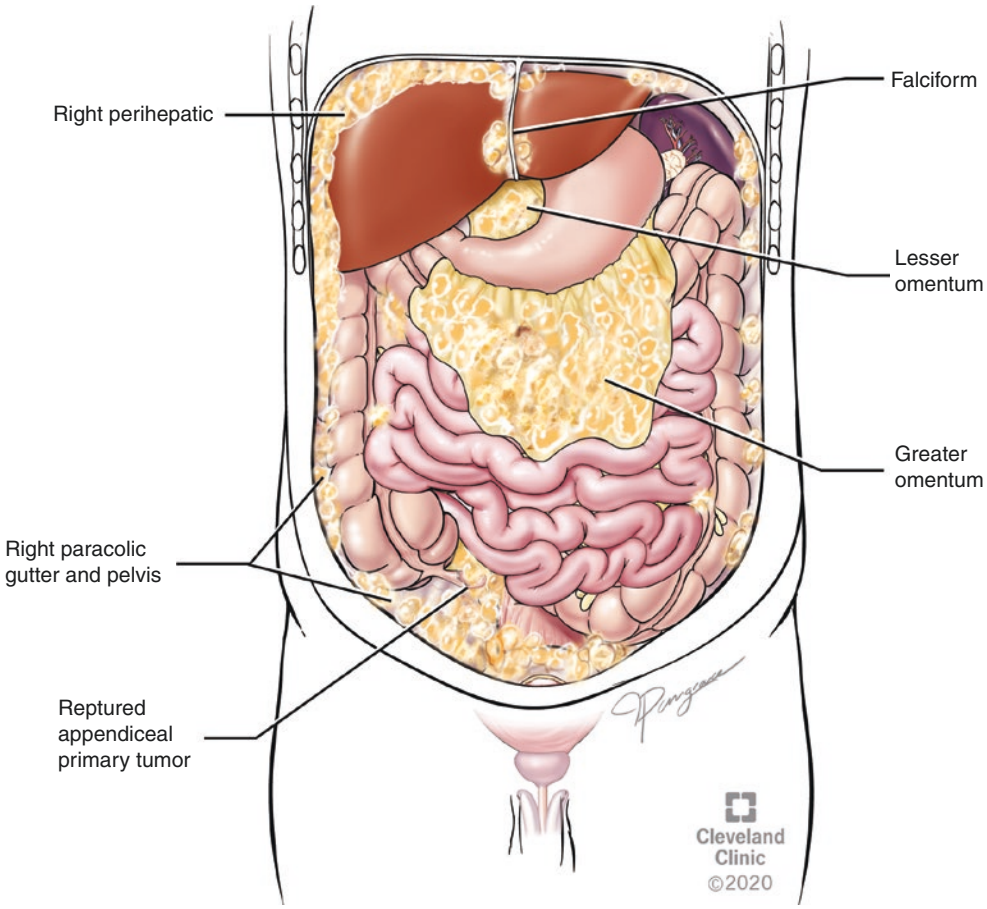

Fig. 35.2 Ruptured appendiceal neoplasm highlighting the "redistribution phenomenon." (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2020. All Rights Reserved)

The concepts of the redistribution phenomenon are applicable to all peritoneal malignancies where distribution and concentration of disease follow these mechanisms.

Colorectal Cancer and the Concept of Resectable Peritoneal Metastases

As outlined previously, "carcinomatosis" implies diffuse peritoneal disease and is a feature of advanced colorectal cancer. Colorectal cancer cells are generally more aggressive, and invasive, compared with low-grade appendiceal neoplasms and commonly invade the small bowel peritoneum, and indeed the wall of the bowel. In these scenarios CRS may not be possible, as removal of large parts of the small bowel will result in degrees of intestinal failure and poor quality of life. Thus, in the context of CRS and HIPEC for advanced colorectal cancer we favor the term "colorectal peritoneal metastases" (CPM) rather than "carcinomatosis." This terminology is analogous to similar terminology for liver, lung, and other metastatic disease, aiming to clarify that colorectal "carcinomatosis" (diffuse peritoneal disease) is not amenable to cure by CRS and HIPEC and that *resectable* CPM is the basis for case selection. Colorectal adenocarcinoma metastasizes by lymphatic, hematogenous, and transperitoneal dissemination. Synchronous CPM occurs in approximately 7% of patients, while a further 10–20% of patients develop metachronous CPM [10, 11]. Risk factors for peritoneal dissemination include T4 stage, possibly intraluminal stenting of an obstructing tumor, tumor perforation, poor differentiation grade, mucinous histology, and signet ring cell histology [12–14].

Various hypotheses exist regarding the pathogenesis of peritoneal metastases, some suggesting direct transperitoneal spread while others suggesting subperitoneal lymphatic dissemination pathways in addition to transperitoneal spread. Regardless of the specific pathway, peritoneal dissemination of free-floating peritoneal tumor cells may occur via the redistribution phenomenon and may follow predictable patterns of disease spread, as occurs in pseudomyxoma peritonei (PMP). These sites include the greater omentum, the pelvis, and ovaries in females and on the right hemidiaphragm with relative sparing of the small bowel [15]. Consequently, it is crucial to focus on these sites (the under surface of the right diaphragm, the omentum, and the pelvis) at cross-sectional imaging, laparoscopy, or laparotomy, when assessing patients with colorectal cancer for peritoneal spread.

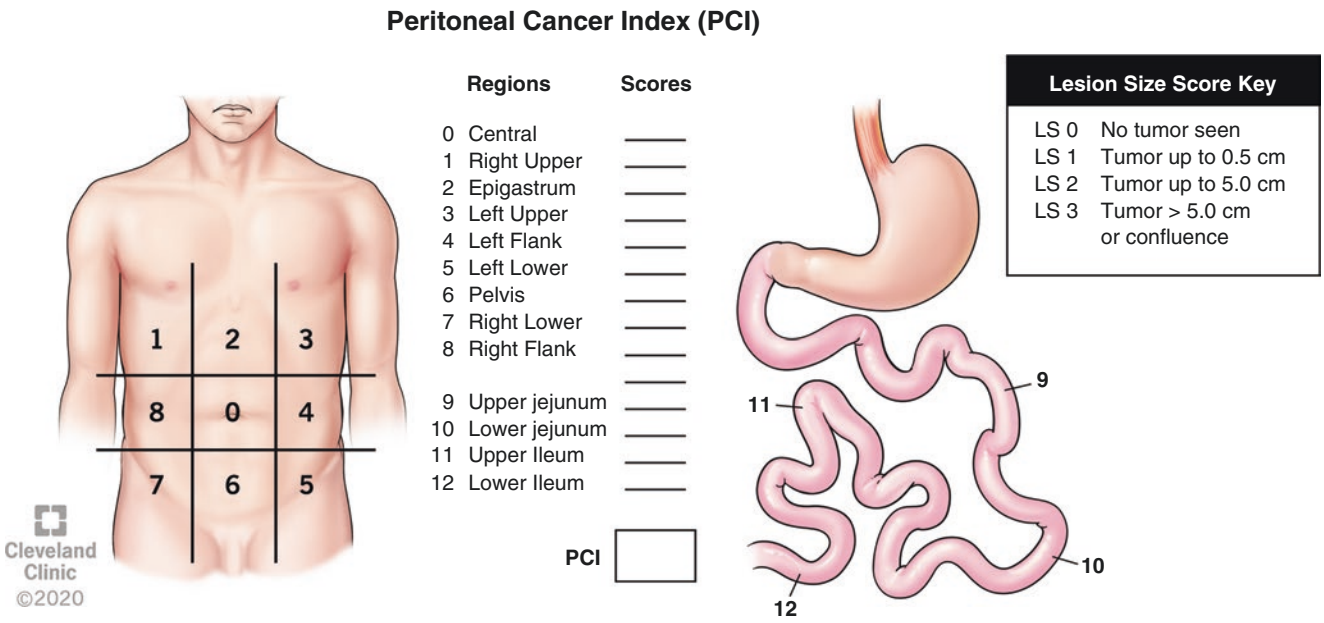

Fig. 35.3 The Peritoneal Cancer Index (PCI). (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2020. All Rights Reserved)

There are some crucial differences with CPM when compared to PMP. Firstly, due to the invasive nature of tumor deposits, small bowel serosal or mesenteric involvement is more common, which has clear implications for treatment and prognosis. Additionally, as a significant proportion of CPM are metachronous and occur in patients who have already undergone surgical resection, tumor deposits often develop along previously dissected tissue planes, such as Toldt's fascia and, in patients with previous rectosigmoid tumors, in the presacral/mesorectal excision plane.

An ongoing issue is that low-volume, diffuse disease is virtually impossible to detect by any current noninvasive imaging modality and neither CT, PET-CT nor MRI accurately detects lesions below 3–5 mm in size. For this reason, diagnostic laparoscopy may provide a more accurate assessment, at least of the accessible peritoneal cavity, if CRS and HIPEC are planned for patients with colorectal peritoneal metastases.

The Peritoneal Cancer Index (PCI)

The extent and distribution of peritoneal malignancy determine the likelihood that the disease can be surgically resected, the extent of the surgical procedure required, and the long-term prognosis in terms of disease control. The two major prognostic factors in patients undergoing surgical treatment of peritoneal malignancy are completeness of tumor resection and extent of peritoneal disease. Unsurprisingly, these prognostic factors are collinear, in that complete cytoreduction is more likely in cases of limited disease.

The most widely used and comprehensive staging system for peritoneal disease is the peritoneal cancer index (PCI), described by Sugarbaker as a record of disease extent assessed at laparotomy (Fig. 35.3) [16]. The abdomen is divided into nine regions with four further regions of the small bowel, giving thirteen regions in total. Lesion size in each region is counted as 0–3, where 0 equals no disease and 3 is tumor masses >5 cm. Thus, PCI score may range from 0 to a maximum of 39.

In patients with CPM, complete cytoreduction and HIPEC result in overall 5-year survival rates of 40–60% in highly selected patients [17–19]. However, pre-resection PCI appears to be an independent predictor of survival after CRS and HIPEC for CPM, even if patients have had complete cytoreduction [20–22]. One of the largest reports on patients treated with CRS and HIPEC for CPM, a retrospective study of 525 patients, treated by a French multicenter group, demonstrated that 5-year overall survival rates were significantly different dependent on the PCI at laparotomy. The 5-year survival was 44% for PCI < 6, 22% for PCI 7–12, and 7% for PCI >19 [22]. In addition, unsurprisingly, the rates of postoperative morbidity and mortality correlated with increasing PCI in this series.

The limitations of PCI are that its accuracy can only be assessed at laparotomy. However, there are increasing attempts to estimate PCI using other methods. Cross-sectional imaging, in the form of CT, PET-CT, and MRI, is being used to give an estimate of PCI. Due to the limitations

of imaging for low-volume disease, this should be classified as "Radiological PCI." It is also possible to estimate "Laparoscopic PCI" during laparoscopic assessment of the peritoneal cavity, which is more feasible and accurate if a primary tumor is in place and there has been no, or little, prior abdominal surgery. In the field of colorectal peritoneal metastases, most patients considered for CRS have had the primary tumor excised, and indeed many may have initially presented as an emergency with bowel obstruction, such that laparoscopic assessment may be difficult, dangerous, and limited by adhesions. In summary, "Radiological and Laparoscopic PCI" are helpful, in that the morbidity of laparotomy is often avoided, although it should be remembered that these assessment modalities commonly underestimate the actual PCI as determined at laparotomy.

PCI has also been applied to measure peritoneal tumor burden in other diseases, such as PMP. However, it is important to realize that the "C" in PCI is for cancer and PCI was not designed to evaluate PMP, which varies from low grade to high grade, both with regard to histologic appearance and disease behavior. Although "PCI" is useful in PMP as a measure of extent of disease, PCI should *not* be used to select patients with PMP for CRS and HIPEC, because PMP patients with high PCI scores are often amenable to complete CRS, and potentially cure, especially when treated in a high-volume specialized unit.

Cytoreductive Surgery: "Complete Cytoreductive (CC)" Scoring System

The concept of cytoreductive surgery (CRS) involves complete macroscopic tumor removal based on fundamental surgical principles and an understanding of the "re-distribution" of tumor within the peritoneal cavity. In this context CRS will usually encompass a radical greater and lesser omentectomy, pelvic and possibly diaphragmatic peritonectomy, and bilateral oophorectomy in females. Depending on the extent of associated bowel resections, a temporary or permanent stoma may be necessary. Temporary stomas are usually fashioned for more extensive left-sided anastomoses but should be considered for all anastomoses, if anatomically possible. There are no definitive data to guide the decision to construct an anastomosis before or after the administration of chemotherapy. Similarly, the choice of stapled or hand-sewn anastomotic technique has not proven to be associated with outcome [23–28].

One of the most important prognostic factors in CRS is the completeness of cytoreduction score (CCS). The CCS is performed by the surgeon at the end of the procedure and classified as follows: CC-0 indicates that no visible macroscopic residual cancer remains on any peritoneal surface; a CC-1 indicates persistent tumor nodules of <2.5 mm in size. It should be noted that any tumor nodule that is smaller than 2.5 mm may be amenable to eradication by intraperitoneal chemotherapy, and thus CC-1 is classified along with CC-0 as a complete cytoreduction (including for PMP from LAMN). CC-2 refers to residual tumors after cytoreduction that are between 2.5 and 25.0 mm; CC-3 refers to residual tumors after cytoreduction that are greater than 25.0 mm (or a confluence of unresectable tumor nodules at any site in the peritoneal cavity).

Table 35.1 Peritonectomy procedures and organ resections in cytoreductive surgery

Peritonectomy	Organ resections
Right parietal	Greater omentum
Left parietal	Lesser omentum
Pelvic	Spleen
Right diaphragmatic	Ovaries/fallopian tubes
Left diaphragmatic	Uterus
Right liver capsulectomy	Gall gladder
Left liver capsulectomy	Partial/total gastrectomy

The principles of cytoreductive surgery have mostly emanated from surgical management of PMP where, paradoxically, the most extensive surgery may be required for what is pathologically the least aggressive disease. The peritonectomy procedures and the main organs resected in patients with PMP are outlined in Table 35.1. In clinical practice, patients with advanced PMP may require a combination of the majority of these procedures. Partial or complete gastric resection is clearly a major procedure and not commonly required, though in a large series reported by DiFabio et al., 12% of all patients with PMP treated by CRS and HIPEC had a partial or total gastrectomy [29]. Clearly such combinations of extensive resections are unlikely to be of benefit to patients with biologically more aggressive disease, such as CPM.

In contrast to PMP, where both CC0 and CC1 are considered a complete cytoreduction, previous studies in CPM have shown that significant survival benefit of CRS and HIPEC for CPM is achieved primarily in patients undergoing a CC0 cytoreduction, and that CC1 has poorer outcomes [17, 18, 30]. Unfortunately, a complete cytoreduction is not achievable in a significant proportion (estimated at approximately 20%) of patients at operation for established CPM, due to either disease volume or distribution [8]. The main drawback to the CC score is that it can only be calculated after the surgical procedure has been completed.

Extensive small bowel involvement is the most frequent reason for (expected) incomplete cytoreduction, in which case the procedure may have to be abandoned (Fig. 35.4). In contrast to PMP, there is little evidence to support a role for surgical debulking procedures in the treatment of extensive CPM; a possible exception may be palliative bilateral salpingoophorectomy in patients with progressive, chemotherapy-resistant, and symptomatic ovarian metastases.

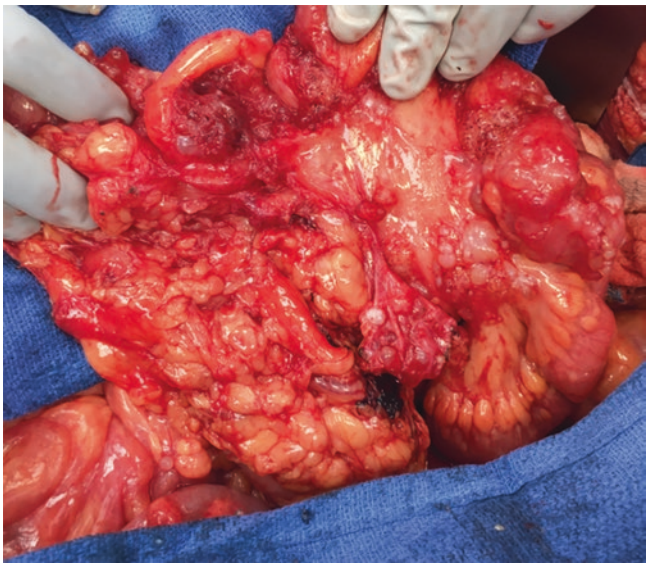

Fig. 35.4 Extensive small bowel involvement precluding a complete cytoreduction in a patient with colorectal peritoneal metastases

The outcome of CRS and HIPEC for colorectal peritoneal metastases depends on various factors, the most important of which are initial disease extent (traditionally, PCI > 19 has been considered a contraindication to surgery) and completeness of cytoreduction [21, 22, 31]. A complete cytoreduction and HIPEC is associated with 5-year survival rates of 40–60% in a highly selected patient population [17, 18, 21, 30–32].

In addition to disease extent and completeness of cytoreduction, prognosis is also adversely affected by signet ring cell histology, presence of systemic metastases, and increased expression of vascular endothelial growth factor (VEGF) by tumor cells [33]. A recent report has also suggested that the outcomes of CRS and HIPEC in patients with inflammatory bowel disease-related colorectal cancer are significantly worse compared to patients without inflammatory bowel disease [34]. In addition, the detection of free cancer cells in peritoneal fluid cytology is associated with reduced survival, although the clinical significance of this finding as an independent prognostic variable is debated [35, 36].

In contrast to traditional belief, the presence of ovarian metastases of colorectal cancer origin is no longer considered to be associated with decreased survival outcomes, provided that a complete cytoreduction is achieved and combined with HIPEC [37, 38].

Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

Hyperthermia has for many years been proposed in the treatment of malignancy and has anti-tumor effects and enhances the effect of several anti-cancer drugs. In the last two decades of the twentieth century, experimental evidence supported the safety and efficacy of perfusion of warm chemotherapy, at temperatures of 42–43 °C, in both animals and humans.

Personal experience by one of the authors (BJM) also noted that perfusion of heated chemotherapy helps to restore patient physiology as patients undergoing CRS are often hypothermic at the end of a long laparotomy, despite efforts to maintain body temperature by "Bear Huggers" and the use of heated intravenous fluids. The normalization of body temperature, and the time taken for chemotherapy perfusion, was noted to markedly reduce the need for reoperation for bleeding in the postoperative period.

In the last decade of the twentieth century, there were a number of names for the concept of heated chemotherapy, which included CHIP (chemo-hyperthermie intraperitonei) by the French, HIPC (heated intraperitoneal chemotherapy) and IPHC (Intra Peritoneal Hyperthermic Chemotherapy) by North American groups, and HIPEC (hyperthermic intraperitoneal chemotherapy) by the Dutch. Moran proposed in 2002 that the most appropriate term to describe the entity was HIPEC and the term HIPEC gained support from the Peritoneal Surface Group International to encompass heated intraperitoneal chemotherapy [39]. The terminology of CRS and HIPEC is now well established and HIPEC has become a globally accepted term, facilitating a common language.

HIPEC is performed after a complete macroscopic cytoreduction. The abdominal cavity is perfused by the open, semi-open, or closed techniques (Fig. 35.5), using either oxaliplatin or mitomycin C. Common regimen utilized for CPM include mitomycin C over 60–90 minutes at 41–43 °C with an open or closed technique, and oxaliplatin over 30 minutes at 43 °C with an open technique. Additionally, simultaneous intravenous infusion of 5-FU has also been included in some protocols. There currently exists no standard regimen of duration, or chemotherapy drug, for either appendiceal mucinous tumors or colorectal peritoneal metastasis. Additionally, various protocols are in place at different institutions and current evidence does not show superiority of one over another.

Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)

An extension of the concept of intraperitoneal chemotherapy was proposed by Marc Reymond and colleagues in 2011 [40]. The concept of pressurized intraperitoneal aerosol chemotherapy (PIPAC) was developed as a treatment strategy for patients with diffuse low-volume disease, in effect carcinomatosis, whereby aerosol chemotherapy is injected at laparoscopy to control disease not amenable to surgical resection. Disease control and palliation of ascites have been reported in ovarian, gastric, and colorectal carcinomatosis, and in peritoneal mesothelioma, with infrequent complica-

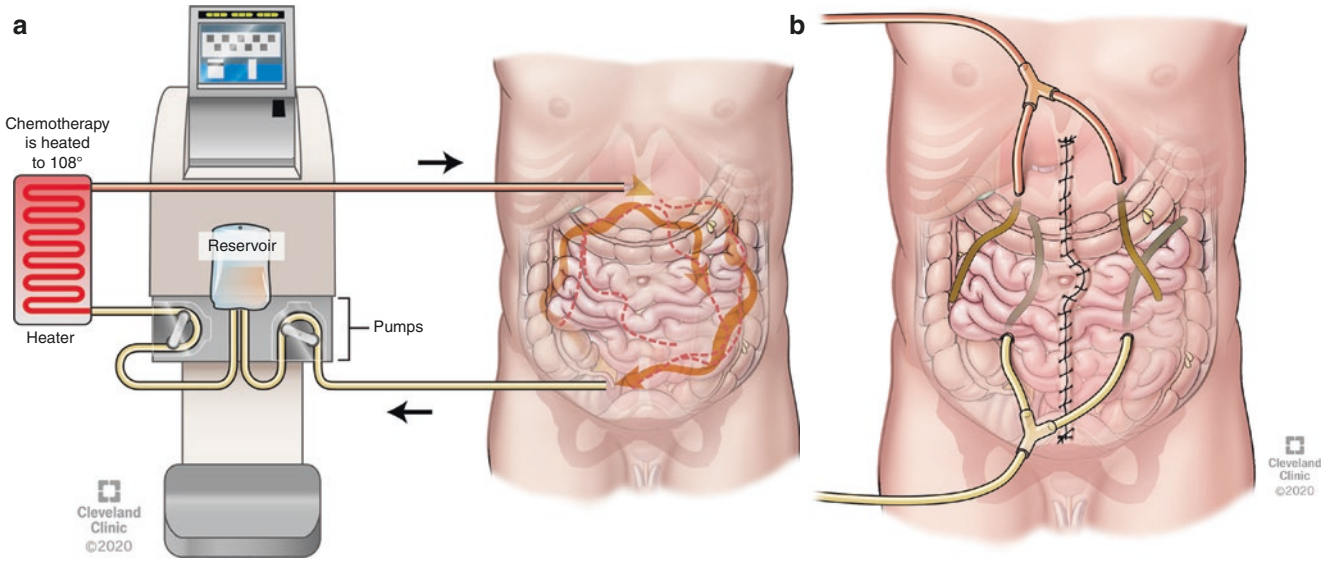

Fig. 35.5 (**a**) Catheters used for chemoperfusion during HIPEC. (**b**) Closed chemotherapy perfusion technique. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2020. All Rights Reserved)

tions. Research is ongoing and there are suggestions that PIPAC might also be useful as a neoadjuvant therapy in highly selected patients with the intent to convert unresectable peritoneal metastases to resectable.

Evidence Base for CRS and HIPEC for Colorectal Peritoneal Metastases (CPM)

Traditionally, patients with CPM were considered incurable and underwent palliative chemotherapy, often with disappointing results. Although systemic therapy for metastatic colorectal cancer has evolved over recent years, particularly with the development of biologic therapies, the survival benefit achieved with modern systemic therapy remains limited. A subgroup analysis of the Dutch CAIRO2 study showed that patients with CPM treated with modern systemic chemotherapy (capecitabine with oxaliplatin) combined with biological agents (bevacizumab and, in selected patients, cetuximab) had a limited median overall survival of 15 months and a median progression-free survival of just 6 months. Moreover, these survival outcomes were significantly worse than those achieved in patients with nonperitoneal metastatic disease [41]. A pooled analysis of two US trials comparing various chemotherapy regimens for metastatic colorectal cancer showed that, in all chemotherapy arms, patients with peritoneal metastatic disease had significantly worse survival than those with nonperitoneal sites of disease, with a median overall survival of just 12.7 months [42].

There is evidence to support CRS and HIPEC for CPM, mainly derived from cases series, but also a few randomized trials. Verwaal and colleagues conducted a phase III randomized controlled trial, first reported in 2003 with longer term follow-up in 2008 [18, 30]. One hundred and five patients were randomized to either receive 5-FU and leucovorin (standard treatment at the time) and palliative surgery or CRS and HIPEC with mitomycin C. The median 2-year survival was significantly higher in patients who had CRS and HIPEC (22.2 vs. 12.6 months) compared with those who had systemic chemotherapy and palliative surgery. Furthermore, patients that underwent HIPEC who had a CC-0 resection had a 5-year survival of 45% [30].

In 2009 Elias et al. reported on a French retrospective series of patients with CPM who had complete cytoreduction and HIPEC following systemic chemotherapy versus those who just received oxaliplatin and/or irinotecan-based chemotherapy alone [17]. Both groups of 48 patients each received a mean of 2.3 lines of chemotherapy. The authors reported a 5-year overall survival of 51% and median survival of 62.7 months in the CRS/HIPEC group versus 13% and 23.9 months in the chemotherapy-only group [43].

There has been much recent discussion on the relative contributions of CRS and HIPEC to survival in patients with CPM. Results from the PRODIGE 7 trial were presented in 2018, though the full results have not yet been published [44]. This was a French multicenter randomized trial in patients with resectable CPM in whom a complete cytoreduction was achieved. Patients were randomized to CRS alone or CRS with oxaliplatin-based HIPEC. The trial finished accrual in 2013. A few striking features have been presented, including the fact that the median survival was the same in both groups (42 months). Patients treated by HIPEC had increased complication rates at 90 days, though no difference in treatment-related mortality was observed, 1.5% in

both groups. These results have been interpreted as indicating that HIPEC is of no additional benefit to patients with CPM who undergo CRS. The peer-reviewed full publication is awaited with interest. While there are no survival benefits, there may be other benefits that have not come to light. One of us (BJM) has proposed that, based on clinical experience, and some experimental evidence, that HIPEC might prolong "obstruction free survival" [45].

There are also suggestions that oxaliplatin lacks effectiveness as an intraperitoneal agent for CPM and mitomycin C may re-emerge as optimal intraperitoneal chemotherapy pending further studies on novel intraperitoneal strategies. What is clear is that optimal CRS can produce good outcomes in highly select patients and that HIPEC may be a beneficial adjunct. A randomized controlled trial in ovarian cancer published in 2018 reported better survival in the HIPEC and CRS arm compared with the CRS alone arm [46].

The Role of Systemic Chemotherapy: Before or After CRS and HIPEC?

There is controversy as to the indication, timing, and efficacy of perioperative systemic chemotherapy in both the neoadjuvant and adjuvant setting. The rationale to administer chemotherapy stems from the fact that approximately 50% of patients that undergo CRS and HIPEC may develop extraperitoneal recurrence [47]. Many patients with CPM have had adjuvant therapy after primary tumor resection and additional further chemotherapy for recurrence. However, there is little evidence to support additional chemotherapy after CRS and HIPEC in the adjuvant setting. A recent retrospective report on 280 patients undergoing CRS and HIPEC for CPM showed no difference in survival associated with timing of systemic chemotherapy, either before or after CRS/HIPEC [48]. A systematic review in 2017 concluded that adjuvant systemic chemotherapy may confer a survival benefit but the role of neoadjuvant therapy is unclear and in some cases may be associated with reduced overall survival [49]. Alternatively, some evidence suggests that subsets of patients may benefit from systemic chemotherapy after recovery from CRS and HIPEC [50].

Neoadjuvant chemotherapy prior to CRS and HIPEC has been used by some investigators as a strategy to downstage peritoneal tumor burden, and to predict favorable tumor biology, similar to its use prior to resection of liver metastases. Waite and colleagues conducted a systematic review on the use of neoadjuvant and adjuvant chemotherapy with CRS and HIPEC and found that seven studies showed little evidence in favor of neoadjuvant therapy [49]. Alternatively, Passot et al. analyzed 115 patients with CPM who received neoadjuvant chemotherapy: patients who had a major or complete response had a significant improvement in survival compared to those who had minor or no response [51]. The authors concluded that histopathologic response to neoadjuvant chemotherapy should be considered as a new prognostic tool in the management of CPM. Clinical experience suggests that neoadjuvant systemic chemotherapy may select good responders (akin to liver metastases) and also allows a trial of time with subsequent re-imaging in initial borderline resectable cases.

Current Guidelines for Initial and Definitive Management of CPM

In general, it is recommended that patients with a definitive, or likely, diagnosis of CPM are referred to, or their case reviewed remotely by physicians at, a peritoneal malignancy treatment center before commencement of treatment (either surgical or chemotherapeutic). If CPM is diagnosed during a surgical procedure, it is recommended that surgical intervention and disruption of anatomical planes are kept to a minimum. In this context, in a case of impending intestinal obstruction, defunctioning stoma formation is preferred over resection [3]. Guidelines for initial management and a proposed treatment algorithm are provided (Figs. 35.6 and 35.7).

Prophylactic CRS and HIPEC in Advanced Cancer

As previously described, low-volume CPM is difficult to detect on imaging and CRS and HIPEC are maximally effective provided complete cytoreduction is achieved. The outcomes of CRS and HIPEC for patients with CPM are dependent on two key factors, complete cytoreduction and extent of peritoneal disease (PCI). For these reasons there has been some focus on preventing CPM and/or early detection of limited disease in patients at high risk of CPM. High-risk factors include the following:

- Limited, synchronous peritoneal metastases completely resected at primary tumor surgery
- Isolated synchronous ovarian metastases
- Primary tumor perforation
- pT4 primary tumor
- Mucinous primary tumor

A number of investigators have targeted these high-risk groups, often at second look laparotomy [52, 53] or by treating high-risk groups with prophylactic HIPEC [54]. Some encouraging results were reported in these reports, but the strength of the evidence is weak due to selection bias.

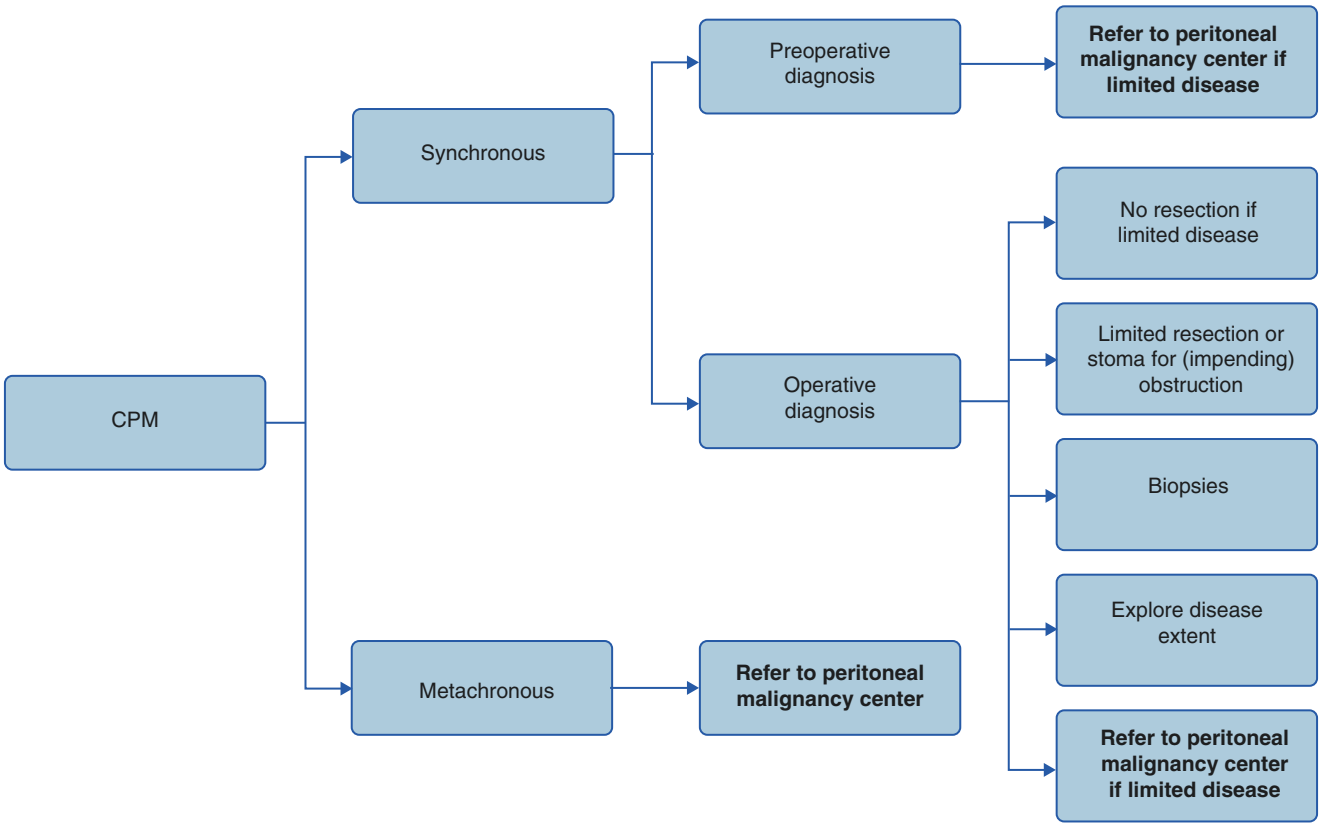

Fig. 35.6 Initial management of colorectal peritoneal metastases. *CPM* colorectal peritoneal metastasis

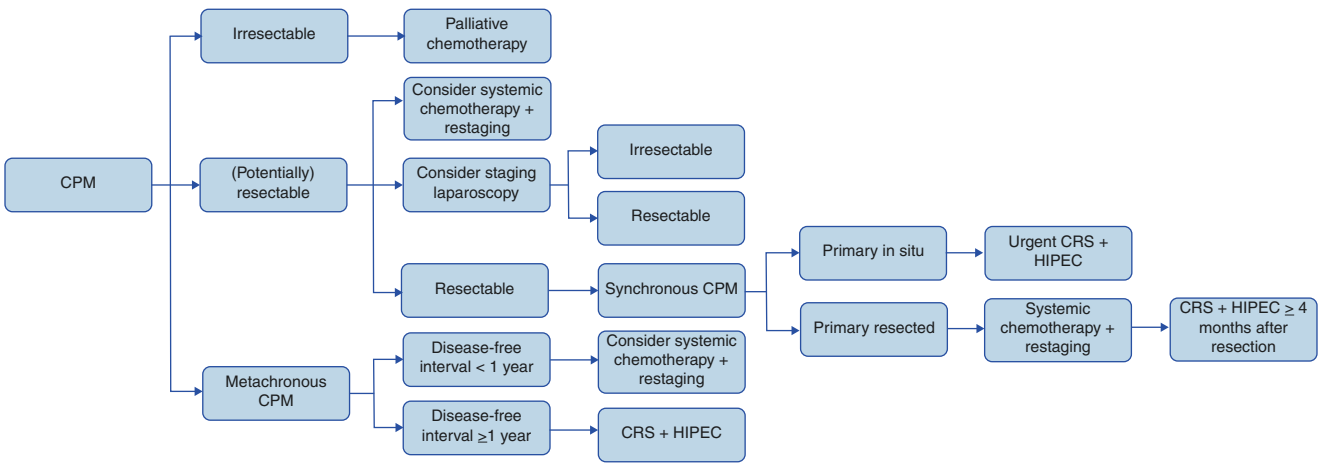

Fig. 35.7 Definitive management of colorectal peritoneal metastases in peritoneal malignancy centersz

Currently there are three distinct strategies under evaluation: a proactive approach, where patients considered to be at high risk of peritoneal dissemination undergo CRS (including resection of the primary tumor combined with resection of organs at high risk of involvement, for example, omentectomy and bilateral salpingo-oophorectomy in females, combined with HIPEC); an adjuvant approach, where selected patients undergo HIPEC in the immediate or delayed postoperative period after primary resection; and a second look approach, where selected patients undergo a systematic second-look operation sometime between 6 months and 1 year after primary resection, with cytoreduction of any observed peritoneal disease and HIPEC. Proactive CRS and HIPEC are currently being investigated in the Italian Promenade trial. Patients with high-risk T3/T4N0 colonic cancer (defined as ≥5 mm invasion beyond the muscularis propria on preoperative imaging) are randomized to either standard surgical resection or proactive cytoreduction (resection of the primary tumor combined with omentectomy, appendectomy, and BSO)

with oxaliplatin-based HIPEC. Both arms are then treated with adjuvant systemic chemotherapy where patients have poor prognostic factors.

A similar trial, the Spanish HIPECT4 study, randomizes patients with T4a/b colorectal cancer to either standard surgical resection or proactive CRS and mitomycin C-based HIPEC [55].

Adjuvant HIPEC is currently being investigated in the Dutch COLOPEC trial. Patients undergoing curative surgery for T4, or perforated colon cancer, without systemic metastases are randomized to either adjuvant systemic chemotherapy or adjuvant HIPEC (by either laparoscopic or open surgery) at the time of or within 10 days of surgery if feasible [56]. If not feasible within 10 days of primary resection, HIPEC is performed 5–8 weeks after primary resection, followed by adjuvant systemic chemotherapy. The primary endpoint is peritoneal recurrence-free survival at 18 months after resection, determined by CT and, if negative, by diagnostic laparoscopy. Initial results have shown that adjuvant oxaliplatin HIPEC in patients with T4 or perforated colon cancer did not result in an improved 18 months "peritoneal metastases free" survival. Long-term results are awaited.

A second-look strategy was published in 2011 by Elias et al. [52]. In total, 41 patients, with no detectable recurrence on imaging and normal tumor markers, had second-look surgery 1 year after primary tumor resection. Patients were recruited based on three tumor-associated factors: resected minimal synchronous macroscopic CPM, synchronous ovarian metastases, and primary tumor perforation. Overall, 21/41 (56%) had peritoneal metastases at second-look operation and underwent a complete cytoreduction; all 41 patients received oxaliplatin-based HIPEC. Five-year overall and disease-free survival rates following second-look surgery were 90% and 44%, respectively. Based on this study, the French ProphyloChip trial was designed and initiated. In this study, all patients with colorectal cancer and at high risk of developing CPM (minimal CPM resected simultaneously with the primary tumor, ovarian metastases, perforation of the primary tumor, iatrogenic rupture of the primary tumor during surgery) initially receive standard adjuvant chemotherapy. Patients with no detectable recurrence were randomized to either ongoing surveillance or a second-look laparotomy and HIPEC. Initial results report no difference in the primary endpoint of 3-year disease-free survival. The full published details are awaited.

Synchronous Colorectal Peritoneal and Other Site Oligo-Metastases

Patients with metastatic disease to both the peritoneum and other sites (liver, lung, etc.) are considered to have acquired their metastases by different mechanisms, such as blood borne and transperitoneal. Thus, they have not typically been considered candidates for CRS and HIPEC. In such cases systemic disease progression may negate attempts at local control of peritoneal disease, and morbidity and mortality of CRS and HIPEC may be detrimental to quality of life and survival. More recently the presence of isolated, treatable metastases, such as liver and lung, has not been considered absolute contra-indications to CRS and HIPEC in patients with limited resectable CPM.

Most of the evidence in this field has emanated from reports on patients with synchronous liver and peritoneal colorectal metastases, two of the most common metastatic sites. Elias and colleagues published outcomes on a small series in 2006 with good outcomes in highly selected cases [57]. Two systematic reviews support this strategy in highly selected cases [58, 59].

The general recommendations are that patients with up to three resectable liver metastases and low PCI (PCI < 10) may benefit, with some cured, when liver resection is combined with CRS and HIPEC. There has been little published on treatment strategies for patients with oligometastatic lung metastases and CPM but from personal experience, similar principles apply whereby treatable (either by surgical excision or ablation) lung metastases are not an absolute contra-indication to CRS and HIPEC in patients with low PCI colorectal peritoneal metastases.

Palliative CRS for CPM

There is increasing evidence that complete tumor removal is a prerequisite for effective CRS and HIPEC in patients with CPM. The morbidity, mortality, and impairment of quality of life of what is termed "tumor debulking" will generally outweigh any benefit. Systemic chemotherapy and best supportive care will provide optimal outcomes in most cases where complete cytoreduction cannot be accomplished. An exception to this approach is in female patients with large ovarian colorectal metastases where progression is common despite systemic chemotherapy, as ovarian metastases can be a sanctuary site from systemic chemotherapy. Palliative surgery may be appropriate in such cases. It is debatable if HIPEC is helpful, but in our experience has limited complications and may prolong obstruction-free survival [45].

Conclusion

The strategies for management and prevention of colorectal peritoneal metastases are evolving globally and much progress has been made in defining a subgroup of patients most likely to benefit from cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. The combination of CRS

and HIPEC has potential to improve outcomes in many patients with CPM, with cure in a proportion. Further work is needed in defining optimal candidates for CRS and HIPEC, and defining the optimal agents used and the relative timing of intraperitoneal and adjuvant systemic chemotherapy. What has clearly emerged is that complete cytoreduction is crucial in achieving the best outcomes for patients.

References

1. Sugarbaker PH, Gianola FJ, Speyer JC, Wesley R, Barofsky I, Meyers CE. Prospective, randomized trial of intravenous versus intraperitoneal 5-fluorouracil in patients with advanced primary colon or rectal cancer. Surgery. 1985;98(3):414–22.
2. Interventional procedure guidance (IPG56) https://www.nice.org.uk/Guidance/ipg56.
3. Moran BJ, Cecil TD. The etiology, clinical presentation, and management of pseudomyxoma peritonei. Surg Oncol Clin N Am. 2003;12(3):585–603.
4. Fallis SA, Moran BJ. Management of pseudomyxoma peritonei. J BUON. 2015;20(Suppl 1):S47–55.
5. Carr NJ, Cecil TD, Mohamed F, et al. Peritoneal surface oncology group international. A consensus for classification and pathologic reporting of Pseudomyxoma Peritonei and associated appendiceal neoplasia: the results of the Peritoneal Surface Oncology Group International (PSOGI) modified Delphi process. Am J Surg Pathol. 2016;40(1):14–26.
6. Glasgow SC, Gaertner W, Stewart D, et al. The American Society of Colon and Rectal Surgeons, clinical practice guidelines for the management of appendiceal neoplasms. Dis Colon Rectum. 2019;62(12):1425–38.
7. Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol. 2012;30(20):2449–56.
8. Moran B, Cecil T, Chandrakumaran K, et al. The results of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in 1200 patients with peritoneal malignancy. Color Dis. 2015;17:772–8.
9. Sugarbaker PH. Pseudomyxoma peritonei. A cancer whose biology is characterized by a redistribution phenomenon. Ann Surg. 1994;219(2):109–11.
10. Lemmens VE, Klaver YL, Verwaal VJ, et al. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. Int J Cancer. 2011;128:2717–25.
11. van Gestel YR, Thomassen I, Lemmens VE, et al. Metachronous peritoneal carcinomatosis after curative treatment of colorectal cancer. Eur J Surg Oncol. 2014;40:963–9.
12. Hompes D, Tiek J, Wolthuis A, et al. HIPEC in T4a colon cancer: a defendable treatment to improve oncologic outcome? Ann Oncol. 2012;23:3123–9.
13. Honore C, Goere D, Souadka A, Dumont F, Elias D. Definition of patients presenting a high risk of developing peritoneal carcinomatosis after curative surgery for colorectal cancer: a systematic review. Ann Surg Oncol. 2013;20:183–92.
14. van Santvoort HC, Braam HJ, Spekreijse KR, et al. Peritoneal carcinomatosis in t4 colorectal cancer: occurrence and risk factors. Ann Surg Oncol. 2014;21:1686–91.
15. Moran BJ, Cecil TD. Treatment of surgically resectable colorectal peritoneal metastases. Br J Surg. 2014;101:5–7.
16. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res. 1996;82:359–74.
17. Elias D, Lefevre JH, Chevalier J, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol. 2009;27:681–5.
18. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol. 2008;15:2426–32.
19. Leung V, Huo YR, Liauw W, Morris DL. Oxaliplatin versus Mitomycin C for HIPEC in colorectal cancer peritoneal carcinomatosis. Eur J Surg Oncol. 2017;43(1):144–9.
20. Sugarbaker PH, Schellinx ME, Chang D, Koslowe P, von Meyerfeldt M. Peritoneal carcinomatosis from adenocarcinoma of the colon. World J Surg. 1996;20:585–91; discussion 592
21. Verwaal VJ, van Tinteren H, van Ruth S, Zoetmulder FA. Predicting the survival of patients with peritoneal carcinomatosis of colorectal origin treated by aggressive cytoreduction and hyperthermic intraperitoneal chemotherapy. Br J Surg. 2004;91:739–46.
22. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol. 2010;28:63–8.
23. Sugarbaker PH. Avoiding diverting ileostomy in patients requiring complete pelvic peritonectomy. Ann Surg Oncol. 2016;23(5):1481–5.
24. Obermair A, Hagenauer S, Tamandl D, Clayton RD, Nicklin JL, Perrin LC, Ward BG, Crandon AJ. Safety and efficacy of low anterior en bloc resection as partof cytoreductive surgery for patients with ovarian cancer. Gynecol Oncol. 2001;83(1):115–20.
25. Yildirim Y, Ertas IE, Nayki U, Ulug P, Nayki C, Yilmaz I, Gultekin E, Dogan A, Aykas A, Ulug S, Ozdemir A, Solmaz U. En-bloc pelvic resection with concomitant rectosigmoid colectomy and immediate anastomosis as part of primary cytoreductive surgery for patients with advanced ovarian cancer. Eur J Gynaecol Oncol. 2014;35(4):400–7.
26. Mourton SM, Temple LK, Abu-Rustum NR, Gemignani ML, Sonoda Y, Bochner BH, Barakat RR, Chi DS. Morbidity of rectosigmoid resection and primary anastomosis in patients undergoing primary cytoreductive surgery for advanced epithelial ovarian cancer. Gynecol Oncol. 2005;99(3):608–14.
27. Sonnendecker EW, Beale PG. Rectosigmoid resection without colostomy during primary cytoreductive surgery for ovarian carcinoma. Int Surg. 1989;74(1):10–2.
28. Riss S, Chandrakumaran K, Dayal S, Cecil TD, Mohamed F, Moran BJ. Risk of definitive stoma after surgery for peritoneal malignancy in 958 patients: comparative study between complete cytoreductive surgery and maximal tumor debulking. Eur J Surg Oncol. 2015;41(3):392–5.
29. Di Fabio F, Mehta A, Chandrakumaran K, et al. Advanced pseudomyxoma Peritonei requiring gastrectomy to acheive complete cytoreduction results in good long-term oncologic outcomes. Ann Surg Oncol. 2016;23(13):4316–21.
30. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol. 2003;21:3737–43.
31. Verwaal VJ, van Ruth S, Witkamp A, et al. Long-term survival of peritoneal carcinomatosis of colorectal origin. Ann Surg Oncol. 2005;12:65–71.

32. Leung V, Huo YR, Liauw W, Morris DL. Oxaliplatin versus Mitomycin C for HIPEC in colorectal cancer peritoneal carcinomatosis. Eur J Surg Oncol. 2017 Jan;43(1):144–9.
33. de Cuba EM, de Hingh IH, Sluiter NR, et al. Angiogenesis-related markers and prognosis after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for metastatic colorectal cancer. Ann Surg Oncol. 2016;23:1601–8.
34. Hammoudi N, Eveno C, Lambert J, et al. Inflammatory bowel disease drastically affects the prognosis of patients treated for peritoneal metastases with combined cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a multicenter study. Eur J Surg Oncol. 2018;44:799–804. https://doi.org/10.1016/j.ejso.2018.03.006.
35. Cotte E, Peyrat P, Piaton E, et al. Lack of prognostic significance of conventional peritoneal cytology in colorectal and gastric cancers: results of EVOCAPE 2 multicentre prospective study. Eur J Surg Oncol. 2013;39:707–14.
36. Trilling B, Cotte E, Vaudoyer D, et al. Intraperitoneal-free cancer cells represent a major prognostic factor in colorectal peritoneal carcinomatosis. Dis Colon Rectum. 2016;59:615–22.
37. Kuijpers AM, Mehta AM, Aalbers AG, et al. Treatment of ovarian metastases of colorectal and appendiceal carcinoma in the era of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Eur J Surg Oncol. 2014;40:937–42.
38. Bignell MB, Mehta AM, Alves S, et al. Impact of ovarian metastases on survival in patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal malignancy of appendiceal and colorectal cancer origin. Color Dis. 2018;20:704–10.
39. Moran BJ, Meade B, Murphy E. Hyperthermic intraperitoneal chemotherapy and cytoreductive surgery for peritoneal carcinomatosis of colorectal origin: a novel treatment strategy with promising results in selected patients. Color Dis. 2006;8(7):544–50.
40. Alyami M, Hübner M, Grass F, Bakrin N, Villeneuve L, Laplace N, Passot G, Glehen O, Kepenekian V. Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications. Lancet Oncol. 2019;20(7):e368–77.
41. Klaver YL, Simkens LH, Lemmens VE, et al. Outcomes of colorectal cancer patients with peritoneal carcinomatosis treated with chemotherapy with and without targeted therapy. Eur J Surg Oncol. 2012;38:617–23.
42. Franko J, Shi Q, Goldman CD, et al. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. J Clin Oncol. 2012;30:263–7.
43. Mirnezami R, Mehta AM, Chandrakumaran K, et al. Cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy improves survival in patients with colorectal peritoneal metastases compared with systemic chemotherapy alone. Br J Cancer. 2014;111:1500–8.
44. Quenet F, Elias D, Roca L, et al. A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. JCO. 2018;36.
45. Moran BJ, Tzivanakis A. The concept of "obstruction-free survival" as an outcome measure in advanced colorectal cancer management. Pleura Peritoneum. 2018;3(1):20180101.
46. van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med. 2018;378(3):230–40.
47. Elias D, Blot F, El Otmany A, et al. Curative treatment of peritoneal carcinomatosis arising from colorectal cancer by complete resection and intraperitoneal chemotherapy. Cancer. 2001;92(1):71–6.
48. van Eden WJ, Kok NF, Jóźwiak K, et al. Timing of systemic chemotherapy in patients with colorectal peritoneal carcinomatosis treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Dis Colon Rectum. 2017;60(5):477–87.
49. Waite K, Youssef H. The role of neoadjuvant and adjuvant systemic chemotherapy with cytoreductive surgery and heated intraperitoneal chemotherapy for colorectal peritoneal metastases: a systematic review. Ann Surg Oncol. 2017;24(3):705–20.
50. Maillet M, Glehen O, Lambert J, et al. Early postoperative chemotherapy after complete cytoreduction and hyperthermic intraperitoneal chemotherapy for isolated peritoneal carcinomatosis of colon cancer: a multicenter study. Ann Surg Oncol. 2016;23(3):863–9.
51. Passot G, You B, Boschetti G, et al. Pathological response to neoadjuvant chemotherapy: a new prognosis tool for the curative management of peritoneal colorectal carcinomatosis. Ann Surg Oncol. 2014;21(8):2608–14.
52. Elias D, Honoré C, Dumont F, et al. Results of systematic second-look surgery plus HIPEC in asymptomatic patients presenting a high risk of developing colorectal peritoneal carcinomatosis. Ann Surg. 2011;254(2):289–93.
53. Delhorme JB, Triki E, Romain B, Meyer N, Rohr S, Brigand C. Routine second-look after surgical treatment of colonic peritoneal carcinomatosis. J Visc Surg. 2015;152(3):149–54.
54. Sammartino P, Sibio S, Biacchi D, et al. Prevention of peritoneal metastases from colon cancer in high-risk patients: preliminary results of surgery plus prophylactic HIPEC. Gastroenterol Res Pract. 2012;2012:141585.
55. Arjona-Sánchez A, Barrios P, Boldo-Roda E, et al. HIPECT4: multicentre, randomized clinical trial to evaluate safety and efficacy of Hyperthermic intra-peritoneal chemotherapy (HIPEC) with Mitomycin C used during surgery for treatment of locally advanced colorectal carcinoma. BMC Cancer. 2018;18(1):183.
56. Klaver CE, Musters GD, Bemelman WA, et al. Adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with colon cancer at high risk of peritoneal carcinomatosis; the COLOPEC randomized multicentre trial. BMC Cancer. 2015;15:428.
57. Elias D, Benizri E, Pocard M, Ducreux M, Boige V, Lasser P. Treatment of synchronous peritoneal carcinomatosis and liver metastases from colorectal cancer. Eur J Surg Oncol. 2006;32(6):632–6.
58. de Cuba EM, Kwakman R, Knol DL, Bonjer HJ, Meijer GA, Te Velde EA. Cytoreductive surgery and HIPEC for peritoneal metastases combined with curative treatment of colorectal liver metastases: systematic review of all literature and meta-analysis of observational studies. Cancer Treat Rev. 2013;39(4):321–7.
59. El-Nakeep S, Rashad N, Oweira H, et al. Intraperitoneal chemotherapy and cytoreductive surgery for peritoneal metastases coupled with curative treatment of colorectal liver metastases: an updated systematic review. Expert Rev Gastroenterol Hepatol. 2017;11(3):249–58.

Colorectal Cancer: Minimally Invasive Surgery

36

Antonino Spinelli

Key Concepts

- Minimally invasive colorectal surgery has evolved considerably, especially in the last 30 years.
- Potential advantages of a minimally invasive approach go beyond smaller incision size: reduced interference with body homeostasis has positive impacts both in the clinical and social spheres.
- MIS for colon cancer has been well accepted for many years, but the application of MIS techniques to rectal cancer is more controversial.
- Techniques utilized to perform proctectomy are not as mature as those to perform colectomy, and potential advantages/risks of minimally invasive proctectomy versus open proctectomy are still debated.

Introduction

Minimally invasive colorectal surgery has evolved considerably, especially in the last 30 years. The first descriptions of laparoscopic-assisted colectomies for cancer were in 1991 by Schlender [1] (one case of right colectomy), Fowler and White [2] (one case of sigmoid resection), and Jacobs et al. [3] (20 cases of right colectomies or sigmoid resection for benign or malignant diseases). In 1992, Phillips et al. [4] described for the first time a laparoscopic, intracorporeal, hand-sewn purse-string suture and transanal natural orifice specimen extraction (NOSE) applied in 51 patients. In 1994, Darzi et al. [5] described a left colon resection with transanal NOSE followed by a triple-stapled intracorporeal colorectal anastomosis. In 1995, Mentges et al. [6] described a technique that consisted in performing a proctotomy in the anterior rectal wall to insert the anvil of a circular stapler into the peritoneal cavity and to perform NOSE by means of transanal endoscopic microsurgery (TEM) platform. Contrary to the prior reports, which emphasized limiting incision size as the primary goal, in 2005, Chang et al. [7] published a series of hand-assisted laparoscopic (HALS) sigmoid colectomy with Pfannenstiel incision, attributing the following advantages to the technique: direct visualization of the colorectal anastomosis obviating the requirement for reestablishing pneumoperitoneum prior to performing anastomosis.

At first glance, one might think that the earlier literature was focused only on technical aspects. This was true early on, as, for example, a 1992 report from Wexner et al. [8] emphasized the benefits of laparoscopy, focusing mainly on perioperative outcomes. However, shortly thereafter, concerns were voiced regarding oncologic outcomes following laparoscopic colectomy, specifically the phenomenon of port site tumor recurrence. In 1994, a report raised concerns about high rates (21%) of port site recurrence, prompting several surgical societies to advise against performing laparoscopy for curable cancer [9]. This was a troubling time for surgeons attempting to perfect laparoscopic colectomy techniques, because if neoplasia was off limits, the majority of laparoscopic colectomies would be performed for inflammatory conditions (diverticulitis and inflammatory bowel disease), which are much more challenging entities from a technical perspective.

Multiple basic science and clinical studies were launched, attempting to determine whether port site recurrences were a common phenomenon and, if so, were they due to suboptimal technique or did they arise from some as yet unknown adverse effect of pneumoperitoneum on cancer cells during mobilization of a visceral malignancy [10–12]. Review of select videos from index colectomies following which port site recurrences occurred suggested that technical issues may

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be the primary concern. Clinical series were published in which port site recurrence rates were approximately 1% (similar to wound implant rates following open surgery), which was reassuring. During this period, data from the American Society of Colon and Rectal Surgeons (ASCRS) registry were published, reporting an incisional recurrence rate of 0.4% after laparoscopic surgery for colon cancer [13].

In the late 1990s and early 2000s, a number of prospective randomized controlled trials (RCTs) were undertaken to investigate the impact of laparoscopic surgery on oncologic and postoperative outcomes following segmental colectomy for curable intraperitoneal colon cancer. All studies came to similar conclusions, namely, that laparoscopic colectomy, when performed by experienced surgeons, was oncologically not inferior to open colectomy [14–19]. Laparoscopy was associated with faster postoperative recovery, about 1 day shorter hospital stay, improved short-term functional outcomes, and better cosmesis. However, by 2–3 months following surgery, there were no major differences in function or quality of life, and laparoscopy was associated with longer operative times and increased cost. Despite the rather modest benefit of laparoscopy demonstrated by RCTs, some surgeons interpreted the data as demonstrating that laparoscopy was clearly superior to open surgery and considered this a free pass to perform any type of colorectal resection laparoscopically. Others took a more measured approach, acknowledging that there is a steep learning curve, with at least 20–152 laparoscopic cases considered as the minimum to achieve basic proficiency in this technique [20–27]. After the publication of RCTs demonstrating non-inferiority of laparoscopic segmental colectomy for cancer, the ASCRS, the American College of Surgeons (ACS), and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) published statements supporting the use of laparoscopy colectomy for cancer by appropriately trained surgeons.

The twenty-first century saw the development of organized approaches to performing laparoscopic colorectal surgery, with early laparoscopic adopters proposing standardized sequential operative steps and port placements for their preferred technique [28–31]. Over the last 20 years, a number of minimally invasive techniques were proposed to overcome some of the limits of straight laparoscopy (see below) [32–39]. Hand-assisted laparoscopic surgery (HALS) was proposed to provide reasonable solutions to some legitimate concerns. For example, HALS allows manual palpation of a rectal tumor for providing adequate distal transection of the rectum as well as decreased operating time for left-sided colectomy and total abdominal colectomy [32, 40]. The advent of robotic technology gave back to surgeons degrees of freedom lost by the use of laparoscopic, non-wristed instruments as well as three-dimensional view, stable camera platform, and tremor filtering. However, the bulkiness of the machine, the fact that the surgeon's assistant at the table only sees a two-dimensional image, lack of haptic feedback, increased operative time, and increased cost are the disadvantages and warrant more objective evaluation prior to pronouncing robotic laparoscopic surgery superior to other approaches [39]. Furthermore, technological advances of "conventional" laparoscopic optics and imaging technology have resulted in 3D laparoscopes that mitigate some of the robot's advantages. In 2010, the technique of transanal total mesorectal excision (TaTME) was proposed, aiming to overcome some of the technical challenges of abdominal rectal resections [33]. TaTME is built on a variety of techniques: transabdominal-transanal proctosigmoidectomy (TATA) [35], transanal endoscopic microsurgery (TEM) [34], transanal minimally invasive surgery (TAMIS) [36], natural orifice specimen extraction (NOSE) [37], and natural orifice transluminal endoscopic surgery (NOTES) [38].

It is important to point out that the potential advantages of a minimally invasive approach go beyond smaller incision size. Reduced interference with body homeostasis has positive impacts both in the clinical (less systemic inflammatory response to surgery, lessened magnitude of wound complications, shorter hospital stay) and social spheres (less work and social inactivity, less disability, less fear and anxiety). In some ways, geriatric, obese, and otherwise vulnerable patients may experience a greater reduction in morbidity than their younger, healthier counterparts [41] .

We have chosen to focus the remainder of this chapter on minimally invasive techniques to treat patients suffering from rectal cancer. We felt this was appropriate given the fact that laparoscopic colectomy for intraperitoneal colon cancer has been well accepted for many years, but the application of MIS techniques to rectal cancer is more controversial. In addition, the techniques utilized to perform proctectomy are not as mature as those to perform colectomy. We will review some of the pertinent literature on the topic, but we will not attempt to perform a systematic review of the evidence available in the literature. Rather, our primary objective is to provide a step-by-step how-to guide for surgeons, as well as to describe potential advantages and technical challenges. The techniques outlined are those preferred by the authors currently. Certainly other techniques have been utilized successfully by other surgeons, although the basic principles for a successful operation are common to all.

Minimally Invasive Rectal Cancer Surgery

Laparoscopic Rectal Cancer Surgery

Laparoscopic proctectomy for rectal cancer is a complex operation and should be performed carefully by a laparoscopic expert who has mastered the learning curve. The mag-

nified view of the pelvis should potentially lead to potential clinical advantages such as the achievement of negative radial margins, spared autonomic nerves, and avoidance of ureteral injury. However, laparoscopy has some technical limitations such as poor ergonomics, two-dimensional view, inflexible instruments, coning, and fulcrum effect that may negatively impact attempts to operate in narrow anatomical fields such as the pelvis. A meaningful example of these limitation is the 12% rate of involved circumferential radial margins (CRM) after laparoscopic restorative proctectomy (versus 6% in the open arm), as well as the 34% rate of conversion from laparoscopic to open operation, as reported in the CLASICC trial [42]. Accordingly, the trial concluded that suboptimal short-term outcomes after laparoscopic-assisted anterior rectal resection for cancer do not yet justify its routine use. However, long-term results after a median follow-up of 5 years showed no differences between laparoscopic and open techniques in overall survival (OS) and disease-free survival (DFS) in rectal cancer surgery [14]. Results of the COREAN trial [43, 44] showed short-term benefits for the laparoscopic approach (decreased blood loss, postoperative pain, and length of hospital stay) and comparable 3-year DFS in patients with non-metastatic mid-low rectal cancer undergoing proctectomy after neoadjuvant chemoradiotherapy. Recently, there has been controversy regarding the safety of laparoscopic proctectomy for rectal cancer. Two large RCTs, ACOSOG Z6051 [18] in the United States, and the ALaCaRT trial [19] in Australia and New Zealand failed to demonstrate noninferiority of the laparoscopic approach, using a composite assessment measure of successful resection (radial margin negative, distal margin negative, and mesorectal grade complete or nearly complete), all of which have been demonstrated to have prognostic significance in other trials. There were no differences in duration of hospital stay; incision length was shorter in the laparoscopic group. The authors of both trials concluded that, based on their data, laparoscopic proctectomy should not be performed for rectal cancer. It is unclear how many surgeons migrated away from laparoscopic proctectomy after publication of those trials. It is somewhat reassuring that, despite the concerns regarding the quality of the mesorectal dissection in the laparoscopic group, the 3-year DFS in the ACOSOG trial was equivalent for the laparoscopic and open groups [18]. A greater understanding of the relative risks and benefits of laparoscopic proctectomy will be gained when long-term oncologic results are mature. Controversy regarding the appropriateness of laparoscopy for rectal cancer should not be surprising, as laparoscopic exposure and retraction in the deep pelvis can be challenging, as a result of bulky uterus and adnexa, redundant pelvic peritoneum, bulky tumors, and narrow pelvis. These factors continue to limit the widespread application of minimally invasive proctectomy for both the laparoscopic and robotic approaches.

Laparoscopic Proctectomy

Indications

Patients presenting with resectable, histologically proven adenocarcinoma of the rectum without documented involvement of the external sphincter are candidates for laparoscopic resection of the rectum with anastomosis. Those with cancer of the upper third of the rectum should be considered for low anterior resection (LAR) with partial mesorectal excision as long as an adequate distal resection margin is achieved. Patients with cancer of the mid and distal thirds of the rectum should be considered for LAR with total mesorectal excision (TME), guaranteeing at least a 1-cm distal resection margin. Patients with cancer of the very low rectum involving the internal anal sphincter can be considered for intersphincteric resection (ISR) with hand-sewn coloanal anastomosis, although there are concerns regarding high +CRM rates and suboptimal functional results [45].

Preoperative Considerations

Patient selection for laparoscopic LAR is the key to a successful operation and a good patient outcome. The only absolute contraindication is the inability to tolerate pneumoperitoneum and steep Trendelenburg positioning. Relative contraindications include morbid obesity, prior pelvic surgery, severe cardiopulmonary disease, and suspected or known massive intra-abdominal adhesions. Ureteral stent placement should be considered for patients with bulky pelvic tumors or prior pelvic surgery. Lighted stents in laparoscopic pelvic surgery have been described and may be of particular use in robotic cases given the lack of haptic feedback, but are not considered essential (Fig. 36.1). The patient should undergo stoma site marking and education, preferably by an enterostomal therapist, as many patients will undergo temporary diverting ileostomy or colostomy.

Surgical Technique

The following techniques are applicable to patients with rectal cancer that does not invade beyond the mesorectal fascia or into adjacent organs on preoperative cross-sectional imaging or physical examination.

Access to the Abdomen and Vessel Ligation

The patient is placed in the lithotomy or supine split-leg position with head, chest, and arms tucked because tilting the table will be necessary (Fig. 36.2). The surgeon stands on the patient's right side. Pneumoperitoneum is established through an open technique at the umbilicus where a 10-mm trocar is inserted for the 30-degree laparoscope camera. A 10-mm (or 12-mm) trocar placed in the right lower quadrant lateral to the rectus muscle sheaths allows the use of a stapling device. Three 5-mm ports are inserted under direct vision in the right upper quadrant, left lumbar, and left lower

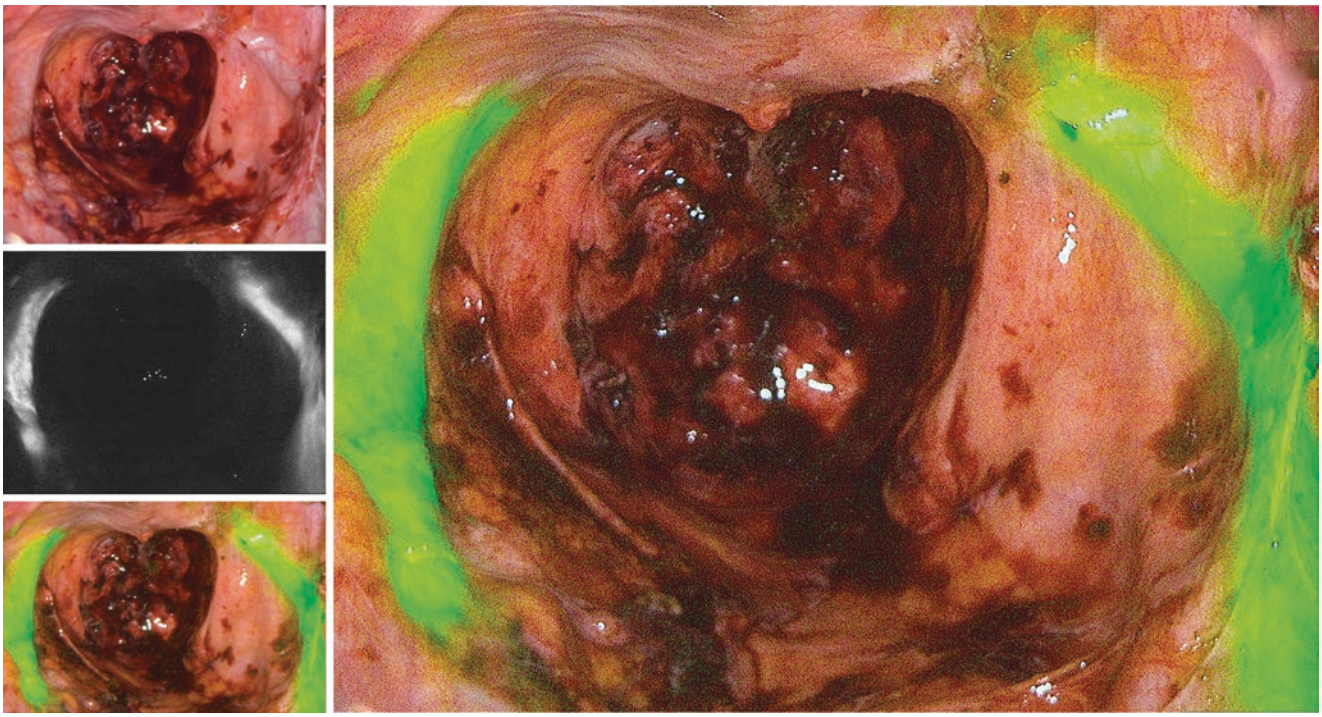

Fig. 36.1 Real-time visualization of ureters through real-time indocyanine green (ICG) angiography under near-infrared light. ICG was injected through mono-J ureteral stents

Fig. 36.2 Laparoscopic proctectomy: patient positioning

quadrant (Fig. 36.3). The left ports are used by the assistant. Following initial inspection of the peritoneal cavity, the table is tilted in Trendelenburg and to the right; this allows placement of the small intestine in the right upper quadrant. Using 5-mm bowel graspers through the left-sided cannulas, the assistant holds the sigmoid ventrally under traction and to the left. In a medial-to-lateral fashion, the inferior mesenteric artery (IMA) is identified, and the retroperitoneum is incised

starting at the sacral promontory and proceeding to the root of IMA, taking care not to injure the superior hypogastric plexus, the left ureter, or the gonadal vessels (Fig. 36.4). Once the origin of the IMA is identified, the peritoneum is incised anteriorly over the pedicle and away from the left colic artery (Fig. 36.4). A gauze can be placed around the IMA and grasped on both sides, helping to lift the vessel during its isolation (Fig. 36.5). The dissection proceeds deep to the inferior mesenteric vein (IMV), sweeping the mesentery of the descending colon away from the retroperitoneum and taking care not to injure the pancreatic tail (Fig. 36.6). The IMV is isolated adjacent to the ligament of Treitz, taking great care to avoid injury to the communicating arterial branches of the left colic artery and left branch of the middle colic artery. The IMA and IMV are then divided after visualizing again the left ureter (Fig. 36.7).

Fig. 36.3 Laparoscopic proctectomy: ports placement

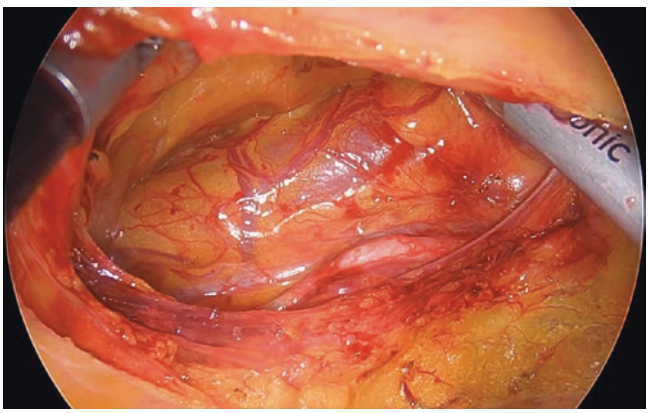

Fig. 36.4 Dissection of the inferior mesenteric artery (IMA). The retroperitoneum is incised starting at the sacral promontory and proceeding to the root of IMA taking care not to injure the superior hypogastric plexus, the left ureter, and the gonadal vessels (clearly visible in this picture)

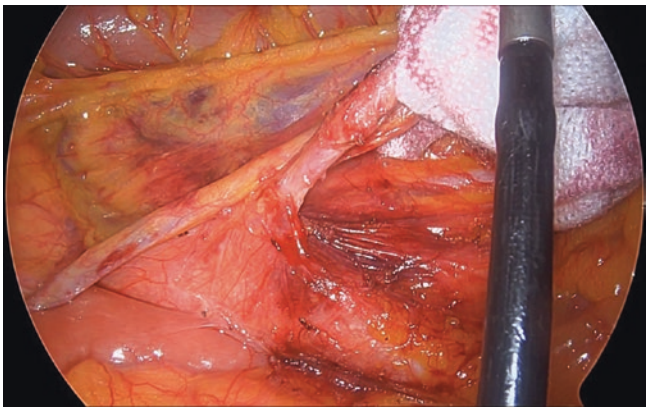

Fig. 36.5 A gauze can be placed around the inferior mesenteric artery (IMA) and grasped on both sides helping to lift the vessel during its isolation

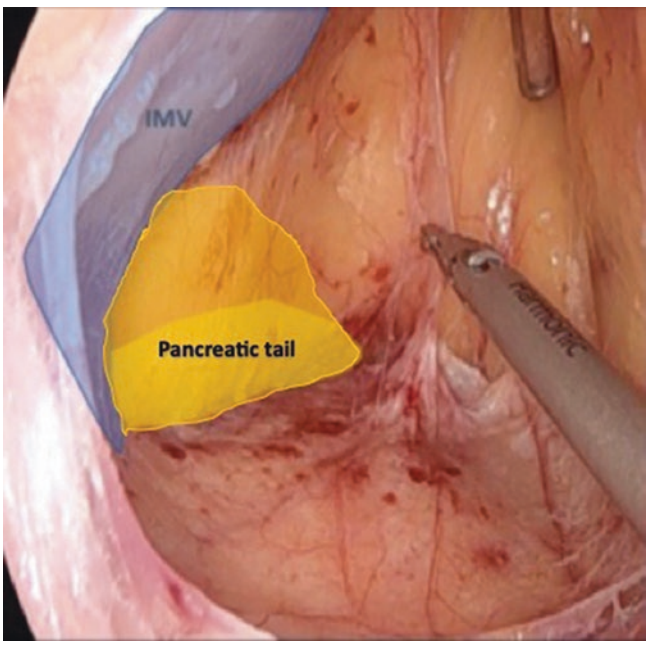

Fig. 36.6 Dissection of the inferior mesenteric vein (IMV). Care must be taken not to injure the pancreatic tail

Splenic Flexure and Left Colon Mobilization

Through the peritoneal window, the left mesocolon is dissected from the underlying retroperitoneal structures, including the gonadal vessels, ureter, Gerota's fascia, and pancreas. The rationale for performing splenic flexure mobilization is to ensure adequate length of the proximal colonic conduit, allowing for a tension-free luminal anastomosis as well as a tension-free mesentery so that blood supply is not compromised. Technical steps to perform splenic flexure mobilization include division of the omental attachments to the transverse colon, mobilization of the left colonic mesentery, and division of the bare area at the root of the mesentery of the distal transverse colon. The following situations warrant special caution: a history of aortic surgery (this can interrupt or reverse the normal circulation in the marginal artery), prior left nephrectomy, and previous colonic surgery with concern regarding arterial flow in the marginal artery (Fig. 36.8). The left colon is then mobilized by dividing the lateral peritoneal attachments along the white line of Toldt. After the mobilization of the left colon, the sigmoid mesocolon is divided.

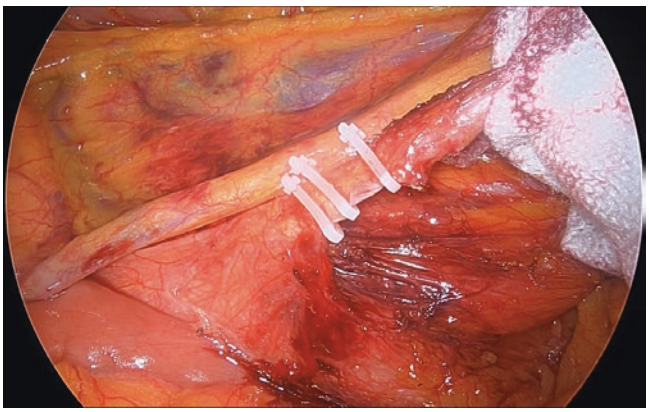

Fig. 36.7 Division of the inferior mesenteric artery (IMA)

Mesorectal Mobilization Using TME Principles

The peritoneum is incised at the lateral border of the mesorectum, medial to the ureters, connecting the plane of dissection anteriorly in the cul-de-sac at the anterior peritoneal reflection. The mesorectal dissection is then typically initi-

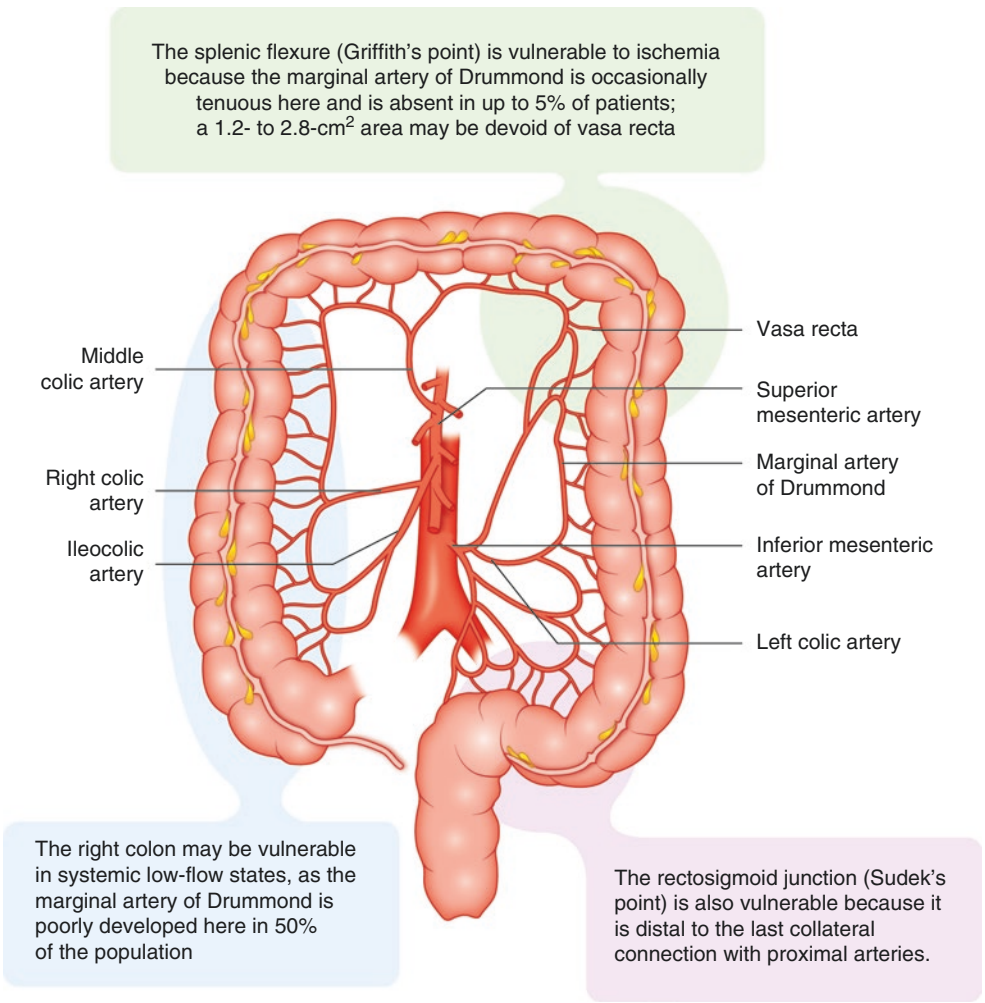

Fig. 36.8 The three critical points for colorectal vascular supply

ated posterior to the mesorectum, at the level of the sacral promontory. At this point, it is important that the assistant takes the redundant colon out of the pelvis; this will help to identify the plane between the parietal and the visceral layers of the endopelvic fascia which is dissected sharply with cautery. Care is taken to identify the hypogastric nerves as they travel anterolaterally across the aortic bifurcation, approximately 2 cm medial to the ureters bilaterally. Dissection along the fascia propria of the rectum (visceral peritoneum) will maintain a correct plane of dissection, avoiding to injure the hypogastric nerves posteriorly, the pelvic plexus laterally, and the anterior cavernous plexus anteriorly. The area of dissection may contain small blood vessels emanating from the pelvic sidewall whose bleeding may be controlled with cautery. The surgeon must be wary of straying into the pelvic sidewall, as this can result to bleeding from branches of the internal iliac vein and artery, as well as nerve injury. Dissection should be in an avascular plane; moderate-significant bleeding indicates you are likely in the wrong plane. Inferior to the level of S3, the rectosacral ligament (Waldeyer's fascia) is divided. Blunt dissection should be avoided to prevent tearing into the mesorectum or presacral fascia and injury to the presacral venous plexus. The angle of dissection follows the curve of the sacrum, proceeding anteriorly to the pelvic floor. Anterior dissection can be challenging in men. The plane of dissection anterior or just posterior to Denonvilliers' fascia should be chosen based on the position of the tumor. If the tumor is anterior in the rectum, dissection is anterior to the Denonvilliers' fascia, exposing the seminal vesicles bilaterally (Fig. 36.9). In females, anterior dissection occurs in the rectovaginal septum. Appropriate traction by the assistant is critical to provide appropriate tissue tension and exposure for dissection. Sometimes, applying perineal pressure can aid in the dissection as this maneuver elevates the pelvic floor. At this point, distal transection guaranteeing a margin ≥1 cm should be performed.

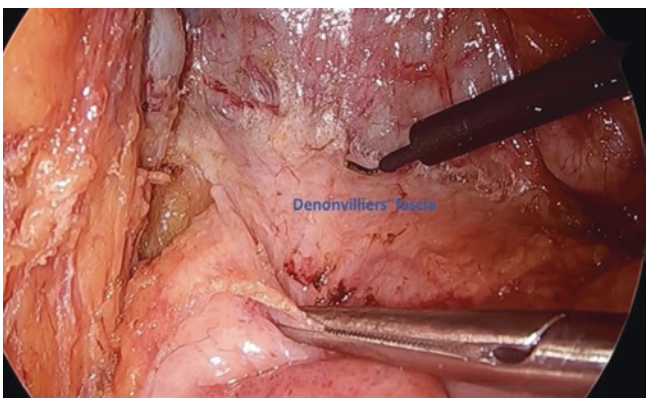

Fig. 36.9 In case of tumors located on the anterior rectal wall, the dissection is performed anteriorly to the Denonvilliers' fascia, exposing the seminal vesicles bilaterally

Precise localization of the tumor is paramount prior to any division of rectum or mesorectum during proctectomy. Video flexible endoscopy, or at least rigid proctoscopy, should be performed intraoperatively to ensure that the chosen transection site encompasses the entire tumor and mesorectum at risk with adequate margins.

When considering the next step in the operation, distal rectal transection, it should be noted that there are technical limitations to performing this maneuver laparoscopically [46]. One is the fulcrum effect of operating a stapler through a port placed in the iliac fossa. Another limitation is the degree of angulation of the currently available staplers. A virtual simulation study has shown that staplers will actually have to go through the iliac bone to achieve a 90-degree angle of rectal transection at the level of the levator ani muscle [47]. A third limitation is the number of cartridges required. Ideally, distal rectal transection should be accomplished perpendicularly with a single staple firing. However, in practice, multiple stapler firings are often needed for rectal transection, possibly increasing the risk of anastomotic leakage [48]. Furthermore, intersecting lateral staple lines (dog ears) obtained after double-stapled anastomosis techniques are also considered weak structural spots, areas possibly prone to leak [49]. Tilting the rectum to the left has been suggested to achieve a 90-degree angle of transection with laparoscopic 45-degree staplers, but this is not always feasible [50]. Additionally, double-stapling following oblique transection of the rectum may result in an anastomotic stricture because of the potential for suboptimal blood supply at the acute angle of transection. In order to avoid multiple firings, the stapler may be inserted through a suprapubic incision. The fulcrum effect, however, will remain unresolved, and the pneumoperitoneum may become unstable. An alternative method is to insert a conventional stapler through a gelatinous hand-assisted device. This has three advantages: the fulcrum effect is ameliorated by the consistency of the gel, pneumoperitoneum is stabilized by the seal of the hand port, and the tumor can be palpated and transection can be performed with a safe distal margin. However, this solution increases costs. If a hand-assisted device is anticipated to be utilized at this point in the case, it is more sensible to place it at the beginning of the case and use it throughout.

The specimen is typically extracted through a Pfannenstiel incision or by the left iliac fossa port, after positioning a wound protector. The descending colon is transected and the anvil is placed. Real-time indocyanine green fluorescence angiography (ICG-FA) may be helpful in assessing the vascular blood supply before transecting the colon [51–53] (Fig. 36.10), although there are no definitive data at this time to prove that ICG-FA is better than other methods of assessing perfusion to the proximal colon conduit. The results of the ongoing IntAct RCT will hopefully clarify this issue [54]. The double-stapled colorectal anastomosis is carried

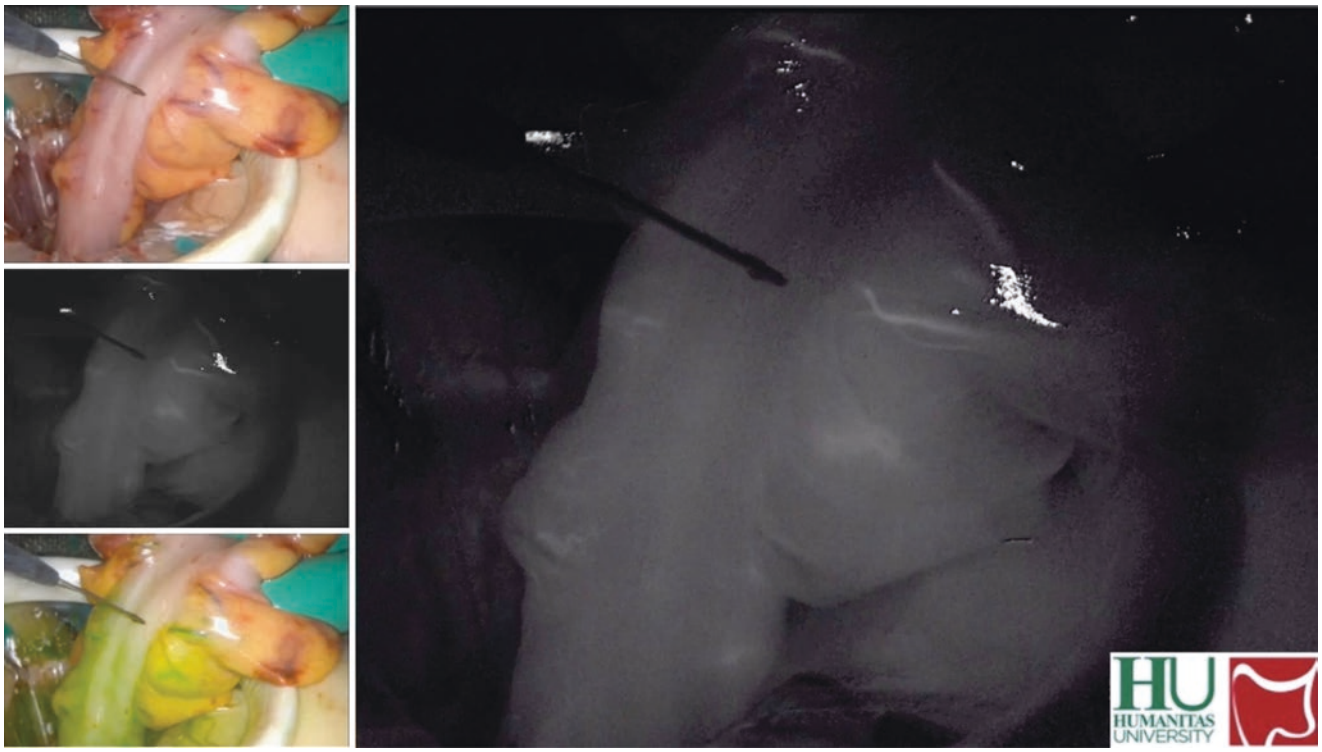

Fig. 36.10 Application of real-time indocyanine green intraoperative fluorescence angiography (ICG-IFA) to assess the vascular blood supply before transecting the colon

out in accordance with the same principles described in conventional surgery. As noted above, intersecting lateral staple lines (dog ears) created after double-stapled anastomosis techniques are considered weak structural spots, possibly prone to leak (Fig. 36.11) [49]. Some techniques have been proposed to avoid at least one dog ear (Fig. 36.11, "tennis racket") or both (Fig. 36.12 "reverse smile" (Fig. 36.13) codi14419-sup-0001-VideoS1.mp4). In the first technique, the spike of the anvil is brought through the rectal stump laterally (as opposed to the middle), eliminating one intersecting staple line and thus one weak structural spot (Fig. 36.11). In the reverse smile maneuver, the spike is brought through the rectal stump in its central part, just posterior to the linear staple line. After the spike is brought through the stump, the shaft of the stapler is retracted slightly and the end of the stapler angled anteriorly. This pulls the two edges of the linear staple line toward the midline posterior to the spike, forming a "reverse smile" (Figs. 36.12 and 36.13). The intent is that the entire linear staple line of the rectal stump will then be excised when the anastomosis is created, essentially transforming a double-stapled into a single-stapled anastomosis (Figs. 36.14, 36.15, and 36.16) [55]. One must take great care to avoid entrapping other pelvic structures in the staple line, such as the vagina, during this maneuver. An alternative anastomotic technique to avoid intersecting staple lines and dog ears after a conventional cross-stapling of the distal rectum has been described [56]. Recently a proof of concept study for transanal distal transection of the rectum and single-stapled anastomosis was proposed to overcome the previously described limits of transection and anastomosis in rectal surgery (Fig. 36.17) (codi14631-sup-0001-VideoS1.mov) [57]. However, these alternative techniques still need a large-scale trial to critically assess their potential benefits. After the anastomosis is completed, leak test using gas (CO2 is preferred), either standard (via proctoscopy) or reverse (via insufflation of the peritoneum) (Fig. 36.18) (codi14399-sup-0001-VideoS1.mp4) [58], is performed. ICG-FA may be performed for a final check of perfusion to the anastomosis (Fig. 36.19). Diverting stoma (loop ileostomy or colostomy) should be considered, particularly in patients with distal anastomosis, prior radiation, or severe comorbidities.

Intersphincteric Resection

When intersphincteric resection (ISR) is contemplated, patients should undergo preoperative evaluation of anal sphincter function. ISR should be reserved for select cases of tumors not amenable to standard LAR, and patients should be carefully informed of the possible functional derangements. ISR entails transanal circumferential incision of the anal mucosa in the intersphincteric groove, which is located distal to the dentate line. ISR leads to en bloc resection of the rectum and internal sphincter; the specimen is extracted transanally. The descending colon is then

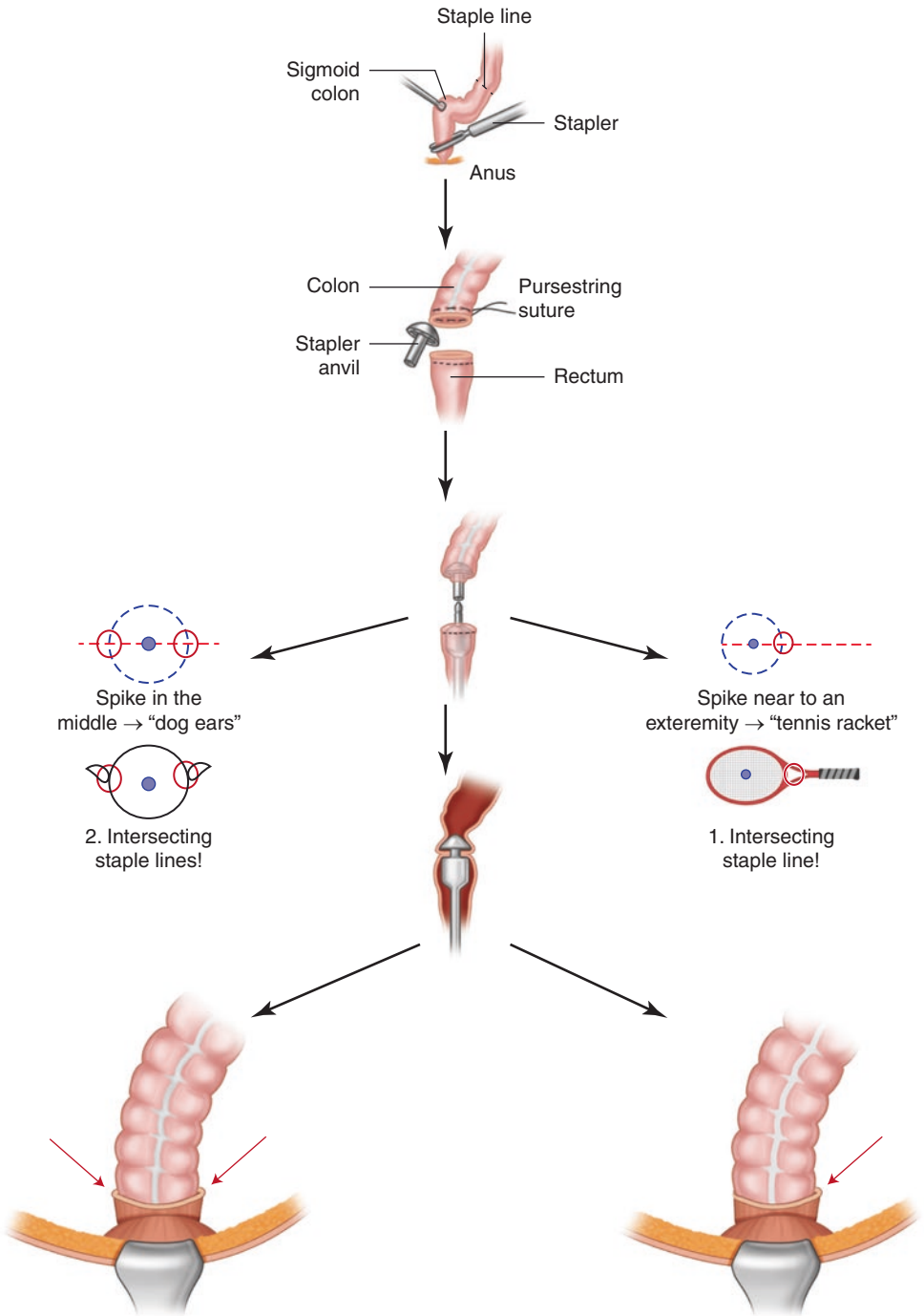

Fig. 36.11 Intersecting lateral staple lines (dog ears) created after double-stapled anastomosis techniques are considered weak structural spots, possibly prone to leak (left). One trick to eliminate one intersecting staple line, and thus one weak structural spot (dog ear), is to bring the spike of the anvil through the rectal stump laterally (as opposed to the middle). This was described as the "tennis racket" technique

divided, and a hand-sewn coloanal anastomosis with absorbable sutures is performed. A proximal diverting stoma is usually performed.

Laparoscopic Abdominoperineal Resection (APR)

Despite surgical options to spare the anal sphincter, APR is still required in approximately 18% of patients with rectal cancer [59]. Although published RCTs compared short- and long-term outcomes after laparoscopic and open rectal resections for cancer, which included APR [14–19, 42–44], a subset analysis for APR cases was not performed. As such, we have limited data to support or refute the use of laparoscopic techniques to perform APR. A prospective randomized trial by Ng et al. [60] specifically evaluated perioperative outcomes in patients with low rectal cancer undergoing open (n = 48) versus laparoscopic (n = 51) APR. The authors reported an earlier return of bowel function (3.1 days vs

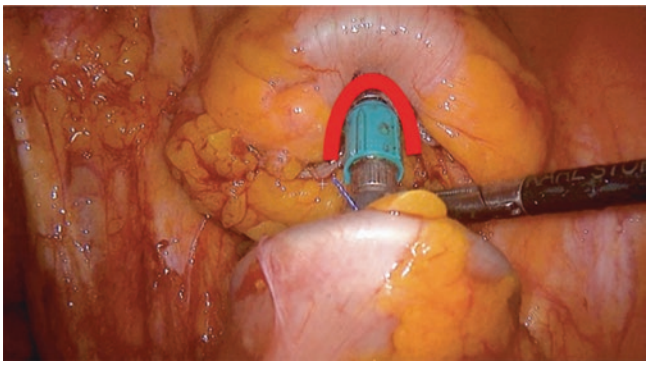

Fig. 36.12 The "reverse smile" technique: the spike is brought through the rectal stump in its central part, just posterior to the linear staple line. Then, the shaft of the stapler is retracted slightly and the end of the stapler angled anteriorly. This pulls the two edges of the linear staple line toward the midline posterior to the spike, forming a "reverse smile"

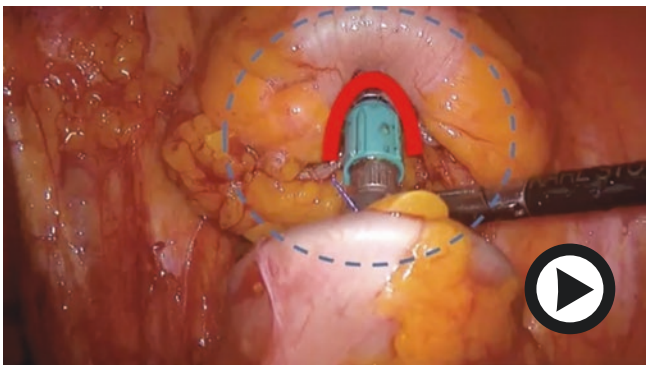

Fig. 36.13 Reverse smile technique. https://doi.org/10.1007/000-33k

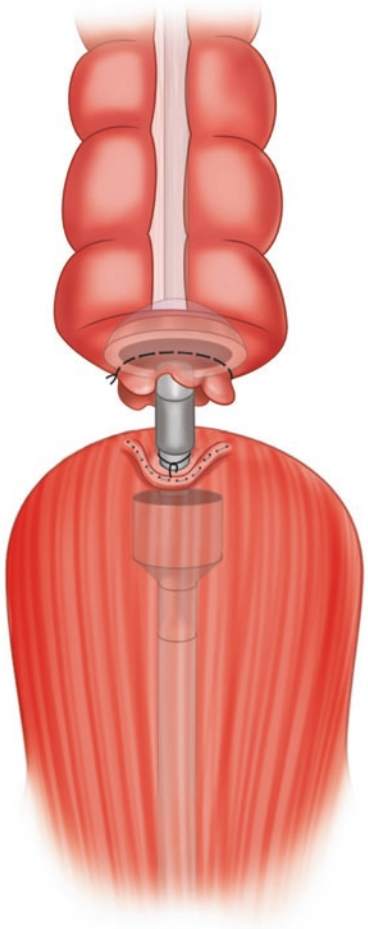

Fig. 36.14 The intent of the reverse smile technique is that the entire linear staple line of the rectal stump will then be excised when the anastomosis is created, essentially transforming a double-stapled into a single-stapled anastomosis

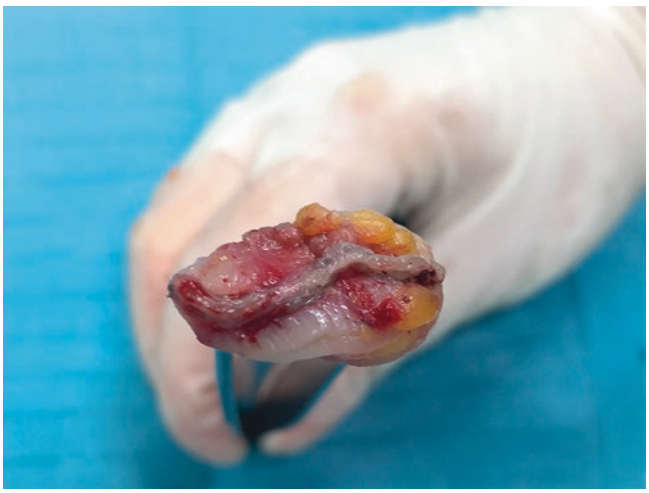

Fig. 36.15 Complete staple line is clearly visible on the donut

4.1 days; $p < 0.001$) and improved time until independent ambulation (4.4 days vs 5.9 days; $p = 0.005$) in the laparoscopic group but higher cost ($9588 vs $7517; $p < 0.001$) and longer operative time (213 min vs 163 min; $p < 0.001$). Consistent with the findings of the CLASICC trial [42], a 5-year survival was equivalent between the two approaches (75% vs 76%; $p = 0.20$). Unfortunately, studies on laparoscopic APR infrequently report CRM involvement rates. Among 19 studies published since 1994 that reported oncologic outcomes of laparoscopic APR, only 6 [61–66] included data on CRM involvement, which ranged from 2% [66] to 21% [62]. Two studies [63, 64], including the Dutch TME trial [64], reported an association between higher tumor stage and CRM involvement. In a subset analysis of the Dutch trial, the rate of positive CRM was 30% in the 455 patients who underwent APR [64]. The relatively high rate of CRM seen in the Dutch randomized trial raises the issue of selection bias in other non-randomized comparisons, in which it is likely that patients with more advanced tumors undergo open operations. In conclusion, existing data on

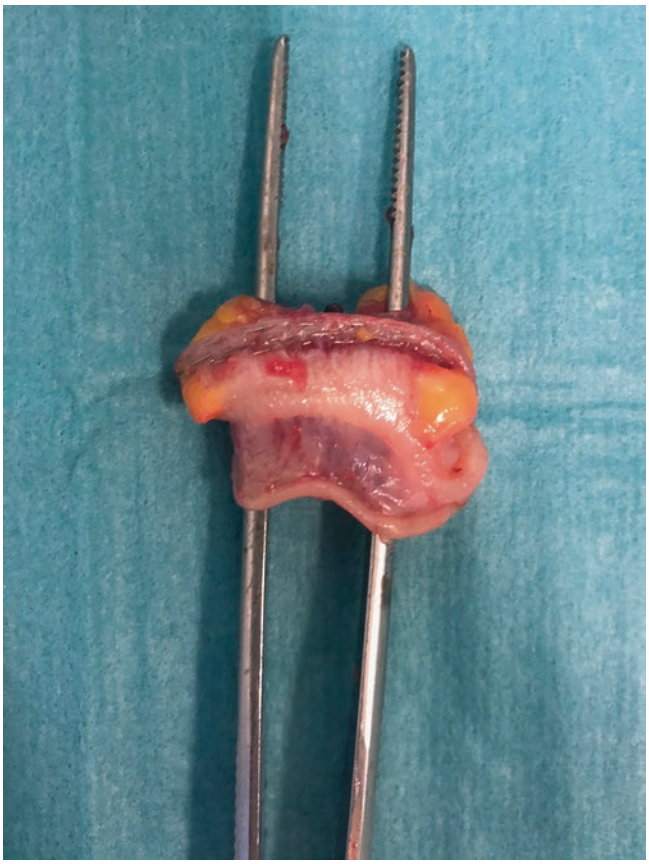

Fig. 36.16 Completed staple line is clearly visible on the donut

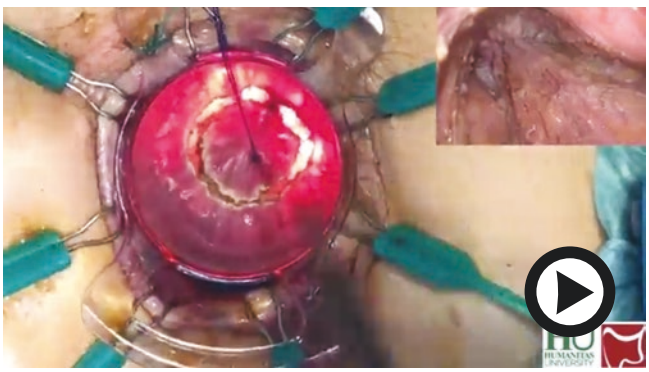

Fig. 36.17 Transanal distal transection of the rectum and single-stapled anastomosis. https://doi.org/10.1007/000-33j

laparoscopic versus open APR suggest that, when performed by skilled surgeons, the laparoscopic approach is associated with reasonable oncologic outcomes with possible faster recovery [66, 67].

Preoperative Considerations

Abdominoperineal resection (APR) is indicated for low rectal cancers, recurrent rectal cancers, as well as salvage therapy for anal cancer or melanoma. Additionally, APR may provide a better quality of life compared to LAR/coloanal anastomosis for patients who have marginal baseline continence or are at risk for severe anterior resection syndrome. The patient should undergo stoma site marking and education, preferably by an enterostomal therapist. A preoperative consult with a plastic surgeon should be considered if a large pelvic defect will result, as flap closure may be indicated.

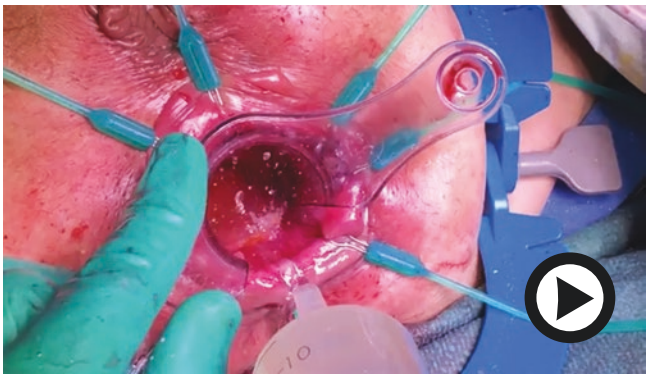

Fig. 36.18 Air leak test. https://doi.org/10.1007/000-33m

Surgical Technique

Abdominal Approach

The abdominal steps for APR are the same as for laparoscopic LAR. One of the two left-sided trocars should be positioned at the colostomy site (preoperatively identified and marked), and a suprapubic trocar can be utilized (instead of having two ports on the left site). After mobilization of the left colon and rectum, the sigmoid colon is divided, and the proximal end of the colon is brought through the abdominal wall to fashion an end colostomy. Ports are closed and the drain (if needed) is placed.

Laparoscopic Perineal Approach

The steps of the traditional perineal procedure are described in the chapter devoted to the principles of rectal cancer surgical treatment. However, another option is to perform the perineal part of the operation via a laparoscopic technique as well. The theoretical advantage of this retrograde method relates to the creation of the dissection plane in the pelvis before entering into the peritoneal cavity, thus avoiding having other pelvic structures impede exposure. As the literature on this approach is still in its infancy, there are little data on feasibility, safety, and outcomes of this approach. Our preferred approach is as follows. The patient is in lithotomy position. The anus is sewn closed and dissection is initiated in the ischiorectal space/extrasphincteric plane. Once the levator ani muscles are divided, a single-port laparoscopic surgery or transanal endoscopic microsurgery device is positioned within the dissected space and secured to the skin to

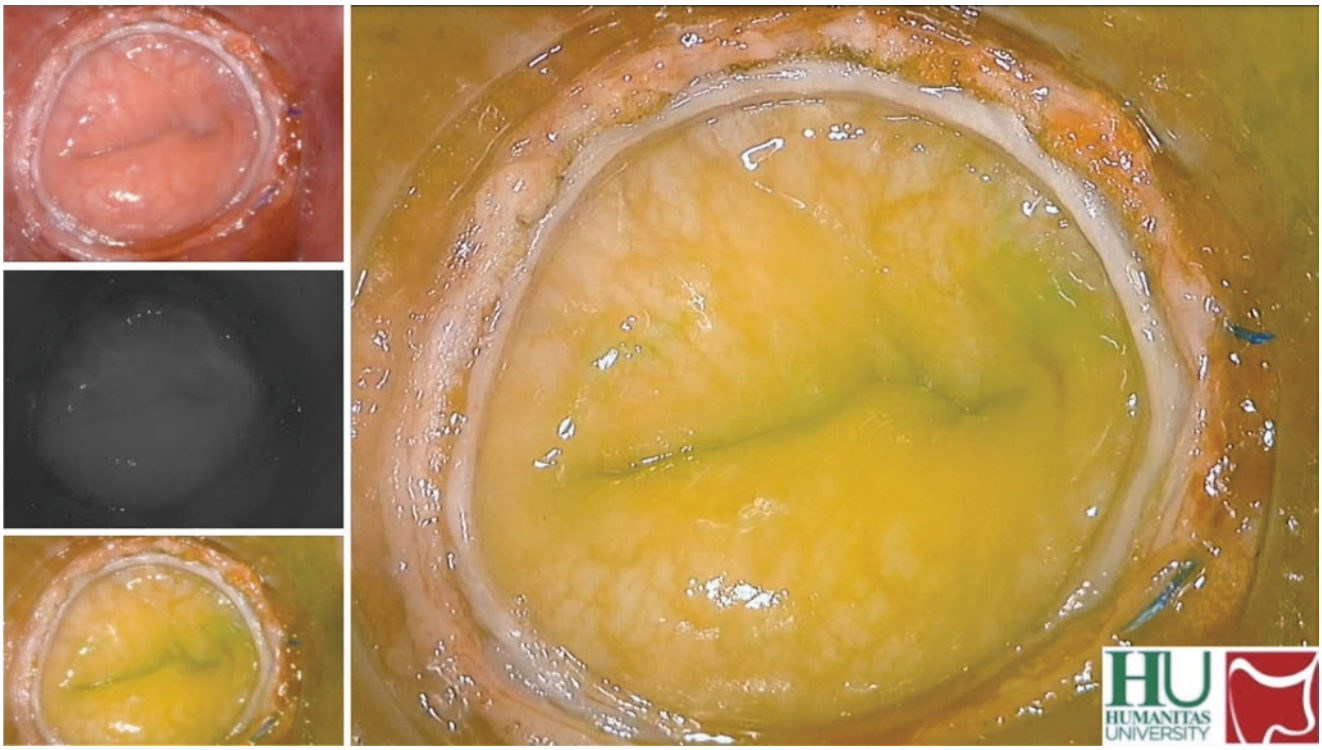

Fig. 36.19 Assessment of the colorectal anastomosis perfusion with real-time indocyanine green intraoperative fluorescence angiography (ICG-IFA)

prevent CO2 leakage and dislodgement of the access device. The space is insufflated to 15 mmHg, which will put the tissue on tension, thereby retracting the anus/rectum into the pelvis and helping to provide a working space with exposed wispy fibers in the mesorectal dissection plane. Laparoscopic hook cautery is used for dissection, and a suction irrigator is used both for smoke evacuation and countertraction. The small working space fills easily with smoke and quickly collapses with suction. This challenge can be overcome by connecting two separate CO2 insufflation lines to the access device or by switching to a system that allows for continuous smoke evacuation and CO2 exchange. The dissection proceeds to the level of the cervix in women and to the seminal vesicles in men or until the prior mobilization plane from above is reached (if the abdominal portion was performed first). The specimen is then removed through the perineal defect.

Robotic Rectal Cancer Surgery

The first robotic proctectomy for cancer was described in 2006 [68]: a magnified 3D view, improved ergonomics and overall dexterity with 7 degrees of freedom, stable camera holding, tremor filtering, motion scaling, and shorter learning curve seemed all promising features to overcome the limits of laparoscopic rectal surgery. Disadvantages of robotic surgery can be attributed to the lack of haptic feedback, longer operative time, and cost [69]. In addition, the potential benefits of the robotic approach for the surgeon seem not to have translated into demonstrable improved outcomes for the patient.

As noted above, laparoscopic proctectomy can be very challenging, especially in males who are obese with irradiated low tumors. Using the nonarticulating laparoscopic instrumentation and obtaining an optimal surgical view can be difficult and lead to high conversion rates [42, 70]. The abovementioned advantages of the robot could overcome these challenges and potentially lead to lower conversion rates [71, 72]. However, the ROLARR RCT [73], which used conversion to open as the primary outcome variable, failed to demonstrate that the robotic approach was associated with a lower conversion rate. Additionally, the ROLARR RCT [73] did not find any difference in short- and long-term outcomes between the robotic and the laparoscopic approaches. Lastly, robotic surgery was on average £980 more expensive than laparoscopic surgery, even when the acquisition and maintenance costs were excluded. Other RCTs [74–76] reported similar short-term, long-term, and functional outcomes between the laparoscopic and robotic approaches. The most time-consuming aspect of robotic surgery is docking, especially when multiple dockings are required. However, recent meta-analyses showed a similar operating time for robotic and laparoscopic proctectomy as a result of gained experience by the surgical team [71, 77].

Robotic proctectomy can be performed using a fully robotic or a hybrid laparoscopic/robotic technique [68, 78] in which the robot is docked only to perform the proctectomy. The choice of approach is up to the surgeon, as there are no studies demonstrating that one is superior to the other. A total robotic approach can be used in low anterior and abdominoperineal resections. For proctectomy with splenic flexure mobilization, a fully robotic approach can be time-consuming and may require two dockings, although the need to re-dock may be obviated by advances in robot technology [79, 80]. The hybrid approach implies that the mobilization of the splenic flexure and left colon and vessel ligation are performed laparoscopically. The robot is docked for rectal mobilization. This approach allows for the robot to be used for maximal benefit, which becomes evident in the narrow pelvis.

While there continues to be a debate regarding the cost-effectiveness of the robot, especially given the current lack of clinical evidence demonstrating its superiority to the laparoscopic approach, it appears to have an expanding role for colorectal surgeons, particularly with the advent of the single-port platform which may have utility in transanal procedures [81].

Robotic Proctectomy

Preoperative Considerations

There are no specific indications and no absolute contraindications for robotic proctectomy. The use of the robot is at the discretion of the surgeon, and indications are those indicated for laparoscopic rectal resection for cancer. The operating room setup should provide adequate space for staff and large equipment and allow the surgeon to have a direct view of the patient from the surgeon's console. The room should also allow docking from several angles.

Surgical Technique

Abdominal Robotic Approach

Port positioning with the da Vinci Xi® and Si® platform is shown in Figs. 36.20 and 36.21.

We describe the operating steps of a totally robotic proctectomy using the Xi platform.

The robot is docked from the patient left side and instruments are inserted under visual control. After a complete exploration of the abdominal cavity, the transverse colon is lifted up with the R1 arm (Fig. 36.22). The lesser sac is entered through an incision through the bare area at the root of the transverse mesocolon at the level of the anterior pancreatic border. Splenic flexure mobilization is carried out with a medial-to-lateral approach along the pancreatic body.

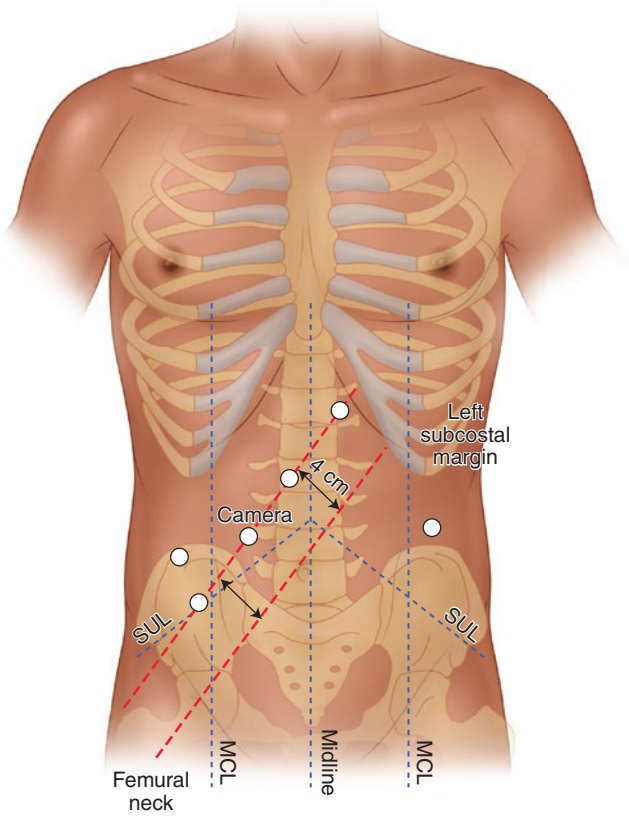

Fig. 36.20 Trocar placement for a fully robotic proctectomy with the da Vinci Xi® platform

A gauze is placed underneath the transverse mesocolon, and the splenic flexure is retracted medially by the assistant. Splenic flexure mobilization is completed in a lateral-to-medial fashion along the white line of Toldt up to the inferior splenic pole, and the plane previously developed is reached.

The next step is the ligation of mesenteric vessels. During this phase, R2 and R4 are the operative arms, whereas R1 is used for stable retraction. A 30°-down robotic camera is mounted on robotic arm R3. The trocar of the assistant in the right flank is used for suction/irrigation, clip applier, gauze introduction, or additional retraction if needed. The assistant grasper and the robotic grasper in R1 lift anteriorly and laterally the sigmoid colon and upper rectum to expose the root of the sigmoid mesocolon and the upper mesorectum. The peritoneum is then incised at the level of the sacral promontory to obtain the avascular presacral plane, and the hypogastric nerves are identified. The robotic monopolar hook on R4 and bipolar grasper on R2 work synergistically for the dissection of the IMA, which is freed from the surrounding lymphatic tissue, providing a wide locoregional lymphadenectomy and preserving the main trunks of the hypogastric plexus at the IMA origin. Before IMA division, Toldt's fascia is identified deep to the IMV in a medial-to-lateral fashion, and left gonadal vessels and left ureter are identified and preserved.

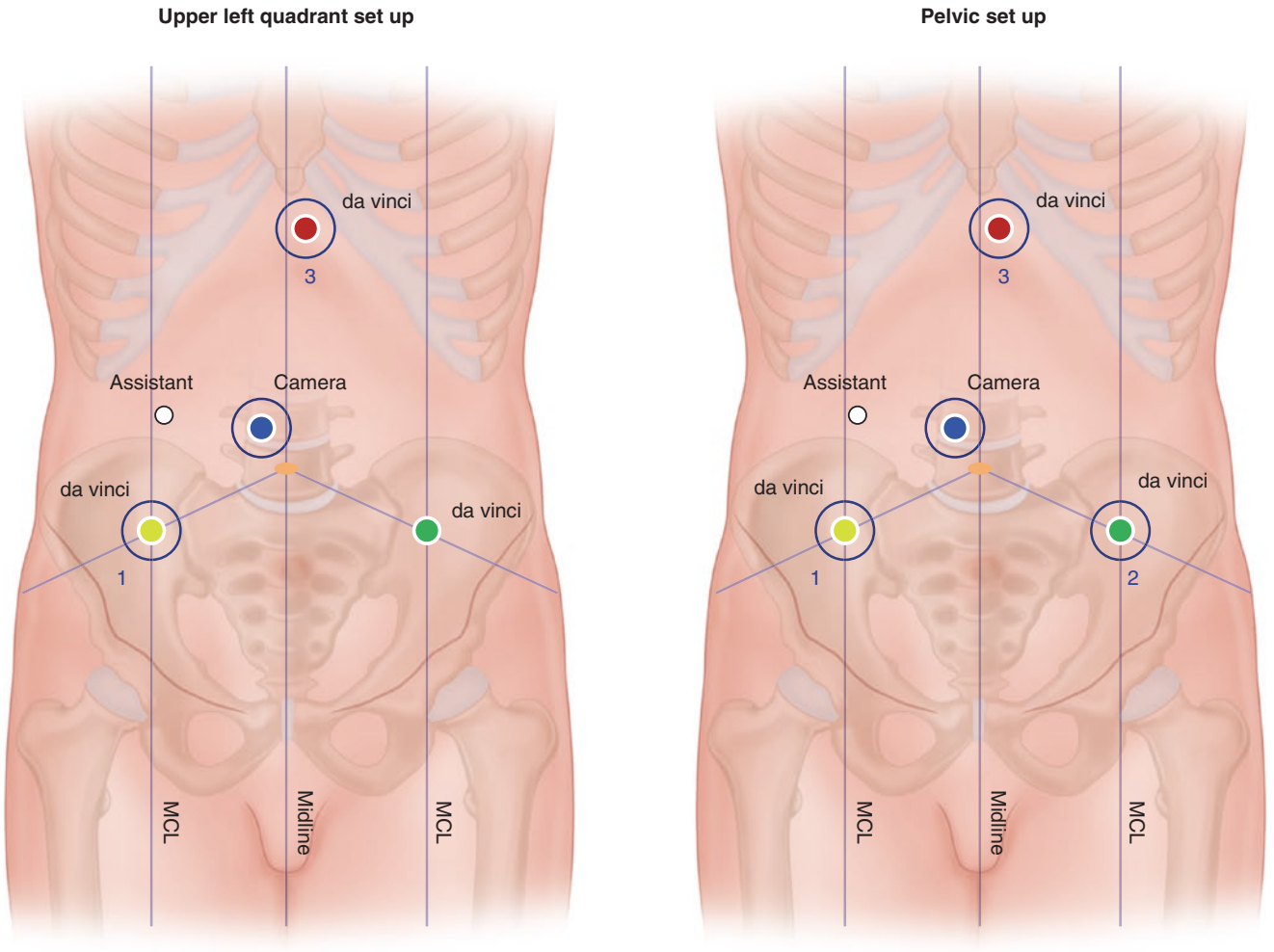

Fig. 36.21 Upper left quadrant setup and pelvic setup to perform a proctectomy with the da Vinci Si® platform

A high ligation of the IMA is then performed. The dissection along the Toldt's fascia, which has been previously identified cranially and caudally to the IMA origin, is completed to a medial-to-lateral fashion preserving the retroperitoneal structures. The IMV is then isolated and divided between clips (or using an energy device) at the inferior border of the pancreas.

Robotic Proctectomy

The canonical principles of TME are followed, emphasizing minimal manipulation of the rectum, identification of embryologic planes, and tumor clearance with negative margins. Bulky anterior tumors close to the vagina or prostate and seminal vesicles are more challenging, especially given the lack of haptic feedback from the robotic arms. In these cases, the identification of proper planes can be more difficult.

During this step, R1 is moved and connected to the left flank 8-mm trocar to achieve optimal access to the mesorectum, whereas R2 and R4 remain in their original position (Fig. 36.23). An additional 8-mm epigastric trocar is placed to maximize the assistance with cranial retraction on the sigmoid colon and simultaneous suction/irrigation or gentle pelvic sidewall retraction. Robotic R2 and R4 are the operative arms, whereas R1 is used to expose the pelvic area with lateral traction on the pelvic sidewall or anterior/upward traction on the Douglas peritoneal reflection, vaginal wall, or seminal vesicles/Denonvilliers' fascia. Frequent repositioning of R1 is fundamental to maintain the adequate countertraction that will allow the dissection to continue to the level of the pelvic floor. Mesorectal mobilization is carried out starting from the posterior plane: whereas the assistant retracts the sigmoid colon anteriorly and superiorly, the surgeon follows the areolar plane deep to the superior hemorrhoidal artery along the presacral fascia, toward the coccyx proceeding as distal as possible. Laterally, the hypogastric nerves are identified and preserved. Dissection is last carried anteriorly; Denonvilliers' fascia/pouch of Douglas is entered by incising the peritoneal reflection between the anterior wall of the rectum and the posterior wall of the vagina or seminal vesicles. R3 can be used as an anterior retractor to

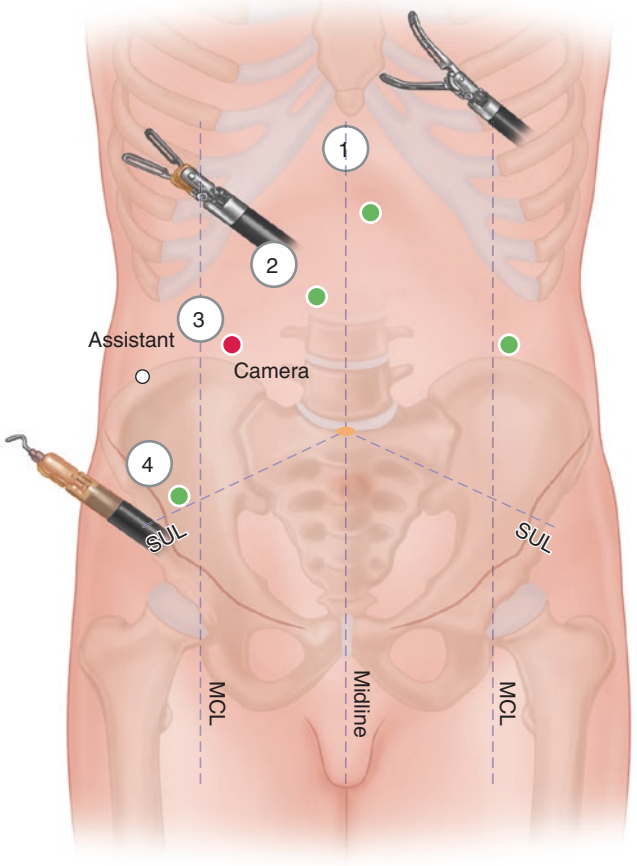

Fig. 36.22 Instrument setup during splenic flexure mobilization with the da Vinci Xi® platform

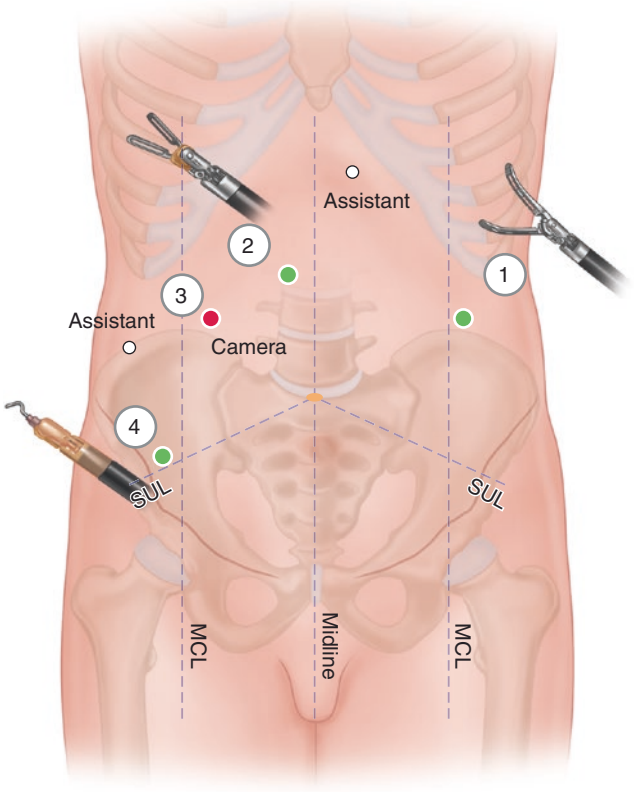

Fig. 36.23 Instrument setup during proctectomy with the da Vinci Xi® platform

keep the bladder, uterus, vagina, or prostate out of the field of dissection. It is important to point out that the left hand of the robotic surgeon (arm 2) should not grasp the mesorectum during the dissection because the robotic instruments are particularly powerful and can lacerate the mesorectal fascia. Dissection is carried out down to the pelvic floor where the levators can be identified. For tumors located at least 2–3 cm from the anorectal ring, a double-stapled colorectal anastomosis can be performed. The bowel is divided via either R1 or R2, using the robotic stapler or by the assistant using a laparoscopic approach, depending on the amount of retraction needed to expose the surface of the rectum. After undocking the robot, the bowel is extracted through a Pfannenstiel incision, and the proximal colon is divided extracorporeally. After insertion of the anvil, the double-stapled anastomosis is performed under laparoscopic vision. The technical aspects of performing the anastomosis are the same as described in the laparoscopic paragraph (see above). Transanal extraction is also possible. After placing a wound protector, the specimen is delivered through the anus, and extracorporeal resection is performed before fashioning the anastomosis. For tumors that are located less than 2–3 cm above the anorectal ring, not invading the external sphincter or levators, a double-stapled anastomosis may be difficult to accomplish under robotic or laparoscopic control without compromising the distal resection margin. In properly selected patients, an ISR with transanal extraction and hand-sewn coloanal anastomosis may be performed.

Robotic APR

The robotic approach can also be applied to APR or extralevator abdominoperineal excision (ELAPE). Once proximal mesorectal mobilization is completed, the dissection is carried distally, taking care to avoid "coning in" at the level of the levators creating a "waist" in the specimen. Rather, a wide resection of the levators near their origin is carried out, extending the dissection distally into the ischiorectal fat as far as feasible just before encountering the perineal skin. Once this is accomplished, the robot is undocked and the perineal phase is started. The few published studies of robotic APR show it is safe and feasible in select patients operated upon by experienced surgeons, with functional outcomes comparable to the laparoscopic approach [82–88]. One study reported lower conversion rates but higher total hospital

charges with the robotic approach compared to laparoscopy [89]. When compared to the open approach, robotic APR showed faster bowel recovery and a trend toward reduced CRM+ [83], although the vast majority of studies are not randomized, and thus selection bias may influence outcomes.

Transanal Total Mesorectal Excision (TaTME)

The concept of TaTME was proposed to overcome the technical challenges encountered with the transabdominal approaches (open, laparoscopic, robotic) in the more difficult cases such as obese, male patients with mid-low rectal cancers. There are concerns that such patients with a narrow, radiated pelvis and bulky mesorectum may currently be undergoing sphincter-sparing resections with an involved CRM, a poor-quality TME, or even an unnecessary abdominoperineal resection (APR). It has been recently claimed that TaTME offers three potential advantages: (1) a longer distal resection margin, thanks to the distal transection under direct visual control, reducing the risk of distal margin tumor involvement, (2) a decreased rate of positive CRM, and (3) improved quality of TME [90]. Additionally, rectal transection performed under visual control avoids multiple stapling and dog ears that together with the single-stapled anastomosis can potentially reduce the risk of leak, even if the comparative benefits of single-stapled over conventional double-stapled anastomosis are still unproven [91]. However, the utilization of TaTME remains controversial, because of the lack of RCTs comparing TaTME to open, laparoscopic, and/or robotic proctectomy and because of concerns regarding safety. Several non-randomized studies, including the results from the TaTME registry group [92], have suggested that TaTME is an oncologically safe and effective technique in select patients, resulting in comparable short-term and oncologic outcomes when compared to the abdominal approaches [90, 92–98]. Recently, a number of criticisms have been raised over the TaTME technique, including concerns about complications such as urethral damage or carbon dioxide embolism [91, 99–101] and multifocal local cancer recurrence potentially related to the use of pelvic insufflation and spread of cancer cells [102], very rarely previously reported in other approaches. However, results from a recent study including six tertiary referral centers focused on local recurrence (LR) after TaTME showed a 2-year LR rate of 3% and no multifocal pattern of recurrence, indicating good locoregional control after TaTME [103]. Standardization of surgical technique, implementation in daily practice, and strict selection criteria are required to further clarify the role of TaTME in the treatment of rectal cancer. Hopefully, the COLOR III multicenter RCT will better define the relative short- and long-term oncologic outcomes after TaTME [104].

Transanal TME

Surgical Technique

Abdominal Approach

The patient is placed in the lithotomy position. Standard steps of the abdominal dissection are performed: left colon and splenic flexure mobilization, division of IMA and IMA, and then mobilization of the proximal mesorectum, paying attention not to injure the urethra and hypogastric nerves during dissection. The transanal mobilization can be performed before, after, or synchronous with abdominal mobilization.

Transanal Approach

Setup and Start

The patient is placed in the lithotomy position, in Trendelenburg, and tilted to the right. A pudendal block with local anesthetic is performed. A self-retaining retractor is then placed to visualize the dentate line. The hooks are placed at the level of the anal verge, retracted, and fixed on the plastic frame (Fig. 36.24). Anal dilators are used to facilitate the placement of the transanal platform. This author's preference is to use a flexible platform which is firstly folded in a U-shaped manner to facilitate its introduction in the lubricated anal canal. The device is adjusted with the introducer beyond the levators and two stitches placed laterally to fix it in place. In cases of very low rectal lesions, it may be desirable to leave the platform unfixed or secured loosely to manipulate the access channel. While positioning the platform, release the tension on the hooks to prevent prolonged dilation of the anal canal. The anal platform should fit snugly on the anal wall in order to prevent air leakage (Fig. 36.25). Trocars are placed in the gel cap at 2, 6, and 11 o'clock. If a continuous insufflation system is used, the trocar is usually placed at 2 o'clock. The cap is then placed on the transanal platform and the lid is closed (Fig. 36.26). At this point, a purse string should be performed using a 0 PDS or Prolene suture on a 26 mm needle, starting at 5 o'clock and continuing clockwise, leaving a 1–2-mm space between stitches. The needle should enter at a 90-degree angle performing small full-thickness bites. The exit point should be the entry point of the next suture, and a constant distance should be maintained from the access channel. Once completed, the purse string should be tied down—I suggest to leave some length when cutting ends for an easier manipulation of the stump (Fig. 36.27). In women, the anterior stitches must be carefully placed to avoid grasping the vaginal wall. While performing this step, the abdominal team clamps the colon at the level of the rectosigmoid junction to prevent colonic distension. The TaTME technique allows for clear identification of the distal edge of the tumor, and then, at the desired distance, the purse-string suture is placed in order to achieve a

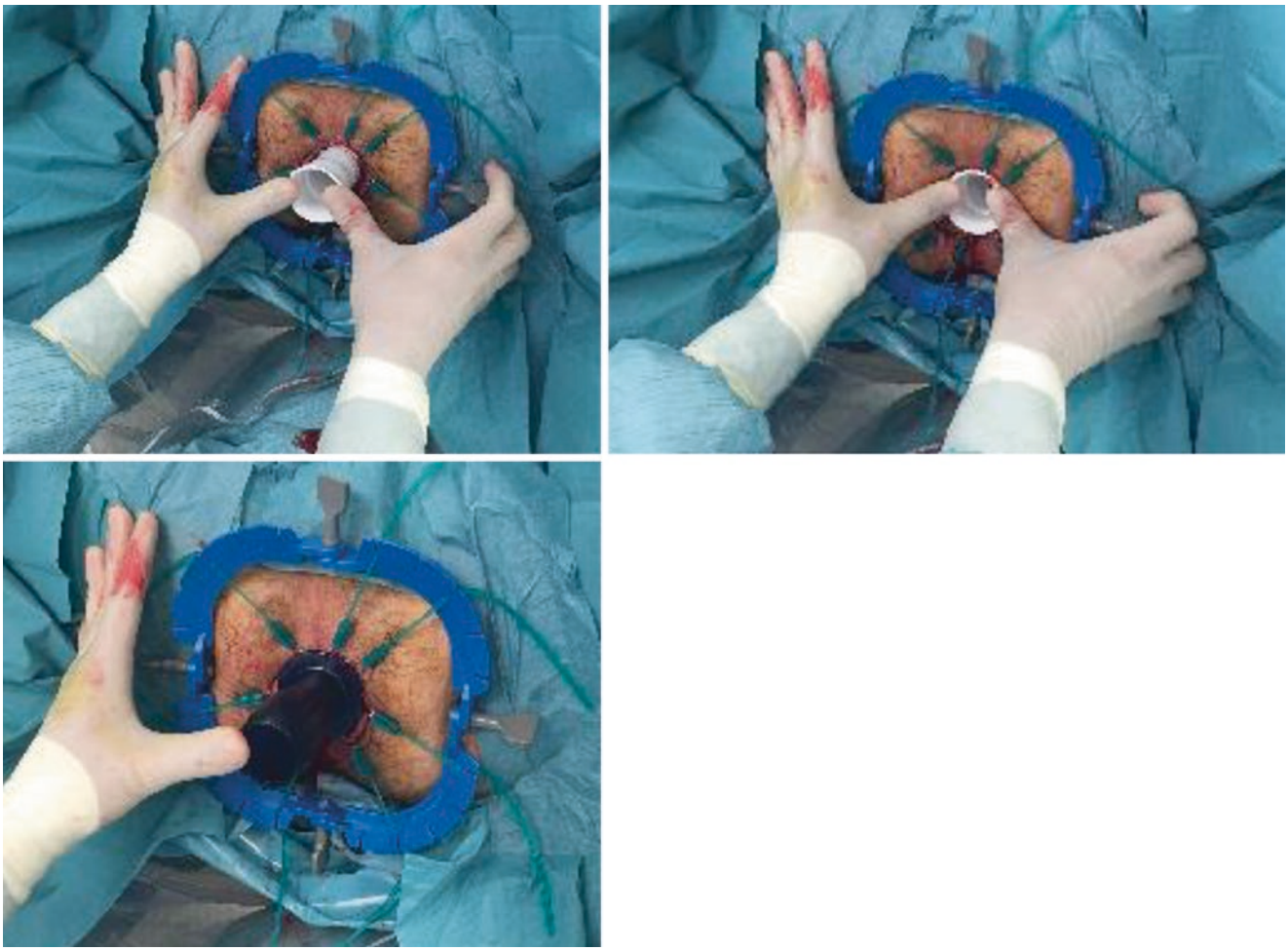

Fig. 36.24 First steps of a transanal total mesorectal excision (TaTME): after pudendal block, a self-retaining retractor is placed to visualize the dentate line. The hooks are placed at the level of the anal verge, retracted, and fixed on the plastic frame. Anal dilators are used to facilitate the placement of the transanal platform

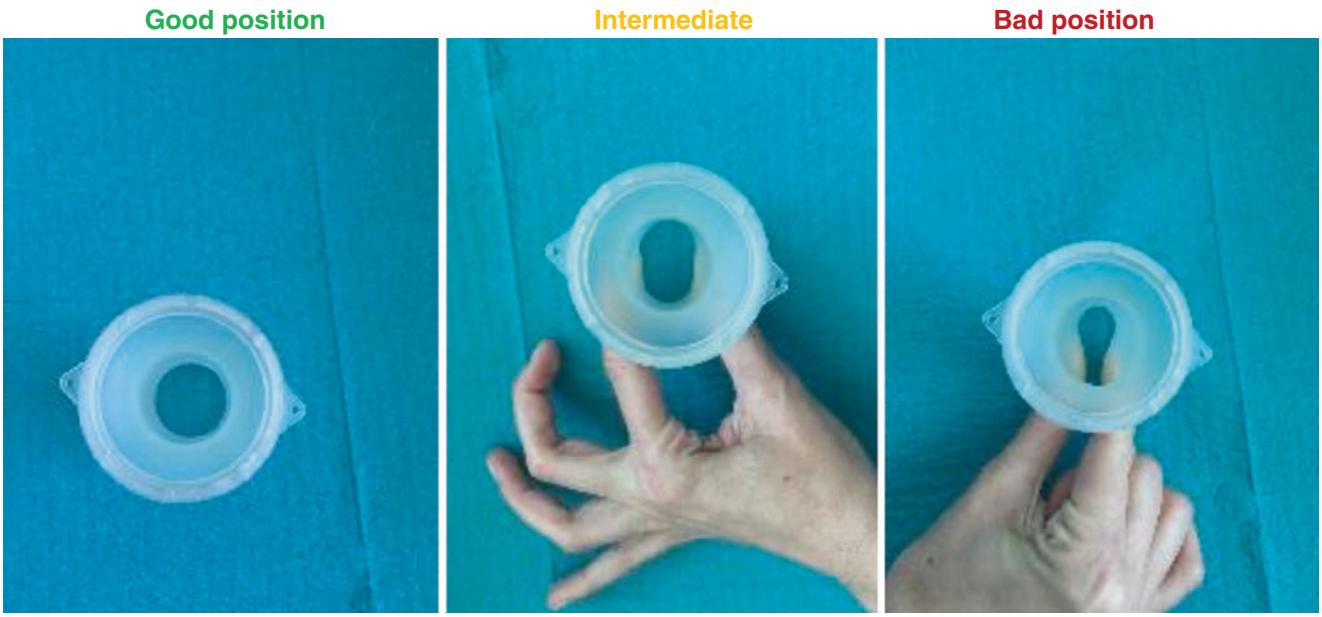

Fig. 36.25 Correct positioning of the anal platform into the anal wall in order to prevent air leakage

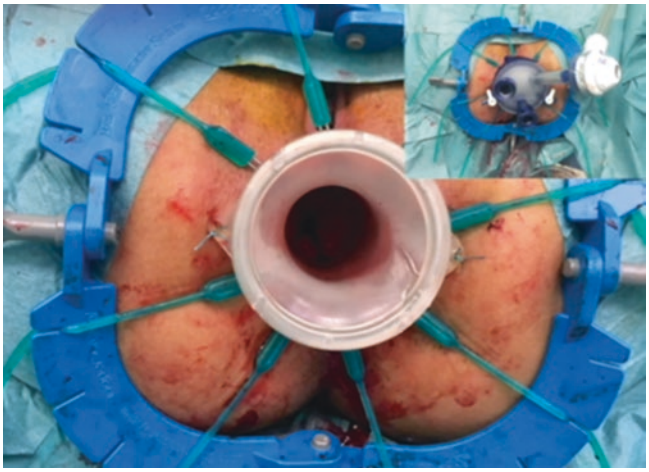

Fig. 36.26 Anal platform positioning and trocars setup on the gel cap

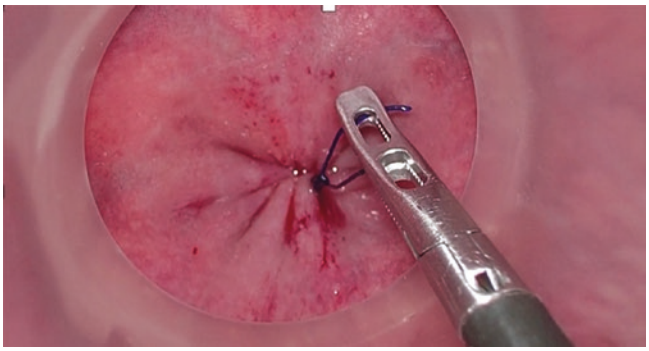

Fig. 36.27 Purse string completed and tied down

distal resection margin. After the purse string is tied, I usually perform a rectal washout. The rationale for performing this maneuver is that it should reduce fecal contamination and potentially lose tumor cell implantation, although there is no clear data that support this contention. Once the purse string is tied down, the cap is placed back on the platform, and the pneumorectum is established. The rectal mucosa is marked circumferentially with electrocautery (hook), about 1 cm from the purse string knot, where the mucosal folds end. A 360° full-thickness rectal wall incision starting at posterolaterally is performed (Fig. 36.28), transecting the rectal wall to continue along the mesorectum. During this phase, it is helpful to maximize the angulation of the hook to achieve the best dissection. If the distance between the tumor and the anorectal junction (ARJ) is >4 cm, place the purse string 3 cm from the anal verge; if the distance between the tumor and the ARJ is 2–4 cm, place the purse string 1 cm distal to the tumor; if the distance is <2 cm, dissection is started without the platform: division of the rectal wall is performed first, and then the rectal purse string is performed before introducing the platform.

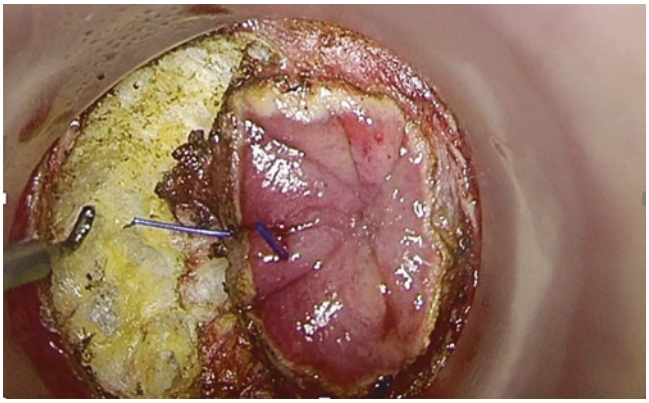

Fig. 36.28 Right lateral dissection during transanal total mesorectal excision (TaTME)

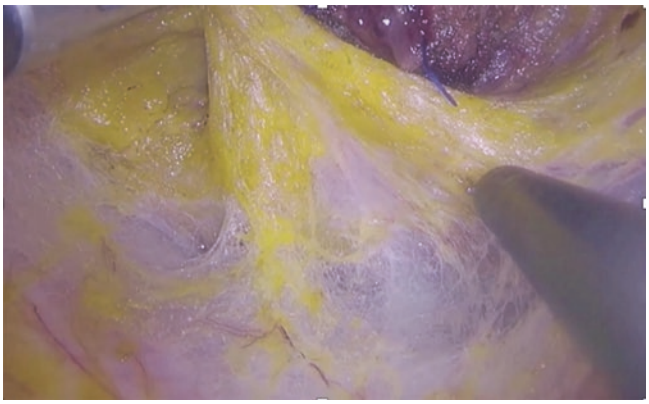

Fig. 36.29 Posterior plane of dissection during transanal total mesorectal excision (TaTME)

Mesorectal Mobilization

Dissection should progress circumferentially, avoiding to tendency to create a funnel. The avascular presacral space posteriorly is the safest area to start the procedure. Lift up the specimen with a grasper to find the posterior plane (Fig. 36.29). Dissection starts posterolaterally. The posterior midline is avoided initially as the anococcygeal ligament may impede progress. Follow the muscle layers of the pelvic floor to localize the correct plane, particularly in males who may have a tight pelvic floor around the rectum. If the dissection deviates too posteriorly, the presacral vessels can be injured with subsequent bleeding. Anteriorly, dissection proceeds in the rectovaginal or rectoprostatic planes which are usually straightforward to find. Pushing against the tissue with the grasper allows the pneumopelvis to reveal the plane (provided that the abdominal mobilization was performed first). Then, the specimen is pulled down with the grasper to find the avascular anterior plane. Dissection starts anterolaterally, paying attention at the urethra in male patients (in the anterior midline), and stops

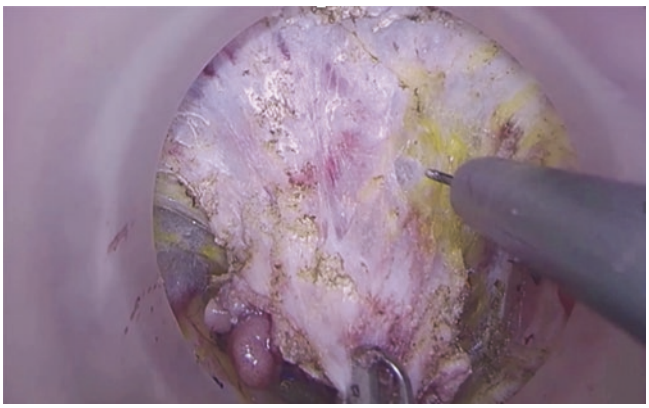

Fig. 36.30 Anterior plane of dissection during transanal total mesorectal excision (TaTME)

close to the neurovascular bundle (2 and 10 o'clock) (Fig. 36.30). Placing a vaginal retractor or palpating the vagina helps to find the plane. In males, it is critical that the dissection stays posterior to the prostate and urethra to avoid prostatic bleeding and urethral injury. On the lateral sides, the parietal fascia should be the landmark; as if dissection is performed too far laterally, nerves and vessels can be injured at 2 and 10 o'clock. This step is easier if performed with synchronous transabdominal and transanal approaches.

Specimen Extraction

The specimen is extracted transabdominally or transanally. The transanal extraction should be performed only if the bulk of the mesorectum is limited. Transabdominal extraction can be performed through a Pfannenstiel incision, on the left or right iliac fossa, or at the stoma site.

Anastomosis

The proximal colon should reach the pelvis with no tension and without torsion. Before transecting the colon, vascular supply is assessed. The proximal purse string is performed, and the detachable anvil of the end-to-end stapler is positioned and secured. A tubular drain can be positioned on the tip of the anvil as a temporary handle, and the colon is repositioned in the abdomen (Fig. 36.31).

At this point, the tension of the elastic bands on the anal retractor is released to get better exposure while performing the Prolene 0 distal purse string on the rectal stump. The rectal cuff purse-string suture should be performed with full-thickness bites without imbricating too much the rectal wall in each bite but avoiding gaps. The first and last stitch should overlap. While performing the distal purse string, pay attention not to imbricate the vagina or the sphincter muscle. The

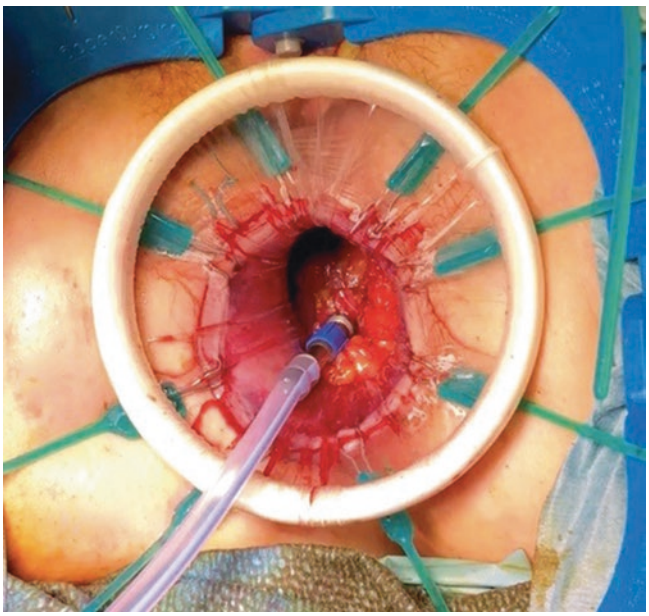

Fig. 36.31 A tubular drain is positioned on the tip of the anvil before repositioning the colon in the abdomen

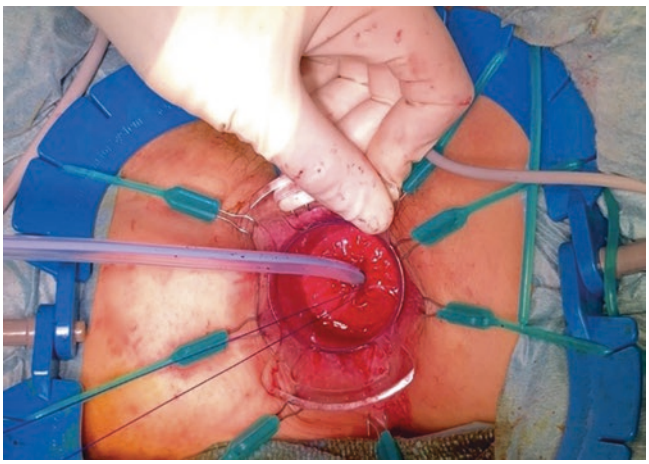

Fig. 36.32 The drain on the tip of the anvil is pulled through the distal purse string. When the spike has gone completely through the purse string, it is tied down

drain on the tip of the anvil is easily grabbed with a clamp introduced through the rectal stump and pulled through the distal purse string. When the spike has gone completely through the purse string, the purse string is tied down (Fig. 36.32). The anvil is then attached to the spike under abdominal monitoring, and a single-stapled colorectal end-to-end or side-to-end anastomosis is performed using the circular stapler. Air leak test (standard or reverse) is performed. Proximal fecal diversion with loop ileostomy of colostomy is typically then performed.

Hand-Assisted Rectal Cancer Surgery

Hand-assisted colorectal laparoscopic surgery (HALS) techniques were developed in the late 1990s [32] with the aim to overcome some of the limitations of the laparoscopic approach. When considering laparoscopic proctectomy in general, excluding those cases in which transanal specimen extraction is performed, an abdominal incision of 4–8 cm is used to extract the specimen. This incision can also be utilized to perform mesentery division and anastomosis directly, provided that adequate mobilization of the colon has been accomplished intracorporeally. If such an incision is to be made at the end of the operation, why not make it at the start of the procedure and utilize it throughout? This incision can be used to perform mobilization of the mesorectum directly if the patient's body habitus is favorable ("hybrid" approach), which may allay fears of compromising quality of mesorectal mobilization by using a laparoscopic approach. The current generation of hand-assisted devices allows this concept to be put into practice to facilitate the performance of laparoscopic colectomy and proctectomy. The optimal device includes a stable, sturdy platform base that crosses the abdominal wall and provides circumferential retraction of the wound with a low vertical profile and a self-sealing membrane that allows for rapid and easy hand exchange and accommodates trocar or stapler placement through the device while maintaining pneumoperitoneum.

The main findings of studies comparing open, straight laparoscopic, and hand-assisted low anterior resection (HALAR) can be summarized as follows [105–115]:

1. HALAR retains many of the benefits of a pure laparoscopic approach.
2. Complication rate and length of stay following HALAR comparable with straight laparoscopic approach.
3. Oncologic outcomes following HALAR comparable with straight laparoscopic or open approaches.
4. Shorter operative time and lower conversion rate with HALAR.
5. Slightly longer incision than straight laparoscopic approach, although of unclear clinical significance.
6. Increased level of inflammatory markers compared to straight laparoscopic approach, although of unclear clinical significance.

Given the concerns with oncologic outcomes following laparoscopic proctectomy as outlined previously, hand-assisted technology allows for the benefits of laparoscopy to be realized while not violating the recommendation to avoid laparoscopic proctectomy for rectal cancer. Mobilization of the proximal colon can be performed laparoscopically, and mesorectal mobilization can be accomplished directly via the base of the hand-assisted device in open fashion, provided the patient's body habitus is not extremely unfavorable.

Hand-Assisted Laparoscopic Proctectomy

Preoperative Considerations

There are no specific indications and no absolute contraindication for hand-assisted proctectomy. Preoperative assessment and indications are similar to those indicated for the previously described approaches.

Surgical Technique

Access to the Abdomen and Vessel Ligation

Access to the abdomen can be performed through a periumbilical port, so that occult unresectable metastatic disease that would prompt the surgeon to abandon proctectomy can be ruled out prior to making a larger incision. Care should be taken to place this port superior enough to avoid planned position of the skirt of the hand-assisted device. Alternatively, a Pfannenstiel or lower midline incision for the hand-assisted device can be performed initially and only 5-mm ports utilized during the operation. The length of the incision depends on the hand size of the surgeon. A general rule is to perform an incision the same length as the surgeon's glove size in centimeters.

For cases where the likelihood of conversion to open operation is high, a lower midline incision for the hand-assisted device is preferred, allowing for easier conversion to a midline laparotomy if necessary. This incision can be made prior to opening any laparoscopic or disposable instruments and extended directly to laparotomy if indicated prior to creating pneumoperitoneum. Used selectively, this technique is associated with an overall low rate of conversion from laparoscopy to laparotomy [116]. The other ports are then placed: typically two 5 mm on the right side and one or two 5 mm trocars on the left side, lateral to the rectus muscle on both sides to avoid the epigastric arteries.

The operating surgeon can stand on the right of the patient using the right hand through the hand-assisted device and the left hand with a dissecting tool. The first step is to place the omentum over the liver and the small bowel to the upper right quadrant of the abdomen. It is often helpful to drape a moist laparotomy pad over the small bowel. The left colon mesentery, the IMA, and IMV are then exposed. The hand is used to identify and follow the sacral promontory and put traction on the IMA. The peritoneum along the inferior aspect of the pedicle is incised, starting at the sacral promontory and working toward the origin of the IMA and IMV. The IMA is isolated at its origin, taking care not to injure the ureter and the main trunks of the hypogastric nerves, and the IMV is isolated adjacent to the ligament of Treitz. During the operation, dexterity with the hand and ensuring that it does not obstruct the field of vision are a must. In general, it is important to keep the hand away from the camera, in a "C-shape" position.

Splenic Flexure and Left Colon Mobilization

The lateral attachments to the colon are taken down using the dissecting tool through the left-sided port, and splenic flexure mobilization is performed (if needed) according to the principles already described. This is sometimes facilitated by having the operating surgeon stand between the legs and utilize the left lower quadrant port for dissection and the left hand in the hand-assisted device for retraction.

Mesorectal Mobilization

The principles of TME remain the same irrespective of the specific technique used. The hand-assisted device offers multiple options in carrying out mesorectal mobilization. The specific technique used is dependent on the preference of the surgeon and the specific characteristics of the patient and tumor:

1. *Open* technique through the hand-assisted port: the lid of the device is removed. Laparotomy pads can be used to pack the small bowel out of the pelvis. Pelvic retractors can be placed to obtain a better view of the pelvis. After mesorectal mobilization is completed, transection of the rectum can be performed using a stapler.
2. *Laparoscopic technique*: the dissection is carried out laparoscopically with or without hand assistance. In this phase, the hand can be used as a retractor. The proximal bowel can be divided with a laparoscopic linear stapler or performed with an open stapler through the hand-assisted device.
3. *Laparoscopic technique pulling the specimen through the hand-assisted device as a retractor*: the colon is divided through the Pfannenstiel incision at the proximal margin, and the divided colon stump is exteriorized through the gelatinous cover of the hand-assisted device to provide traction and help to complete posterior mesorectal dissection.

The distal transection is then performed, and an end-to-end or side-to-end double-stapled colorectal anastomosis is performed as previously described.

References

1. Schlinkert RT. Laparoscopic-assisted right hemicolectomy. Dis Colon Rectum. 1991;34(11):1030–1.
2. Fowler DL, White SA. Laparoscopic-assisted sigmoid resection. Surg Laparosc Endosc. 1991;1(3):183–8.
3. Jacobs M, Vardeja JC, Goldstein HS. Minimally invasive colon resection (laparoscopic colectomy). Surg Laparosc Endosc. 1991;1(3):144–50.
4. Phillips EH, Franklin M, Carroll BJ, et al. Laparoscopic colectomy. Ann Surg. 1992;216(6):703–7.
5. Darzi A, Super P, Guillou PJ, et al. Laparoscopic sigmoid colectomy: total laparoscopic approach. Dis Colon Rectum. 1994;37(3):268–71.
6. Mentges B, Buess G, Schäfer D, et al. Transanal endoscopic microsurgery and combined operations. In: Moreno-González E, Escartín P, Lygidakis NJ, editors. Joint meeting of surgery, gastroenterology and endoscopy. Madrid, Spain: Jarpyo; 1995. p. 339–45.
7. Chang YJ, Marcello PW, Rusin LC, et al. Hand-assisted laparoscopic sigmoid colectomy: helping hand or hindrance? Surg Endosc. 2005;19(5):656–61.
8. Wexner SD, Johansen OB, Nogueras JJ, et al. Laparoscopic total abdominal colectomy. A prospective trial. Dis Colon Rectum. 1992;35(7):651–5.
9. Berends FJ, Kazemier G, Bonjer HJ, et al. Subcutaneous metastases after laparoscopic colectomy. Lancet. 1994;344:58.
10. Reilly WT, Nelson H, Schroeder G, et al. Wound recurrence following conventional treatment of colorectal cancer. A rare but perhaps underestimated problem. Dis Colon Rectum. 1996;39:200–7.
11. Fleshman JW, Nelson H, Peters WR, et al. Early results of laparoscopic surgery for colorectal cancer. Retrospective analysis of 372 patients treated by Clinical Outcomes of Surgical Therapy (COST) Study Group. Dis Colon Rectum. 1996;39:S53–8.
12. Allardyce RA. Is the port site really at risk? Biology, mechanism and prevention: a critical view. Aust NZJ Surg. 1999;69:479–85.
13. Ramos JM, Gupta S, Anthone GJ, et al. Laparoscopy and colon cancer. Is the port site at risk? A preliminary report. Arch Surg. 1994;129(9):897–9.
14. Green BL, Marshall HC, Collinson F, et al. Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer. Br J Surg. 2013;100(1):75–82.
15. Nelson H, Sargent D, Wieand HS, et al. Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. N EnglbJ Med. 2004;350(20):2050–9.
16. Veldkamp R, Kuhry E, Hop WC, et al. Colon cancer Laparoscopic or Open Resection Study Group (COLOR). Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomized trial. Lancet Oncol. 2005;6(7):477–84.
17. Lacy AM, García-Valdecasas JC, Delgado S, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomized trial. Lancet. 2002;359:2224–9.
18. Fleshman J, Branda ME, Sargent DJ, et al. Disease-free survival and local recurrence for laparoscopic resection compared with open resection of stage II to III rectal cancer: follow-up results of the ACOSOG Z6051 randomized controlled trial. Ann Surg. 2019;269(4):589–95.
19. Stevenson ARL, Solomon MJ, Brown CSB, et al. Disease-free survival and local recurrence after laparoscopic-assisted resection or open resection for rectal cancer: the Australasian laparoscopic cancer of the rectum randomized clinical trial. Ann Surg. 2019;269:596–602.
20. Schlachta CM, Mamazza J, Seshadri PA, et al. Defining a learning curve for laparoscopic colorectal resections. Dis Colon Rectum. 2001;44(2):217–22.
21. Kang JC, Jao SW, Chung MH, et al. The learning curve for hand-assisted laparoscopic colectomy: a single center surgeon's experience. Surg Endosc. 2007;21(2):234–7.
22. Avital S, Hermon H, Greenberg R, et al. Learning curve in laparoscopic colorectal surgery: our first 100 patients. Isr Med Assoc J. 2006;8(10):683–6.
23. Li JC, Hon SS, Ng SS, et al. The learning curve for laparoscopic colectomy: experience of a surgical fellow in an university colorectal unit. Surg Endoscopy. 2009;23(7):1603–8.
24. Park IJ, Choi GS, Lim KH, et al. Muldimensional analysis of the learning curve for laparoscopic colorectal surgery: lessons from 1000 cases of laparoscopic colorectal surgery. Surg Endosc. 2009;23(4):839–46.

25. Son GM, Kim JG, Lee JC, et al. Multidimensional analysis of the learning curve for laparoscopic rectal cancer surgery. J Laparoendosc Adv Surg Tech A. 2010;20(7):609–17.
26. Li JC, Lo AW, Hon SS, et al. Institution learning curve of laparoscopic colectomy – a multidimensional analysis. Int J Color Dis. 2012;27(4):527–33.
27. Miskovic D, Ni M, Wyles SM, et al. Learning curve and case selection in laparoscopic colorectal surgery: systematic review and international multicenter analysis of 4852 cases. Dis Colon Rectum. 2012;55(12):1300–10.
28. Senagore AJ, Delaney CP, Brady KM, et al. Standardized approach to laparoscopic right colectomy: outcomes in 70 consecutive cases. J Am Coll Surg. 2004;199(5):675–9.
29. Senagore AJ, Duepree HJ, Delaney CP, et al. Results of standardized technique and postoperative care plan for laparoscopic sigmoid colectomy: a 30-month experience. Dis Colon Rectum. 2003;46(4):503–9.
30. Yan J, Trencheva K, Lee SW, et al. Treatment for right colon polyps not removable using standard colonoscopy: combined laparoscopic-colonoscopic approach. Dis Colon Rectum. 2011;54(6):753–8.
31. Bergamaschi R, Schochet E, Haughn C, et al. Standardized laparoscopic intracorporeal right colectomy for cancer: short term outcome in 111 unselected patients. Dis Colon Rectum. 2008;51(9):1350–5.
32. Litwin DE, Darzi A, Jakimowicz J, et al. Hand-assisted laparoscopic surgery (HALS) with the HandPort system: initial experience with 68 patients. Ann Surg. 2000;231(5):715–23.
33. Sylla P, Rattner DW, Delgado S, et al. NOTES transanal rectal cancer resection using transanal endoscopic microsurgery and laparoscopic assistance. Surg Endosc. 2010;24(5):1205–10.
34. Buess G, Kipfmüller K, Ibald R, et al. Clinical results of transanal endoscopic microsurgery. Surg Endosc. 1988;2(4):245–50.
35. Marks G, Bannon J, Marks J. Transanal-abdominal Transanal radical proctosigmoidectomy with coloanal anastomosis for distal rectal cancer. In: Baker R, Fisher J, Nyhus L, editors. Mastery of surgery. 3rd ed. Boston: Little Brown and Comnpany Inc; 1996. p. 1524–34.
36. Albert MR, Atallah SB, deBeche-Adams TC, et al. Transanal minimally invasive surgery (TAMIS) for local excision of benign neoplasms and early-stage rectal cancer: efficacy and outcomes in first 50 patients. Dis Colon Rectum. 2013;56:301–7.
37. Palanivelu C, Rangarajan M, Jategaonkar PA, et al. An innovative technique for colorectal specimen retrieval: a new era of "natural orifice specimen extraction" (N.O.S.E.). Dis Colon Rectum. 2008;51(7):1120–4.
38. Whiteford MH, Denk PM, Swanström LL. Feasibility of radical sigmoid colectomy performed as natural orifice transluminal endoscopic surgery (NOTES) using transanal endoscopic microsurgery. Surg Endosc. 2007;21:1870–4.
39. Delaney CP, Lynch AC, Senagore AJ, Fazio VW. Comparison of robotically performed and traditional laparoscopic colorectal surgery. Dis Colon Rectum. 2003;46(12):1633–9. https://doi.org/10.1007/bf02660768.
40. Marcello PW, Fleshman JW, Milsom JW, et al. Hand-assisted laparoscopic vs. laparoscopic colorectal surgery: a multicenter, prospective, randomized trial. Dis Colon Rectum. 2008;51(6):818–26; discussion 826–8. https://doi.org/10.1007/s10350-008-9269-5.
41. Kolarsick PA, Sacchi M, Spinelli A, et al. Minimizing the impact of colorectal surgery in the older patients: the role of minimally invasive surgery in the geriatric population. Eur J Surg Oncol. 2020;46(3):333–7.
42. Guillou PJ, Quirke P, Thorpe H, et al. MRC CLASICC trial group. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomized controlled trial. Lancet. 2005;365(9472):1718–26.
43. Kang SB, Park JW, Jeong SY, et al. Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): short-term outcomes of an open-label randomized controlled trial. Lancet Oncol. 2010;11(7):637–45.
44. Jeong SY, Park JW, Nam BH, et al. Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomized controlled trial. Lancet Oncol. 2014;15(7):767–74.
45. Saito N, Ito M, Kobayashi A, et al. Long-term outcomes after intersphincteric resection for low-lying rectal cancer. Ann Surg Oncol. 2014;21(11):3608–15. https://doi.org/10.1245/s10434-014-3762-y.
46. Akiyoshi T, Kuroyanagi H, Oya M, et al. Factors affecting the difficulty of laparoscopic total mesorectal excision with double-stapling technique anastomosis for low rectal cancer. Surgery. 2009;146(3):483–9.
47. Branningan AE, De Buck S, Suetens P, et al. Intracorporeal rectal stapling following laparoscopic total mesorectal excision: overcoming a challenge. Surg Endosc. 2006;20(6):952–5.
48. Braunschmid T, Hartig N, Baumann L, et al. Influence of multiple stapler firings used for rectal division on colorectal anastomotic leak rate. Surg Endosc. 2007;31(12):5318–26.
49. Roumen RM, Rahusen FT, Wijnen MH, et al. "Dog-ear" formation after double-stapled low anterior resection as a risk factor for anastomotic disruption. Dis Colon Rectum. 2000;43(4):522–5.
50. Kuroyanagi H, Oya M, Ueno M, et al. Standardized technique of laparoscopic intracorporeal rectal transection and anastomosis for low anterior resection. Surg Endosc. 2008;22(2):557–61.
51. Jafari MD, Wexner SD, Martz JE, et al. Perfusion assessment in laparoscopic left-sided/anterior resection (PILLAR II): a multi-institutional study. J Am Coll Surg. 2015;220(1):82–92.
52. Hasegawa H, Tsukada Y, Wakabayashi M, et al. Impact of intraoperative indocyanine green fluorescence angiography on anastomotic leakage after laparoscopic sphincter-sparing surgery for malignant rectal tumors. Int J Color Dis. 2020;35(3):471–80.
53. Otero-Pineiro AM, de Lacy FB, Van Laarhoven JJ, et al. The impact of fluorescence angiography on anastomotic leak rate following transanal total mesorectal excision for rectal cancer: a comparative study. Surg Endosc. 2020; https://doi.org/10.1007/s00464-020-07442-6.
54. Armstrong G, Croft J, Corrigan N, et al. IntAct: intra-operative fluorescence angiography to prevent anastomotic leak in rectal cancer surgery: a randomized controlled trial. Color Dis. 2018;20(8):O226–34.
55. Foppa C, Sacchi M, Spinelli A. The reverse smile trick: how to transform a double-stapled anastomosis into a single-stapled anastomosis – a video vignette. Color Dis. 2018;20(11):1054–5.
56. Crafa F, Smolarek S, Missori G, et al. Transanal inspection and management of low colorectal anastomosis performed with a new technique: the TICRANT study. Surg Innov. 2017;24(5):483–91.
57. Spinelli A, Carvello M, D'Hoore A, et al. Integration of transanal techniques for precise rectal transection and single-stapled anastomosis: a proof of concept study. Color Dis. 2019;21(7):841–6.
58. Yassin NA, Foppa C, Taliente F, et al. Transanal anastomotic techniques for rectal cancer: the reverse air leak test – a video vignette. Color Dis. 2018;20(11):1051.
59. Nissan A, Guilleim JG, Paty PB, et al. Abdominoperineal resection for rectal cancer at a speciality center. Dis Colon Rectum. 2001;44(1):27–35.
60. Ng SS, Leung KL, Lee JF, et al. Laparoscopic assisted versus open abdominoperineal resection for low rectal cancer: a prospective randomized trial. Ann Surg Oncol. 2008;15(9):2418–25.

61. Fleshman JW, Wexner SD, Anvari M, et al. Laparoscopic vs open abdominoperineal resection for cancer. Dis Colon Rectum. 1999;42(7):930–9.
62. Shukla PJ, Barreto SG, Hawaldar R, et al. Feasibility of laparoscopic abdominoperineal resection for large-sized anorectal cancers: a single institution experience of 59 cases. Indian J Med Sci. 2009;63(3):109–14.
63. Raftopoulos I, Reed JF III, Bergamaschi R. Circumferential resection margin involvement after laparoscopic abdominoperineal excision for rectal cancer. Color Dis. 2012;14(4):431–7.
64. Den Dulk M, Marijnen CA, Putter H, et al. Risk factors for adverse outcome in patients with rectal cancer treated with an abdominoperineal resection in the total mesorectal excision trial. Ann Surg. 2007;246(1):83–90.
65. Kipling SL, Young K, Foster JD, et al. Laparoscopic extralevator abdominoperineal excision of the rectum: short-term outcomes of a prospective case series. Tech Coloproctol. 2014;18(5):445–51.
66. Wang Z, Zhang XM, Liang JW, et al. Evaluation of short-term outcomes after laparoscopically assisted abdominoperineal resection for low rectal cancer. ANZ J Surg. 2014;84(11):842–6.
67. Odermatt M, Flashman K, Khan J, et al. Laparoscopic-assisted abdominoperineal resection for low rectal cancer provides a shorter length of hospital stay while not affecting the recurrence on survival: a propensity score-matched analysis. Surg Today. 2016;46(7):798–806.
68. Pigazzi A, Ellenhorn JD, Ballantyne GH, et al. Robotic-assisted laparoscopic low anterior resection with total mesorectal excision for rectal cancer. Surg Endosc. 2006;20(10):1521–5.
69. Kenngott HG, Fischer L, Nickel F, et al. Status of robotic assistance - a less traumatic and more accurate minimally invasive surgery? Langenbeck's Arch Surg. 2012;397(3):333–41.
70. Ng KH, Ng DC, Cheung HY, et al. Laparoscopic resection for rectal cancer: a lesson learned from 579 cases. Ann Surg. 2009;249(1):82–6.
71. Trastulli S, Farinella E, Cirocchi R, et al. Robotic resection compared with laparoscopic rectal resection for cancer: systematic review and meta-analysis of short-term outcome. Color Dis. 2012;14(4):e134–56.
72. Halabi WJ, Kang CY, Jafari MD, et al. Robotic-assisted colorectal surgery in the United States: a nationwide analysis of trends and outcomes. World J Surg. 2013;37(12):2782–90.
73. Jayne D, Pigazzi A, Marshall H, et al. Effect of robotic-assisted vs conventional laparoscopic surgery on risk of conversion to open laparotomy among patients undergoing resection for rectal cancer: the ROLARR randomized clinical trial. JAMA. 2017;318(16):1569–80.
74. Baik SH, Ko YT, Kang CM, et al. Robotic tumor-specific mesorectal excision of rectal cancer: short-term outcome of a pilot randomized trial. Surg Endosc. 2008;22(7):1601–8.
75. Kim MJ, Park SC, Park JW, et al. Robot-assisted versus laparoscopic surgery for rectal cancer: a phase II open label prospective randomized controlled trial. Ann Surg. 2018;267(2):243–51.
76. Debakey Y, Zaghloul A, Farag A, et al. Robotic-assisted versus conventional laparoscopic approach for rectal cancer surgery, first Egyptian academic center experience, RCT. Minim Invasive Surg. 2018;2018:5836562. https://doi.org/10.1155/2018/5836562.
77. Yang Y, Wang F, Zhang P, et al. Robotic-assisted versus conventional laparoscopic surgery for colorectal disease, focusing on rectal cancer: a meta-analysis. Surg Oncol. 2012;19(12):3727–36.
78. Hellan M, Stein H, Pigazzi A. Totally robotic low anterior resection with total mesorectal excision and splenic flexure mobilization. Surg Endosc. 2009;23(2):447–51.
79. Toh JWT, Zakaria A, Yang I, et al. Totally robotic single docking low anterior resection for rectal cancer: pearls and pitfalls. Tech Coloproctol. 2017;21:893–5.
80. Hill A, McCormic J. In experienced hands, does the robotic platform impact operative efficiency? Comparison of the Da Vinci Si versus Xi robot in colorectal surgery. J Robot Surg. 2020; https://doi.org/10.1007/s11701-020-01055-w.
81. Bae SU, Jeong WK, Bae OS, et al. Reduced-port robotic anterior resection for left-sided colon cancer using the Da Vinci single site (®) platform. Int J Med Robot. 2016;12(3):517–23.
82. Douissard J, Obias V, Johnson CS, et al. Totally robotic vs hybrid abdominoperineal resection: a prospective multicenter analysis. Int J Med Robot. 2019;16(2):e2073. https://doi.org/10.1002/rcs.2073.
83. Kim JC, Lee JL, Kim CW. Comparative analysis of robot-assisted vs open abdominoperineal resection in terms of operative and initial oncological outcomes. Ann Surg Treat Res. 2018;95(1):37–44.
84. Kamali D, Reddy A, Imam S, et al. Short-term surgical outcomes and patient quality of life between robotic and laparoscopic extralevator abdominoperineal excision for adenocarcinoma of the rectum. Ann R Coll Surg Engl. 2017;99(8):607–13.
85. Eftaiha SM, Pai A, Sulo S, et al. Robot-assisted abdominoperineal resection: clinical, pathologic and oncologic outcomes. Dis Colon Rectum. 2016;59(7):607–14.
86. Park EJ, Baik SH, Kang J, et al. Short-term outcomes of the modifies extralevator abdominoperineal resection for low rectal cancer. Surg Endosc. 2016;30(4):1672–82.
87. Kim JC, Kwak JY, Yoon YS, et al. A comparison of the technical and oncologic validity between robot-assisted and conventional open abdominoperineal resection. Int J Color Dis. 2014;29(8):961–9.
88. Alimoglu O, Atak I, Kilic A, et al. Robot-assisted laparoscopic abdominoperineal resection for low rectal cancer. Int J Med Robot. 2012;8(3):371–4.
89. Moghadamyeghaneh Z, Phelan M, Smith BR, et al. Outcomes of open, laparoscopic, and robotic abdominoperineal resections in patients with rectal cancer. Dis Colon Rectum. 2015;58(12):1123–9.
90. Lacy AM, Tasende M, Delgado S, et al. Transanal total mesorectal excision for rectal cancer: outcomes after 140 patients. J Am Coll Surg. 2015;221(2):415–23.
91. Penna M, Hompes R, Arnold S, et al. Incidence and risk factors for anastomotic failure in 1594 patients treated by transanal total mesorectal excision. Results from the international TaTME registry. Ann Surg. 2019;269(4):700–11.
92. Penna M, Hompes R, Arnold S, et al. Transanal total mesorectal excision. International registry results of the first 720 cases. Ann Surg. 2017;266(1):111–7.
93. Detering R, Roodbeen S, van Oostendrop SE, et al. Three year nationwide experience with transanal total mesorectal excision for rectal cancer in the Netherlands: a propensity score-matched comparison with conventional laparoscopic total mesorectal excision. J Am Coll Surg. 2019;228:235–44.
94. Denost Q, Adam JP, Rullier A, et al. Perineal transanal approach. A new standard for laparoscopic sphincter-saving resection in low rectal cancer, a randomized trial. Ann Surg. 2014;260:993–9.
95. de Lacy FB, van Laarhoven JJEM, Pena R, et al. Transanal total mesorectal excision: pathological results of 186 patients with mid and low rectal cancer. Surg Endosc. 2018;32:2442–7.
96. Fernandez-Hevia M, Delgado S, Castells A, et al. Transanal total mesorectal excision in rectal cancer. Short-term outcomes in comparison with laparoscopic surgery. Ann Surg. 2015;261:221–7.
97. Perdawood SK, Thinggaard BS, Bjoern MX. Effect of transanal total mesorectal excision for rectal cancer: comparison of short-term outcomes with laparoscopic and open surgeries. Surg Endosc. 2018;32:2312–21.
98. Roodbeen S, Penna M, Mackenzie H, et al. Transanal total mesorectal excision (TaTME) versus laparoscopic TME for MRI-

defined low rectal cancer: a propensity score-matched analysis of oncologic outcomes. Surg Endosc. 2019;33:2459–67.
99. Dickson EA, Penna M, Cunningham C, et al. Carbon dioxide embolism associated with transanal total mesorectal excision surgery: a report from the international registries. Dis Colon Rectum. 2019;62(7):794–801.
100. Atallah SB, DuBose AC, Burke JP, et al. Uptake of transanal total mesorectal excision in North America: initial assessment of a structured training program and the experience of delegate surgeons. Dis Colon Rectum. 2017;60:1023–31.
101. Mege D, Hain E, Lakkis Z, et al. Is trans-anal total mesorectal excision really safe and better than laparoscopic total mesorectal excision with a perineal approach first in patients with low rectal cancer? A learning curve with case-matched study in 68 patients. Color Dis. 2018;20:O143–51.
102. Wasmuth HH, Faerden AE, Myklebust TA, et al. Transanal total mesorectal excision for rectal cancer has been suspended in Norway. Br J Surg. 2020;107(1):121–30.
103. Roodbeen SX, Spinelli A, Bemelman WA, et al. Local recurrence after transanal total mesorectal excision for rectal cancer: a multicenter cohort study. Ann Surg. 2020; https://doi.org/10.1097/SLA.0000000000003757.
104. Deijen C, Velthuis S, Tsai A, et al. COLOR III: a multicentre randomized clinical trial comparing transanal TME versus laparoscopic TME for mid and low rectal cancer. Surg Endosc. 2016;30:3210–5.
105. Tjandra JJ, Chan MK, Yeh CH. Laparoscopic- vs hand-assisted ultralow anterior resection: a prospective study. Dis Colon Rectum. 2008;51(1):26–31.
106. Pietrabissa A, Moretto C, Carobbi A, et al. Hand-assisted laparoscopic low anterior resection: initial experience with a new procedure. Surg Endosc. 2002;16(3):431–5.
107. Yano H, Ohnishi T, Kanoh T, et al. Hand-assisted laparoscopic low anterior resection for rectal carcinoma. J Laparoendosc Adv Surg Tech A. 2005;15(6):611–4.
108. Liu FL, Lin JJ, Ye F, et al. Hand-assisted laparoscopic surgery versus the open approach in curative resection for rectal cancer. J Int Med Res. 2010;38(3):916–22.
109. Pendlimari R, Holubar SD, Pattan-Arun J, et al. Hand-assisted laparoscopic colon and rectal cancer surgery: feasibility, short term, and oncological outcomes. Surgery. 2010;148(2):378–85.
110. Gezen FC, Aytac E, Costedio MM, et al. Hand-assisted versus straight-laparoscopic versus open proctosigmoidectomy for treatment of sigmoid or rectal cancer: a case-matched study of 100 patients. Perm J. 2015;19(2):10–4.
111. Koh FH, Tan KK, Lieske B, et al. Endowrist versus wrist: a case-controlled study comparing robotic versus hand-assisted laparoscopic surgery for rectal cancer. Surg Laparosc Endosc Percutan Tech. 2014;24(5):452–6.
112. Sanamalavicius NE, Gupta RK, Dulskas A, et al. Clinical outcomes of 103 hand-assisted laparoscopic surgeries for left-sided colon and rectal cancer: single institutional review. Ann Coloproctol. 2013;29(6):225–30.
113. Pyo DH, Huh JW, Park YA, et al. A comparison of hand-assisted laparoscopic surgery and conventional laparoscopic surgery in rectal cancer: a propensity score analysis. Surg Endosc. 2016;30(6):2449–56.
114. Zhou X, Liu F, Lin C, et al. Hand-assisted laparoscopic surgery compared with open resection for mid and low rectal cancer: a case-matched study with long-term follow-up. World J Surg Oncol. 2015;13:199.
115. Tajma T, Mukai M, Noguchi W, et al. Comparison of hand assisted laparoscopic surgery and conventional laparotomy for rectal cancer: interim results from a single center. Mol Clin Oncol. 2015;3(3):533–8.
116. Jacobs C, Read TE. "Peek port": avoiding conversion during laparoscopic colectomy—An Update. Surg Endoscopy. 2019; https://doi.org/10.1007/s00464-019-07165-3.

Minimally Invasive Complete Mesocolic Excision with Extended Lymphadenectomy for Colon Cancer

37

Patricia Sylla

Key Concepts

- Complete mesocolic excision and central vascular ligation (CME + CVL) refers to en bloc dissection of the colon and mesocolon along the embryologic planes with preservation of the mesocolic envelope, central ligation of the feeding vessels, extended lymphadenectomy, and adequate bowel resection.
- CME + CVL most closely matches Japanese D3 lymphadenectomy which requires en bloc resection of paracolic (D1), intermediate (D2), and central (D3) nodal stations along the feeding vessels.
- CME + CVL/D3 dissection increases the risk of potential organ injury, particularly during right colectomy where nodal tissue is dissected off the anterior surface of the superior mesenteric vein and its tributaries. Thorough knowledge of variations in vascular anatomy at the root of the mesentery is needed.
- In experienced hands, the minimally invasive surgical (MIS) approach to CME + CVL/D3 dissection results in acceptable conversion rates and perioperative and oncologic outcomes equivalent to that of open CME.
- The lack of standardized operative assessment for CME + D2 vs D3 dissection, and limited adoption of quality indicators to assess CME specimens, has made direct comparison of long-term oncologic outcomes between the groups challenging.
- There is no conclusive evidence to support routine use of CME + CVL/D3 versus CME + D2 dissection for colon cancer. It should be considered in cases were nodal metastasis is suspected based on preoperative staging and/or intraoperative assessment.
- Several ongoing randomized controlled trials comparing outcomes between CME + D2 and CME + D3 dissection for colon cancer incorporate video-based assessment of CME techniques and morphometric assessment of CME specimens.
- There is increasing enthusiasm for MIS CME in Europe and in the USA. Standardization of performance assessment and adoption of CME quality indicators will be needed in order to assess the impact of CME + CVL on long-term oncologic outcomes of right and left colon cancer resections.

Introduction

The concept of dissection in the avascular plane surrounding the mesorectum and removal of the mesorectum at risk for nodal metastases was given a moniker ("total mesorectal excision (TME)" and popularized by Bill Heald. Dissection along the embryologic planes also increases the chances of R0 resection for tumors which has not broached the mesorectal fascia. These techniques have universally been adopted as standard of care for the curative resection of rectal cancer. Implementation of TME techniques, combined with improvements in staging modalities and neoadjuvant/adjuvant treatment regimens, have led to substantial reduction in local recurrence rates [1–3]. Over the last two decades, these principles have been adapted to minimally invasive approaches, including laparoscopic and robotic-assisted techniques and, most recently, transanal endoscopic TME (taTME).

The same surgical principles have been increasingly applied to curative resection of colon cancer, with growing interest in the extent of nodal harvest and anatomic details of excision of the mesentery. It has long been known that the number of lymph nodes removed in colorectal cancer speci-

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mens directly correlates with improved staging and prognosis, and there is ample evidence that extended nodal dissection improves survival for stage I–III colon cancer [4–7]. In their seminal publication in 2009, Hohenberger et al. promoted the concept of extended lymphovascular clearance described by Jamieson in 1909, advocated by Enker in 1979, and already in routine practice in Japan since the late 1990s [4, 8–10]. Hohenberger et al. termed this technique "complete mesocolic excision" (CME) which included (1) sharp en bloc dissection of the colon and mesocolon with complete removal of the mesenteric envelope along the embryologic plane between the mesocolic and parietal fascia; (2) extirpation of all lymphovascular tissue extending from the pericolic area to the lymph nodes at the base of the feeding arteries; (3) central vascular ligation (CVL) or high vascular tie at the most proximal extent of the feeding arteries and veins; and (4) adequate length of bowel resection in order to ensure adequate lymph node dissection [9]. Although the original description of CME with CVL for right colon cancer inferred that a Kocher maneuver be performed in order to expose the base of the mesenteric vessels, modern CME practice has evolved toward a modified approach that closely matches the Japanese Society for Cancer of the Colon and Rectum (JSCCR) definition of D3 lymphadenectomy, whereby only anterior dissection of the superior mesenteric vein (SMV) is required [11–13].

As opposed to the Japanese definition of D2 and D3 dissection which implies complete mesocolic dissection en bloc with the anatomically defined lymph node station(s), the term CME + CVL is a misnomer in the literature, where the extent of lymphadenectomy completed is variable and subject to interpretation. This has led to lack of consistency with regard to surgical techniques and assessment of CME specimen quality and challenges interpretation of oncologic outcomes across studies [14]. In order to align CME terminology throughout this chapter, the term "CME + CVL" refers to CME performed with radical lymphadenectomy which corresponds to the JSCCR definition of D3 lymph node dissection (CME + D3).

The difference between "conventional" and CME + CVL dissections is not analogous when considering left versus right colectomy. Many surgeons routinely ligate the inferior mesenteric artery (IMA) at the aorta during proctectomy for rectal cancer (CME + D2 dissection); thus the concept of CME + D3 for left-sided colon tumors, which requires exposure of the aortic wall in order to remove additional nodal tissue at the base of the IMA, has not been a dramatic step up in complexity. However, the same cannot be said for CME + D3 for right-sided tumors. The anatomical challenge posed by safe exposure and dissection of SMV tributaries and trunk of Henle and added risk of injury and long learning curve has added to surgeons' reluctance to adopt this approach for right and transverse colectomy, especially in the absence of high-level evidence demonstrating long-term oncologic benefits relative to standard CME + D2 resections. This chapter will review the rationale for CME + D2 or D3 dissection, highlight relevant anatomical landmarks, and describe surgical techniques for right- and left-sided resections, with a focus on minimally invasive approaches. Short- and long-term outcomes will also be critically assessed with emphasis on current gaps in knowledge.

CME and Extended Lymphadenectomy: Definitions

Lymph Node Classification

The level of nodal dissection is best described using the Japanese classification of colonic regional lymph nodes, which describes three levels. Lymph nodes are classified as epicolic or paracolic (D1) located along the marginal artery, intermediate (D2) along major arterial branches, and main/central (D3) at the origin of the superior mesenteric artery (SMA) or IMA. The scope of lymph node dissection is also based on lymph node classification and graded as D1, D2, and D3 dissection (Fig. 37.1 and Table 37.1) [12, 13].

D1, D2, and D3 Lymphadenectomy

The 2005 JSCCR guidelines and subsequent 2010 and 2019 updates are based on the latest results from the JSCCR colorectal registry. Levels of dissection are defined as follows:

D1 dissection refers to complete dissection of epiploic lymph nodes attached to the colon and paracolic lymph nodes along the marginal artery in the relevant colon segments and no or incomplete dissection along the tumor-supplying arteries (Fig. 37.1).

D2 dissection is defined as complete removal of epicolic, paracolic (D1 nodes), and intermediate (D2) lymph nodes along the tumor-supplying arteries (ileocolic, right colic, middle colic, left colic, sigmoid, and IMA from the origin of the last sigmoid artery to the origin of the left colic artery). For right-sided colonic tumors, D2 dissection includes ligation of the ileocolic artery (ICA) at its root, at the level of the lower border of the duodenum. If the right branch of the middle colic or main middle colic artery is to be ligated as part of extended right colectomy (for ascending colon/hepatic flexure tumors), high ligation could be performed without exposing the SMV. For left-sided tumors, D2 dissection includes ligation of the IMA just proximal to the left colic artery origin (Fig. 37.1).

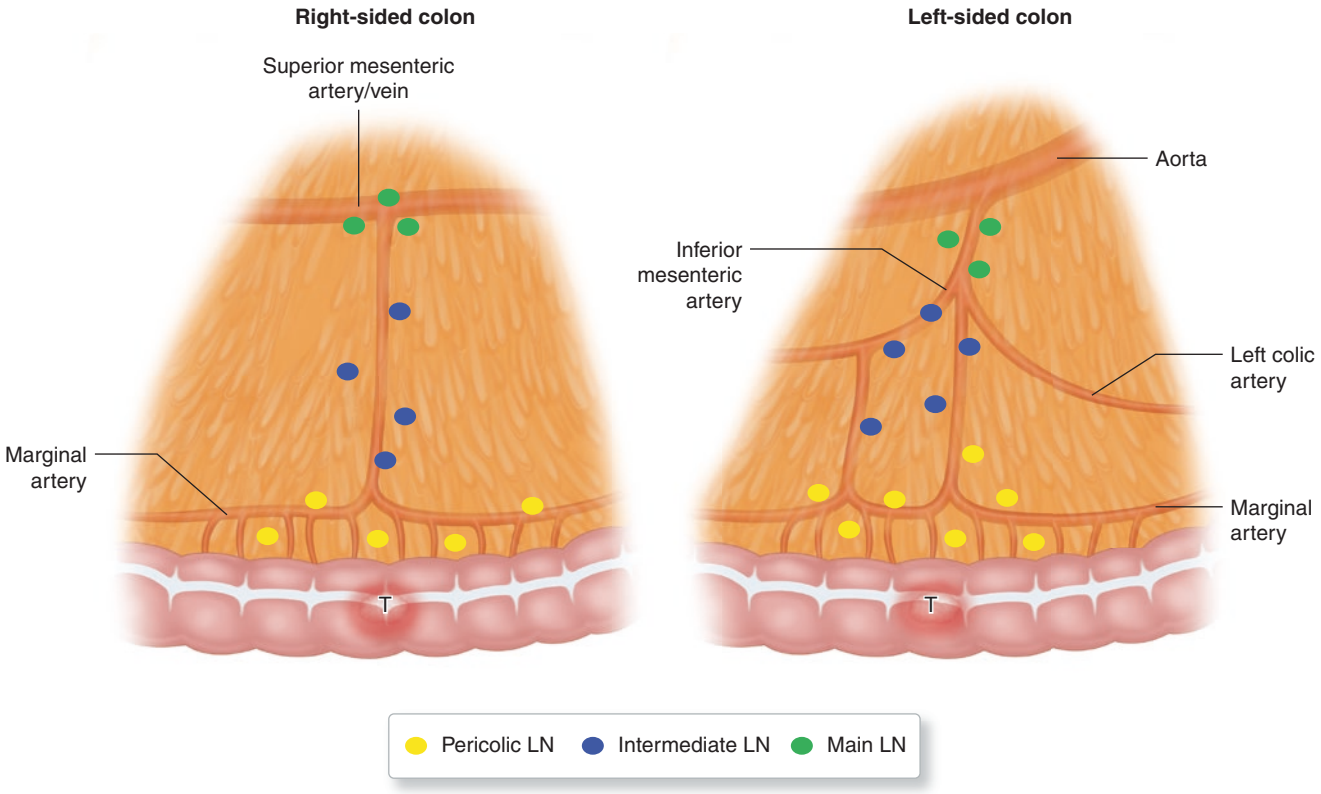

Fig. 37.1 Classification of regional lymph nodes of colon cancer [13]

Table 37.1 Definitions of location and dissection of mesocolic lymph nodes

D1	Complete dissection of epicolic lymph nodes attached to the colon and paracolic lymph nodes along the marginal artery in the relevant colon segments and no or incomplete dissection along the tumor-supplying arteries
D2	Complete dissection of D1 and intermediate lymph nodes along the tumor-supplying arteries (ileocolic, right colic, middle colic, left colic, sigmoid, or inferior mesenteric arteries from the origin of the last sigmoid artery to the origin of the left colic artery)
D3	Complete dissection of D1 to D2 and central lymph nodes, for left-sided tumors along the inferior mesenteric artery between the aorta and the left colic artery and for right-sided including mid-transverse tumors, lymph nodes along the superior mesenteric vein and lateral to the superior mesenteric artery
D4	Complete D1 to D3 and along aorta and inferior vena cava or superior mesenteric artery/superior mesenteric vein central to the origin of the middle colic artery
Alternative definition of location of lymph node metastases (JSCCR)	
n(1)(+)	Lymph node metastasis in D1 area, but within 5 cm proximal or distal from the tumor edges
n(2)(+)	Lymph node metastasis in D1 area >5 cm proximal or distal from the tumor edges or in D2 area
n(3)(+)	Lymph node metastasis in D3 area
n(4)(+)	Lymph node metastasis in D4 area (considered distant metastases)

Suffixes + and – added to the D-area designation refer to the status of the lymph node metastases reported by the pathologist. Suffixes (p) and (c) added to D2 to refer to peripheral and central part of D2, where D2p in some studies is included in the specimen in conventional resections
JSCCR Japanese Society for Cancer of the Colon and Rectum

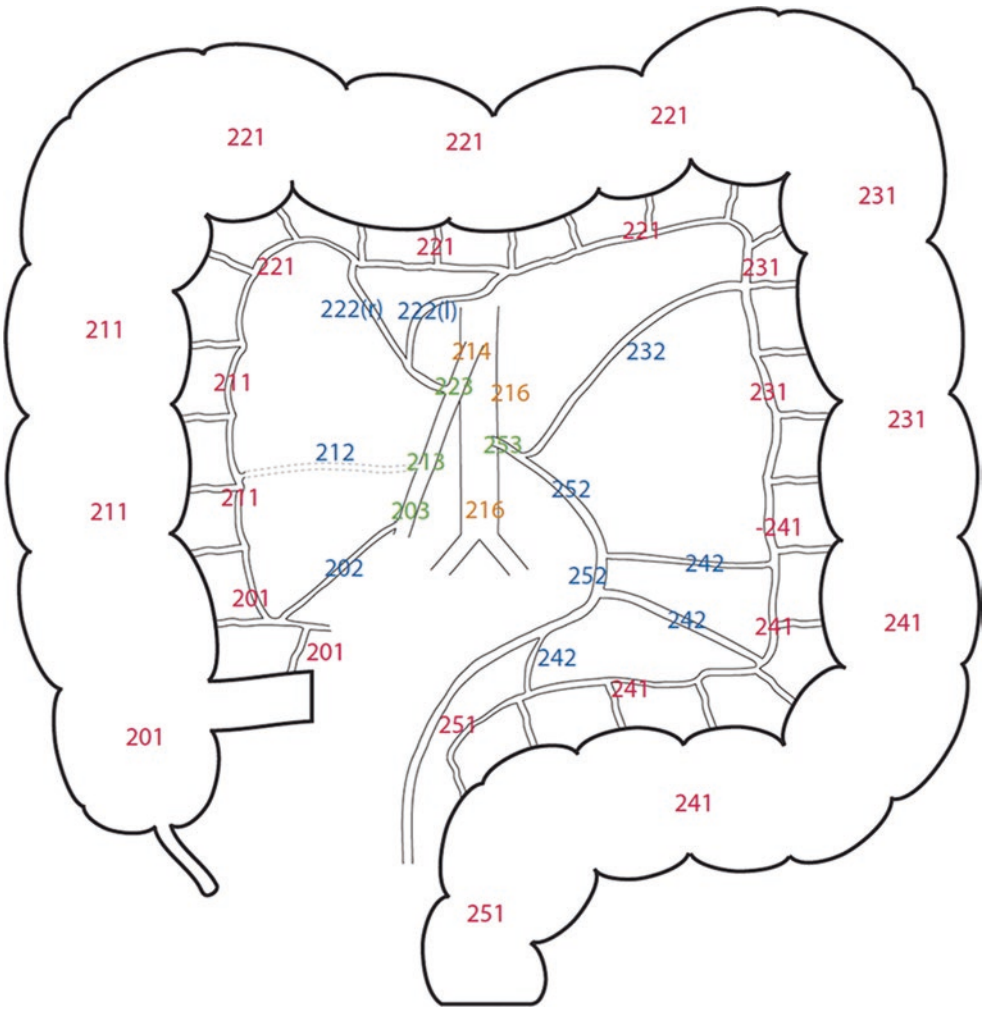

Fig. 37.2 Mesocolic lymph node stations according to the Japanese Society for Cancer of the Colon and Rectum. D1-D4 defined by colors: D1 red, D2 blue, D3 green, and D4 yellow. Right colic artery (dotted). (Reused with permission [27]. Copyright © Wolters Kluwer)

D3 dissection is defined as complete removal of D1, D2, and central (D3) lymph nodes. For right-sided tumors, the anterior surface of the SMV is exposed (dissection of the SMA is not required), and vessels are transected at their origin with removal of all nodal tissue along the SMV and lateral to the SMA including nodal groups 203 and 213 (Figs. 37.1 and 37.2). En bloc resection of nodal group 223 is also removed for extended right colectomy. For left-sided tumors, the IMA is divided at its base from the aorta, and the aortic wall is exposed (dissection deeper than the embryonic layer), with removal of all nodal tissue between the aorta and the left colic artery including nodal group 253 (Fig. 37.2). With extended left colectomy, removal of nodal group 223 is also required, with exposure of the SMV.

The scope of lymph node dissection with CME is based on preoperative clinical staging and/or intraoperative assessment of visible/suspected lymph node metastasis (Table 37.1). In Japan, in addition to standard radiologic staging by either computed tomography (CT) scan or magnetic resonance imaging (MRI), endoscopic assessment of the depth of tumor invasion plays an important role in clinical T staging (cT). Advanced endoscopic techniques including chromoendoscopy and narrow-band imaging (NBI) are routinely used to predict depth of invasion, with occasional use of endoscopic ultrasound [11, 15–17]. For pTis tumors completely removed endoscopically, lymph node dissection is not typically required, but if bowel resection is elected, D1 dissection can be performed. For pT1 tumors removed endoscopically, D2 dissection is recommended due to an approximately 10% risk of D1/D2 lymph node (LN) metastasis and 1.9% risk of D2 node metastasis based on JSCCR registry data [11]. For cT2 cancer, at least D2 dissection is recommended, although D3 dissection can be considered given the 0.7–1% risk of central/main node metastases and lack of accuracy of imaging-based preoperative cT staging. For cT3/T4 tumors, D3 dissection is the standard of care. In the 2000–2004 JSCCR registry that reviewed 25,617 patients treated for colorectal cancer, lymph node metastasis around the origin of the feeding vessel (main/central/D3 node) was found in 0.9%, 2.3% and 5.7% and 6.7% for pT2, pT3, and pT4a and pT4b tumors, respectively [11, 12].

It should be noted that outside of centers with expertise in endoscopic assessment of depth of tumor invasion, recom-

mendations for level of nodal dissection based on standard preoperative radiology-based tumor staging are difficult to utilize clinically, as this assessment can only be determined with certainty postoperatively, after histologic evaluation of the resected colectomy specimen. The only exception would be patients with superficial tumors undergoing complete endoscopic removal prior to colectomy.

Quality Indicators of CME Resections

Analogous to proctectomy specimen grading with photodocumentation of the anterior, lateral, and posterior surface, quality indicators in CME resection include (1) documentation of mesocolic plane dissection; (2) number of lymph nodes harvested (which may include classification of lymph nodes based on the JSCCR classification of lymph node stations); (3) specimen morphometry, which documents the distance from the vascular tie to the tumor, the distance from the vascular tie to the colon, and the area of mesentery resected (in mm^2); and (4) large bowel length/small bowel length [10, 18]. Grading of plane of mesocolic dissection and specimen morphometry can be documented based on high-resolution specimen photographs taken of the front and back of the unfixed unopened specimen, with the mesentery laid out flat without stretching, placed alongside a ruler (Fig. 37.3). In Japanese practice, and especially since publication of the JSCCR guidelines, it is a standard practice for Japanese surgeons to map lymphatic stations directly onto surgical specimens, which not only validates completion of D2 vs D3 lymphadenectomy but permits precise evaluation of the pattern of lymphatic spread in colon cancer and correlation to oncologic outcomes [11, 19]. Since publication of the 2005 JSCCR guidelines recommending D3 dissection for stage II/III colorectal cancer, adoption of D3 dissection among Japanese surgeons has increased 58.4% in 2001 to 75% in 2010 as assessed by photodocumentation of D3 specimens in the JSCCR tumor registry [9].

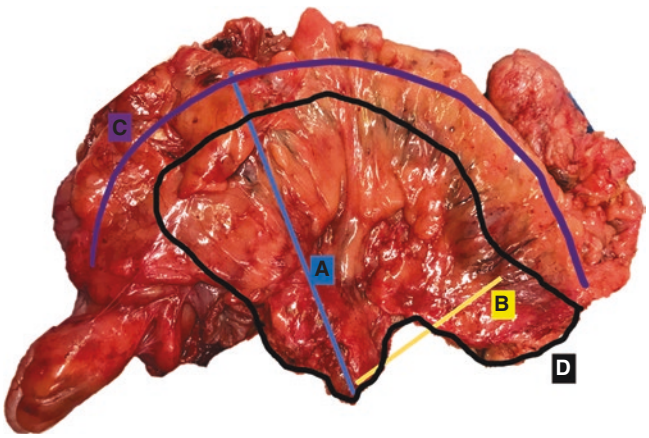

Fig. 37.3 Morphometric assessment of CME + D3 right colectomy specimen. (**A**) Distance from the high vascular tie to the tumor. (**B**) Distance from the high vascular tie to the closest bowel wall, (**C**) length of large bowel, (**D**) surface are of mesentery

Differences between tissue morphometry of colon cancer specimens resected using non-CME (NCME, England), CME with CVL (Germany), and D3 dissection (Japan) were evaluated based on review of specimen photographs. There were no significant differences in tumor location, pT, and pN stage between the groups. The length of resected bowel and area of mesentery were significantly greater in the NCME and CME + CVL specimens. The distance from the vascular tie to the bowel wall was similar between the CME + CVL and D3 specimens; all were longer than in NCME specimens. The rates of mesocolic plane surgery and number of lymph nodes were highest in the CME + CVL group, followed by D3 resection specimens [20]. These differences reflect the JSCCR guidelines that promote the concept that when the tumor has an associated distinct main mesenteric vessel, bowel resection should proceed 5 cm beyond a feeding vessel in the direction of the lymph flow and 10 cm away from the tumor in the opposite direction [12]. This is based on Japanese studies that have shown that longitudinal spread >10 cm beyond the tumor occurs rarely (0% for left-sided, 1–4% for right sided tumors); hence bowel resection margins are rarely >10 cm in Japanese D3 specimens [21, 22]. This is in contrast with the principles of CME, which advocates removal of the next feeding vessel beyond the 10 cm bowel margin, to ensure adequate lymphovascular clearance [22]. The differences in absolute length of resected specimens may also reflect differences in body habitus between the populations.

When assessing and comparing studies that evaluate the impact and NCME and CME techniques with CVL/D2/D3 dissection, it is critical to understand which CME quality indicators were used to validate completion of good-quality CME. Currently, there is no consensus on which of the above quality indicators are the most critical when evaluating/comparing the quality of CME resections. While the number of lymph nodes in surgical specimens has been used as a surrogate for quality of surgical resections, that variable must be interpreted with caution, as the number of nodes harvested can be impacted by variability in both patients and pathologic processing techniques and diligence and is thus subject to bias. As described by West and Hohenberger in 2009, documentation of the grading of the plane of surgery (into the muscularis propria plane, intramesocolic plane, or mesocolic plane) and tissue morphometry (area of mesentery removed, distance from the vascular ties to the tumor and to the closest bowel wall, length of large and small bowel) should be included in order to achieve uniformity across studies [18]. Using the above quality indicators, West and Hohenberger were able to demonstrate that CME with cen-

tral ligation removed significantly more tissue than NCME resections, in addition to increasing the number of lymph nodes harvested [18]. Standardized pathologic quality control is critical in the appraisal of the impact of CME techniques on long-term oncologic outcomes. Contemporary trials evaluating outcomes of CME + D2/D3 dissection have incorporated assessment of CME quality indicators in order to validate completion of CME + D3 by participating surgeons [23]. Likewise, in the JCOG 0404 RCT comparing open and laparoscopic D3 dissection for stage III colon cancer, quality control for D3 dissection was ensured by central peer review of photodocumentation of the completed D3 dissection surgical field, and of the surgical specimen, highlighting surgical margins [24].

Rationale for Adoptions of CME for Colon Cancer

As noted above, there is not universal agreement as to what constitutes "CME," "CME + CVL," or "conventional" dissection, which hampers comparisons of outcomes. In addition, it is nearly impossible to perform randomized studies of CME vs conventional colectomy, as surgeons would be unlikely to alter their techniques substantially between patients, with the possible exception of level of nodal harvest at the root of the mesentery. Thus, most published studies of CME versus conventional colectomy utilize historical controls or compare outcomes between hospitals or geographic regions, which introduce the likelihood of hidden cofounders and substantial bias. In addition, some studies retrospectively subgroup patients by stage, which does not have a clinical correlate as it is difficult to reliably differentiate stage III versus stage II disease preoperatively. While removing the colonic mesentery in its fascial envelope and achieving negative circumferential margins of resection for the primary tumor are clearly of benefit to the patient, determining the optimal level of vascular division at the root of the mesentery has been more difficult. Lastly, in an ideal world, patients with true stage I and stage II disease should garner no benefit from lymphadenectomy. Extended lymphadenectomy would thus pose excess risk in these patients and provide no benefit. "Improved" oncologic outcome from extended lymphadenectomy in patients with stage I/II disease would therefore reflect stage migration, or inherent inaccuracies in histologic staging, the magnitude of which may be co-linear with differences in basic surgical techniques, further confounding the analysis.

Impact of CME on Mesocolic Dissection Grade

Regardless of the exact extent of lymphadenectomy performed, CME dissection, which dictates that colon and mesocolon resection proceeds along the embryologic mesocolic plane with preservation of intact fascial layers, has been associated with good outcomes. Similar to Quirke's grading of the quality of TME dissection, dissection of the colonic mesentery can occur along the muscularis propria (poor plane), intramesocolic (intermediate plane), or mesocolic resection plane (good plane). When comparing CME specimens with those from "standard" oncologic resection for colon cancer, West et al. demonstrated significantly greater amount of mesentery and colon length, a higher lymph node yield, and a higher proportion of specimens with mesocolic plane resection among the CME group [18]. Furthermore, based on a review of 399 specimens photographed and graded according to the plane of mesocolic dissection, mesocolic dissection was confirmed in 32% of specimens and was associated with a 27% 5 year survival advantage rate in stage III colon cancer relative to dissection along the muscularis propria plane [25]. Notably, a higher rate of mesocolic resection plane was achieved during left-sided CME than right-sided or transverse CME, which may again be related to the higher complexity of vascular dissections for right-sided and transverse colon lesions. The Danish Colorectal Cancer Group (DCCG) compared outcomes of CME adoption in 2008 at one institution relative to outcomes of NCME performed at three other hospitals. Relative to NCME procedures, CME was an independent predictive factor for higher DFS, especially for stage I/II disease [26]. In an ongoing prospective non-randomized trial comparing CME + D3 with NCME colon resection, where specimen morphometry was assessed based on photodocumentation of surgical specimens, CME was associated with improved 3-year local recurrence-free survival in stage II and III patients [23]. Overall, current evidence supports adoption of tumor-specific mesocolic excision for colon cancer, similar to tumor-specific TME, with complete resection of the mesocolic envelope and lymphadenectomy beyond paracolic nodes (D2 or D3 dissection).

The Impact of CME on Lymph Node Harvest, Central Node, Skip, and Occult Metastases

CME has consistently demonstrated an association with increased lymph node harvest, which improves the accuracy of staging, and can upstage tumors and prompt consideration of adjuvant chemotherapy. A recent systematic review of retrospective studies comparing outcomes between colectomy performed for colon cancer with or without CME demonstrated that in 10 of 12 studies, lymph node harvest was significantly higher in the CME group [14]. In addition to increasing lymph node harvest, CME with D3 dissection may remove clinically suspicious nodes detected intraoperatively, as well as lymph node micrometastases not otherwise detectable pre- or intraoperatively. Likewise, extended

lymphadenectomy would permit removal of skip metastases, i.e., tumor metastases found in central lymph nodes in the absence of pericolic or intermediate lymph node involvement, which is reported in 0–19.8% of stage III colon cancers [27–29].

The pattern of locoregional lymph node metastasis in colon cancer remains poorly understood, with two opposing theories. In the Halsted model, progression of metastasis occurs in a stepwise fashion from the primary tumor to pericolic, intermediate, and central nodes and ultimately to distant organs. In the Fisher model, metastatic progression is non-linear and can bypass proximal nodal basins altogether [30–33]. Pattern of nodal spread has different implications on the theoretical impact of radical D3 lymphadenectomy. In the Fisher model, removal of all lymphatic tissue at all three nodal stages is unlikely to impact oncologic outcomes. However, in the Halsted model, systematic removal of central lymph nodes in stage III disease during D3 dissection, including potential skip metastases, may improve staging and local disease control and impact long-term oncologic outcomes, independently of adjuvant treatment.

While the incidence of pericolic, intermediate, and central lymph node metastases increases with tumor stage, the incidence of occult central node metastasis in clinically staged II colon cancer, traditionally treated with CME + D2, is not considered negligible in the JSCCR guidelines that currently recommend D3 dissection for stage II and III colorectal cancer. The incidence of D3 nodal metastases based on pT stage among 23,579 stage I–III colorectal cancers was 0.9% in pT2 and up to 2.3% in pT3 tumors based on results from the 2000–2004 JSCCR cancer registry [12]. Based on these results, the JSCCR guidelines indicate that D3 rather than D2 dissection can be considered for cT2 tumors because "about 1% of cT2 cancer is accompanied by main lymph node metastasis and preoperative diagnosis of depth of invasion is not very accurate" [11, 12]. Implementation of these guidelines are facilitated by the widespread use of advanced endoscopic techniques in Japan to improve preoperative staging of colorectal lesions, including chromoendoscopy, image-enhanced endoscopy (NBI), and/or endoscopic ultrasound assessment of depth of tumor invasion [15–17].

As would be expected, the incidence of D3+ metastasis increases with tumor stage. In stage III disease, the incidence of apical/central node metastasis has been reported as high as 19.7%, as in a series of 244 stage III right colon cancers treated with CME + D3 (with a rate of skip metastasis of 19.8%) [28]. Among 1355 stage III colon cancers treated with D3 dissection across 71 Japanese centers and with a minimum of 5-year follow-up from the 2000–2002 JSCCR registry, the rate of D3+ nodes was 8.3% [34]. In an ongoing prospective non-randomized trial comparing 220 CME + D3 with 110 non-CME right and left colon cancer resection, with validation of D3 completion based on photodocumentation, the incidence of central node metastases in D3+ specimens was 13.8% in stage III disease, with a rate of skip metastasis of 2.7% [23].

With respect to the oncologic implications of central node metastases, in that same JSCCR registry of 1355 stage III colon cancers, after adjusting for tumor and node classification and other prognostic factors, central node metastasis was independently associated with cancer-specific death (HR 2.29; 95% CI 1.49–3.52) [34]. Similarly, the presence of metastatic central lymph nodes at the origin of the IMA has been shown to correlate with advanced tumor stage and has been associated with worse disease-free survival, despite adjuvant treatment [35–38]. Some authors argue that these findings support high ligation of the IMA at the aorta with CME and D3 dissection in order to reduce the risk of residual unsuspected metastatic IMA lymph nodes, and optimize nodal staging [37]. A recent review of the 1999–2007 JSCCR database of 4034 stage III tumors treated with D3 dissection demonstrated significant differences in the pattern of central node metastasis between right- and left-sided stage III colon cancer and the impact of the rate of D3+ metastasis on survival [19]. Although the number of lymph nodes harvested was equivalent between right and left colon cancer resections (20.3 vs 19.2, respectively), the rate of D3+ nodes (8.5% vs 3.7%) and skipped node metastases (13.7% vs 9%) were significantly higher in right- vs left-sided tumors, respectively. The 5-year disease-free survival (DFS) was similar between right- and left-sided cancer, but the 5-year unadjusted overall survival (OS) was significantly worse in right-sided cancers (77.4% vs 80.9%). By multivariate analysis, although D3+ status was associated with worse OS in left-sided cancer, neither DFS nor OS were affected by the pattern of lymph node metastasis in right-sided cancer. These findings suggested differences in the prognostic significance of D3+ nodes based on tumor location and suggest that D3 dissection may have a greater impact on survival in stage III left-sided colonic cancer [19].

Overall, these results support the recommendation of extended right colectomy with CME + D2 dissection at a minimum, with consideration for CME+ D3 dissection for suspected clinical stage III cancer based on the 3.7–19.7% risk of central node metastasis and potential prognostic significance of this finding in stage III disease. This recommendation takes into account the shortcomings of preoperative staging by CT scan in predicting nodal involvement. It has been argued that CME + D3 dissection may help upstage tumors and improve local control by reducing the risk of residual metastatic or unsuspected micrometastatic lymph nodes and may improve survival relative to D2 dissection alone, particularly in stage III colon cancer. However, there are no definitive data to support that contention. As one might expect, there is a limit to the benefits of lymphadenectomy. At some distance from the tumor, finding involved

lymph nodes is simply a marker for disseminated disease, instead of local disease that can be surgically removed. To date, it has been difficult to quantify the potential benefit versus risk of extending lymphadenectomy beyond the level of the commonly named vessels at the root of the mesentery.

Anatomical Considerations

Surgeons looking into adopting CME+CVL must have thorough knowledge of the common and less common variations in central vascular anatomy, especially as it relates to variations in the arterial and venous anatomy near the SMV and SMA. Several anatomical reports in cadavers and radiologic reviews have mapped out variations in configurations of the gastrocolic trunk of Henle and its tributaries (GCT), the confluence of the right gastroepiploic vein (RGEV), superior (or accessory) right colic vein (SRCV) and anterior superior pancreaticoduodenal vein (ASPDV), tributaries of the SMV, as well as the variable relationships between the ileocolic, middle colic, and superior mesenteric vessels. This knowledge is critical to safely complete D3 dissection during right colectomy, lower the risk of inadvertent ligation of incorrect vessels, and avoid bleeding from direct vascular injury or inadvertent traction injury to venous tributaries.

Several classifications of this anatomy have been described, mostly based on cadaveric dissections but more recently derived from intraoperative review of minimally invasive cases [38, 39]. Most classifications focus on delineating common and less common variations in the presence or absence of a GCT/GPCT and the configurations of its tributaries (confluence of the RGEV, SRCV, and ASPDV); the anatomy of the SMV tributaries (ileocolic, right colic, and middle colic vein); and the anatomy of the SMA branches (ileocolic right colic and middle colic artery) and their crossing relationship with the SMV. This simple classification can help surgeons correctly identify common and less common variations in the vascular anatomy near the SMV and recognize anomalous configurations, but requiring careful reappraisal of surgical anatomy and landmarks.

Variations in Configuration of the GCT/GPCT

The majority of anatomic classifications refer to the GCT as the confluence of the RGEV, ASPDV, and colic veins, although in others, this confluence is referred to as the gastro-pancreatico-colic trunk (GPCT) [38]. When present (37.8–89% of cases), subtypes of the GCT are based on the presence and location of the SRCV [39] or on whether 1, 2, or 3 right colic veins (RCV) merge with the trunk. In the most common configuration, a single colic vein joins the RGEV and ASPDV (55.8% [38], while other configurations include additional colic veins). In 20.7–21.6% of cases, there is no common trunk between the colic and gastroepiploic vein.

Variations in the Anatomy of SMV Tributaries

One, two, and three middle colic veins can be found in 72.1–74.1%, 22.4–26.1%, and 1.8–3.5% of patients, respectively [38, 39]. In cadaveric and clinical studies, the MCV drains directly into the SMV in 86–89%. Although a SRCV can be identified in 28.8–83.6% of cases, a RCV is only identified in 19–24.3% but always drains directly into the SMV. A single ICV is found in 100% of cases, which drains directly into the SMV in 92.8–100% of cases or alternatively into the GCT or the jejunal truck [38, 39]. In few cases, the ICV may not travel with the ICA and may enter the SMV 3 cm cranial to the base of the ICA.

Variations in Arterial Anatomy and Relationship to SMV

A single ileocolic artery originates from the SMA in 100% of cases and crosses the SMV either anteriorly or posteriorly [38, 39]. A right colic artery (RCA) is identified in 10–63% [38]. It originates from the SMA in 33% or alternatively from the ICA or middle colic artery (MCA) and crosses the SMV anteriorly in 87–97%. The SMA typically courses just left and posterior to the SMV. The MCA arises from the SMA in 100% of cases and is a single artery in 88%, double (11.7%) with finding of three MCAs exceedingly rare.

During SMV dissection, variations in anatomy that are critical for surgeons to identify in order to avoid injury include whether the ICA crosses anteriorly or posteriorly to the SMV and where the ICV drains into the SMV, which could be a few centimeters cranial to base of the ICA. The surgeon should also; and identify the ASPDV, SRCV, and RCV as the first venous tributaries of the Henle trunk, as the dissection proceeds to separate the right mesocolon from the head of the pancreas. Early identification will reduce the risk of inadvertent venous tearing from overzealous traction.

The anatomy of the IMA is more consistent. The IMA splits into left colic artery and superior rectal (hemorrhoidal) artery 2–3 cm from its origin at the aorta. The left colic artery courses superiorly toward the splenic flexure and the superior rectal artery courses inferiorly toward the rectum at the root of the sigmoid mesentery. It should be noted that there is no universally agreed upon nomenclature regarding the IMA and its branches, as some surgeons assert that the IMA becomes the superior rectal artery when it "crosses the common iliac artery," after it has given off some of the sigmoidal branches.

Laparoscopic Approach for CME + D3 Dissection

Applying CME+CVL principles to laparoscopic or robotic colectomy can be challenging, primarily due to the technical difficulty of vascular dissection and skeletonization at the root of the mesentery. There is an associated increased operative time, risk of vascular injury, and long learning curve [40]. Conversion rates range in the literature from 5% to 22% [26, 41, 42]. However, as with other complex MIS procedures, when performed by surgeons with the appropriate training and expertise, laparoscopic CME + D3 dissection is associated with equivalent OR time, morbidity rates, and oncologic outcomes relative to the open approach. The MIS approach may improve short-term outcomes, including incision-related postoperative morbidity, bowel function recovery, and length of hospital stay [41]. Relative contraindications to the laparoscopic or robotic approach to CME + CVL are similar to those for conventional cancer surgery and include the emergency setting, hemodynamic instability, inability to tolerate pneumoperitoneum, prior extensive abdominal surgery, T4 disease when en bloc resection is anticipated to be difficult, and large/bulky tumors.

In the European literature, experience with laparoscopic CME is growing rapidly. Based on the largest and oldest experience from Denmark, adoption of laparoscopic CME increased to 49% based from the 2008 to 2013 Danish DCCG dataset, with conversion rates dropping slightly during the course of the study, from 22% to 19.9% [26, 42]. For right colectomy with CME, laparoscopic adoption was 33% with a 21% conversion rate, reflecting the difficulties unique to CME + D3 dissection and often necessitating an open approach to achieve adequate exposure of the vascular anatomy near the SMV [43].

In a recent systematic review and meta-analysis of one randomized trial and seven case-control trials comparing laparoscopic with open CME with central lymphadenectomy, despite significant heterogeneity in the data from lack of consistency in reported outcomes and of standardized perioperative protocols, a trend toward longer operative time and shorter length of hospital stay was noted with the laparoscopic approach. Laparoscopic CME was associated with a significantly lower wound infection rate. No differences could be found with respect to lymph node yield, local and distant recurrence, or overall survival [44]. With respect to training, when performed by supervised trainees, laparoscopic colon cancer resection with CME and CVL/D3 dissection was equivalent to open CME with respect to the macroscopic specimen assessment and mesocolic plane resection rate [45].

A large multicenter randomized trial compared open vs laparoscopic CME + D3 dissection enrolling patients from 2004 to 2009 across 30 Japanese centers, with procedures performed by surgeons with a minimum of 30 open and 30 laparoscopic CME + D3 operations previously completed. When comparing 521 open versus 527 laparoscopic CME + D3 for stage II/III right- and left-sided cancer, the conversion rate was 5.4%, with longer OR time and a higher rate of intraoperative organ injury in the laparoscopic CME group, although not statistically significant (3.6% vs 1.7%). Injuries that occurred during laparoscopic surgery and not during open procedures included injuries to the duodenum, arterial injuries, and gastrocolic trunk injuries [41]. The laparoscopic approach was associated with lower blood loss, faster resolution of ileus, and shorter length of hospital stay relative to open [41]. Postoperative morbidity was also lower with laparoscopic CME (14.3% vs 22.3%) with similar median number of lymph node harvested. Overall, 86% of stage III patients in each group received adjuvant chemotherapy, with no differences in 5-year OS (90.4% vs 91.8%, open vs lap) or DFS (80% vs 79%, open vs lap) [46]. Central review of procedural videos and intraoperative photographs were used for quality control, and all specimens were processed according to the Japanese classification of colorectal carcinoma. Overall, in the hands of highly experienced surgeons, laparoscopic CME + D3 dissection was demonstrated to be safe for patients with stage II/III colon cancer, and the laparoscopic approach was associated with improved short-term outcomes and equivalent oncologic outcomes relative to the open approach.

With respect to anticipated difficulties for surgeons to transition from D2 to D3 dissection, studies comparing outcomes between laparoscopic or robotic D2 and D3 resections have not identified increased surgical risks or worse outcomes with MIS D3 dissection. Analysis of the first 100 patients accrued in the ongoing COLD trial (D2 vs D3 dissection), where 79–84% of procedures were completed laparoscopically, demonstrated no differences in OR time, blood loss, conversion rates (12% vs 13%, respectively), or 30-day complications (47 vs 48% Clavien-Dindo grade I–IV, respectively) between the groups [29], which supports the notion that experienced D2 surgeons can transition to D3 dissection with excellent results. There were three injuries during D3 dissection that included left gonadal artery transection and two small bowel injuries, the latter requiring conversion. Participating surgeons were required to have a minimum of 20 case experience with D2 and 20 cases with D3 lymphadenectomy and to have submitted unedited videos for technique assessment as a requirement for study participation [29]. Similarly, In the USA, Sammour et al. recently described their institutional experience with laparoscopic and robotic CME + D3 performed in 141 patients compared to 56 CME + D2 cases. Although D3 dissection was preferentially used in patients with favorable anatomy and based

on preoperative staging, CME + D3 was associated with a lower conversion rate (1% vs 3.5%) and similar blood loss, perioperative complication rate (10.6% vs 17.9%) and lymph node harvest [47].

Several additional reports describe the use of the robotic approach becoming increasingly used in these complex procedures [48, 49]. In a recent retrospective comparison of 101 laparoscopic vs 101 robotic-assisted CME for stage I–III right colon cancer over a 10 year period, Spinoglio et al. demonstrated longer OR time with the robotic approach but lower conversion rates (0% vs 6.9%) and no differences in complications, lymph node harvest, and 5-year OS or DFS [50], although reporting of the extent of lymphadenectomy or other quality indicators of CME resection was not provided.

Techniques of MIS CME + D3 for Right-Sided and Transverse Colon Cancer

Medial to Lateral Approach

Similar to conventional oncologic resection for right colon cancer, i.e., CME + D2 dissection, the avascular plane between the mesocolon and the retroperitoneum is dissected with intact visceral peritoneum until the second portion of the duodenum and head of pancreas are exposed medially and the mesocolon has been mobilized all the way toward the right and proximal transverse colon. Attention is then turned to the anterior aspect of the SMV which is exposed as the mesocolon package is entirely dissected off these vessels. The ileocolic vessels are ligated at the root of the SMV and SMA, respectively, and the dissection continues cephalad, anterior to the SMA and SMV, heading cephalad toward the right colic vessels, the CGT, and the middle colic vessels. The right colic vessels (if present) are dissected and transected at their base, and the CGT is carefully dissected with preservation of the ASPDV and RGEV. The RCV and/or SRCV are transected. Finally, the middle colic vessels are dissected at their base of the SMA and SMV. Following D3 dissection, the principles of tumor-specific CME are subsequently followed with respect to extent of colonic mobilization and division of the middle colic vessels, based on tumor location. Arterial flow from the IMA retrograde to the transverse colon should be assessed prior to division of the main trunk of the MCA, especially in patients of advanced age or with a history of atherosclerotic disease. For cecal and ascending colon tumors, the main and left branch of the middle colic artery are spared, and only the right branch of the middle colic artery and vein are divided. For tumors of the hepatic flexure or transverse colon, the middle colic vessels are usually divided at their base (Figs. 37.4 and 37.5, courtesy of Dr. Ito Masaaki and Dr. Hiro Hasegawa). For distal

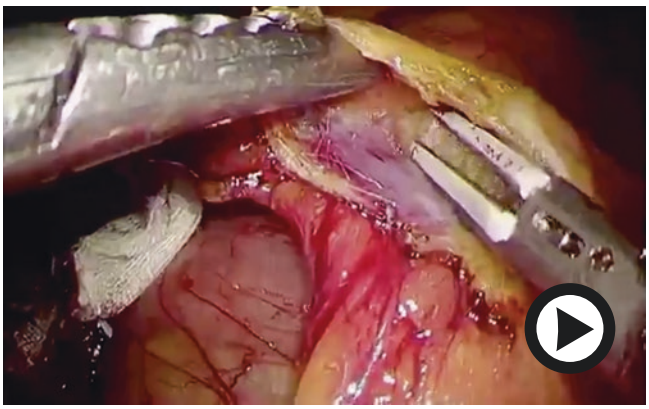

Fig. 37.4 Medial to lateral approach for laparoscopic right colectomy with CME + D3 dissection for tumor at the hepatic flexure. (Courtesy of Dr. Masaaki Ito and Hiro Hasegawa and Takeshi Sasaki). https://doi.org/10.1007/000-33p

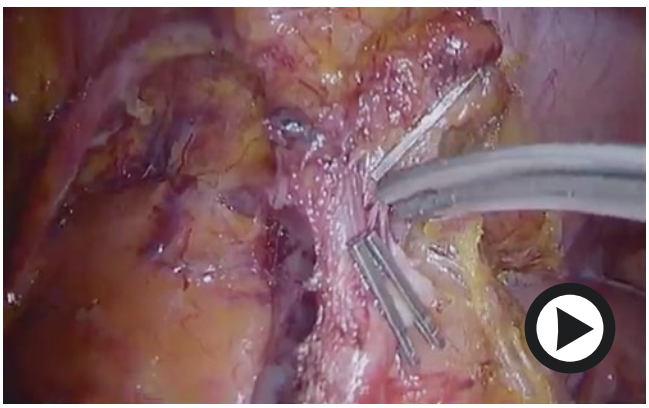

Fig. 37.5 Medial to lateral approach for laparoscopic left colectomy with CME + D3 dissection for tumor in the distal transverse colon. (Courtesy of Dr. Masaaki Ito and Dr. Hiro Hasegawa and Takeshi Sasaki) https://doi.org/10.1007/000-33n

transverse colon tumors, left colectomy is performed with sparing of the right branch of the middle colic artery. The IMV is also ligated with takedown of the splenic flexure (Figs. 37.6 and 37.5). Omentectomy is performed inferior to the gastroepiploic vessels which are preserved unless infiltrated with tumor. The plane below the mesocolon and the lesser sac is merged, and the hepatocolic ligament is divided. Finally, the lateral peritoneal attachments of the right colon are mobilized in order to complete mobilization of the right colon in preparation for specimen exteriorization. Intracorporeal or extracorporeal reconstruction can then be planned, based on surgeons' preference.

Alternatively, a "SMV-first approach" has been popularized with robotic CME + D3 dissection [29, 46]. The base of the mesocolon is exposed, the transverse colon retracted superiorly, and an incision is made inferior to the ileocolic vessels and extending it more proximally until the SMV is identified. All lymphatic/areolar tissue anterior to the surface of the SMV is dissected en bloc,

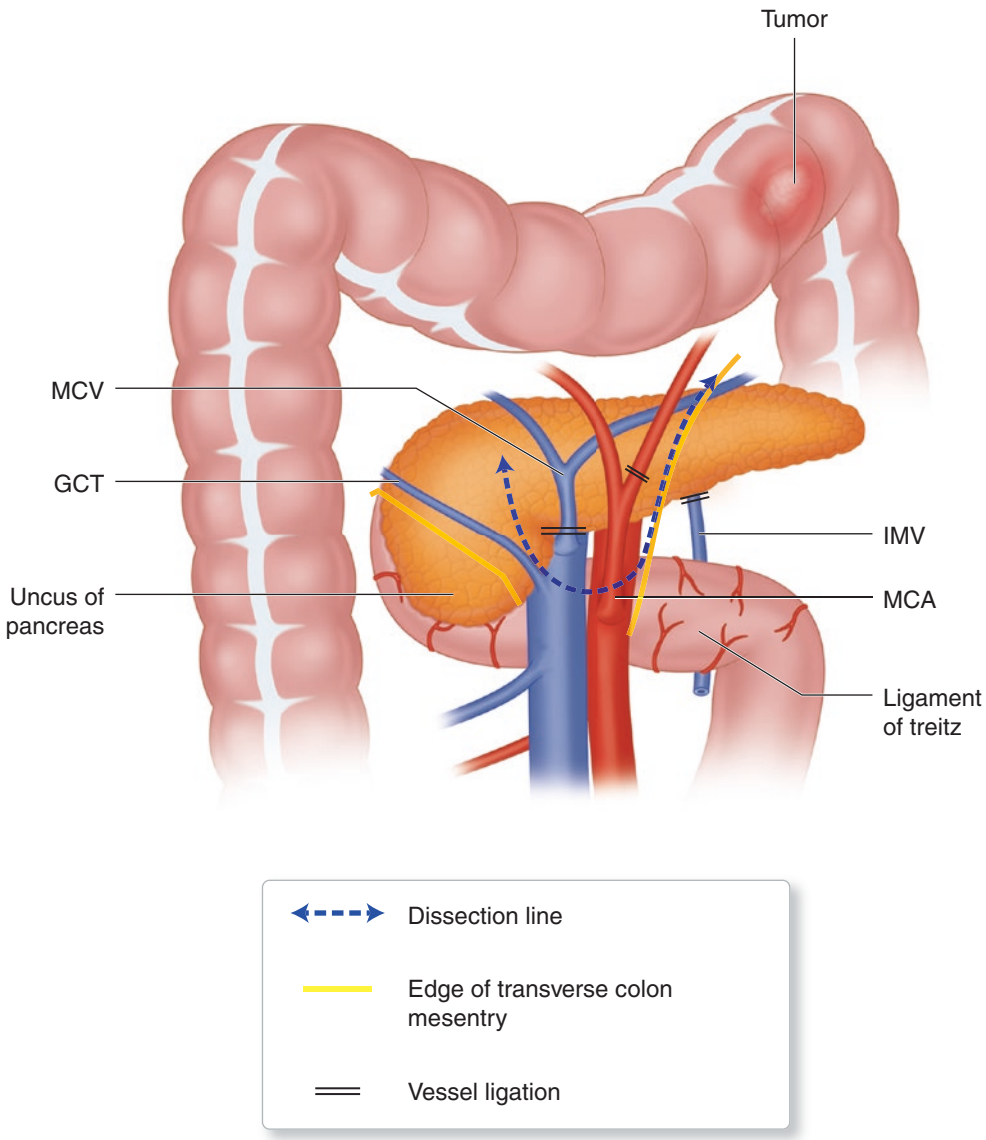

Fig. 37.6 Left colectomy with CME + D3 for a distal transverse colon cancer. The main feeding vessel to be ligated is the left branch of the middle colic artery (MCA) with preservation of the right branch of the MCA

heading cephalad. Then the tributaries of the SMV are sequentially divided, starting with the ICV, followed by ligation of the ICA off the base of the SMA. Medial to lateral mobilization of the mesocolon off the retroperitoneum may be carried out then or subsequent to completion of the SMV dissection. Otherwise, cephalad dissection along the SMV is continued until the middle colic vessels are identified. A right colic artery may be identified and divided, followed by ligation of the MCA or its branches, based on tumor location. The GCT is subsequently identified and dissected along the right anterolateral aspect of the SMV.

Retrofascial Uncinate First Approach This technique was developed by Stefan Benz et al. and is based on an open-book model to best understand the vascular and meso-/fascial anatomy of the operation. In this model, the different planes (mesogastric, mesocolic, and ileocolic) are depicted as pages of a booklet with the GCT serving as the vertical axis and the pancreas serving as the back of the book [51]. The avascular plane between the pages must be dissected according the principles of CME and prior to dividing the vessels in order to avoid vascular injury. Following standard laparoscopic port placement, nine steps are described to complete CME + D3, with associated "critical views" that help provide guidance on satisfactory completion of each step (Figs. 37.7 and 37.8).

Step 1 The small bowel is retracted into the right upper quadrant, exposing the duodeno-jejunal flexure. The peritoneum is incised at the inferior/posterior border of the visible duodenum (Fig. 37.9a). Dissection of the duodenum is carried out in a medial to lateral fashion, and this retromesenteric dissection is extended caudally along the entire

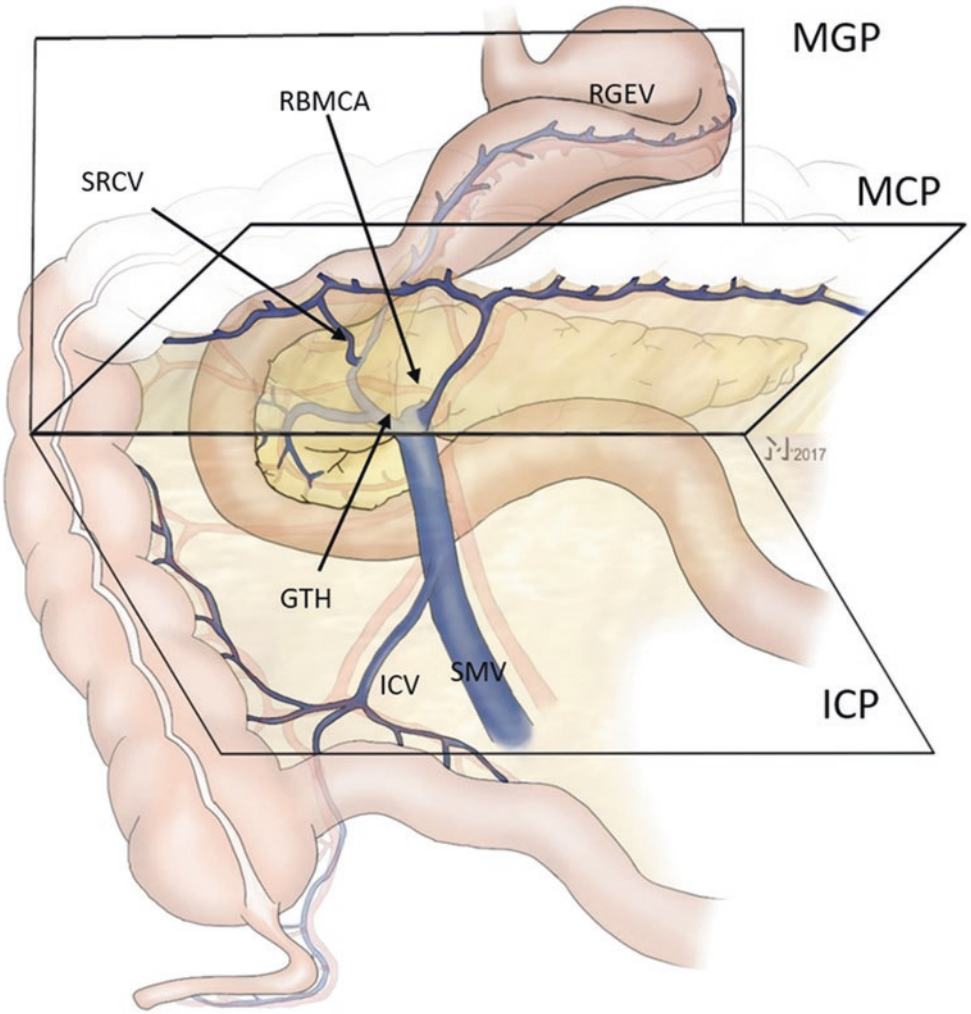

Fig. 37.7 CME + D3 approach using the retrofascial uncinate first approach. This technique is based on an open-book model to best understand the vascular and meso-/fascial anatomy of the operation. In this model, the different planes (mesogastric, mesocolic, and ileocolic) are depicted as pages of a booklet with the GCT serving as the vertical axis. The avascular plane between the pages must be dissected according the principles of CME and prior to dividing the vessels. RGEV right gastroepiploic vein, GTH gastrocolic trunk of Henle, RBMCA right branch of the middle colic artery, SRCV superior right colic vein, MCV middle colic vein, SMV superior mesenteric vein, ICV ileocolic vein, MGP mesogastric page, ICP ileocolic page, MCP mesocolic page [51]. (Courtesy of Dr. Stefan Benz)

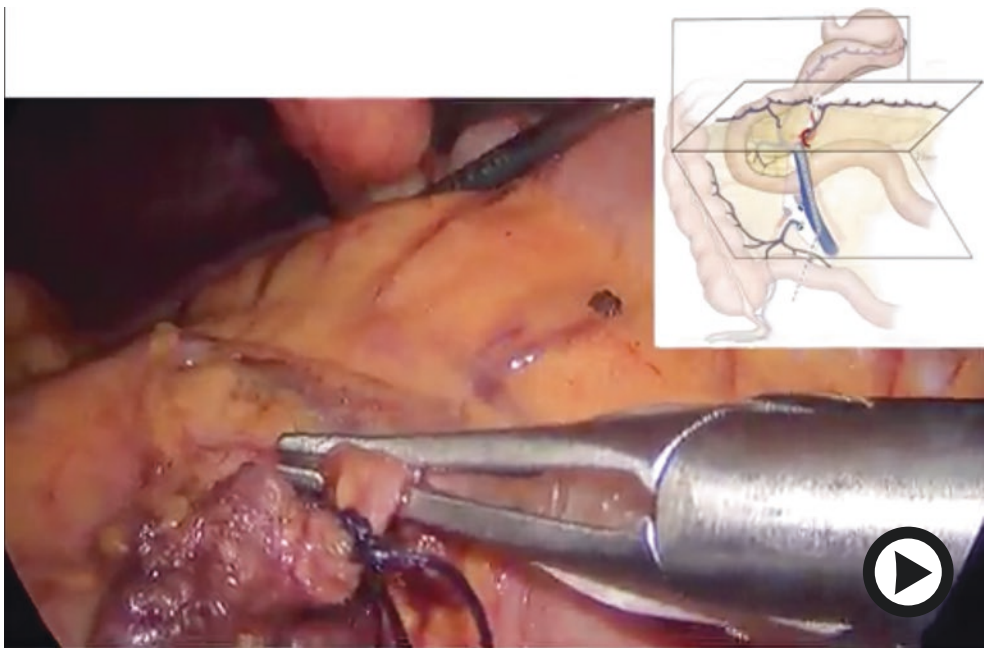

Fig. 37.8 Retrofascial uncinate first approach for laparoscopic right colectomy with CME + CVL. (Courtesy of Dr. Stefan Benz). https://doi.org/10.1007/000-33q

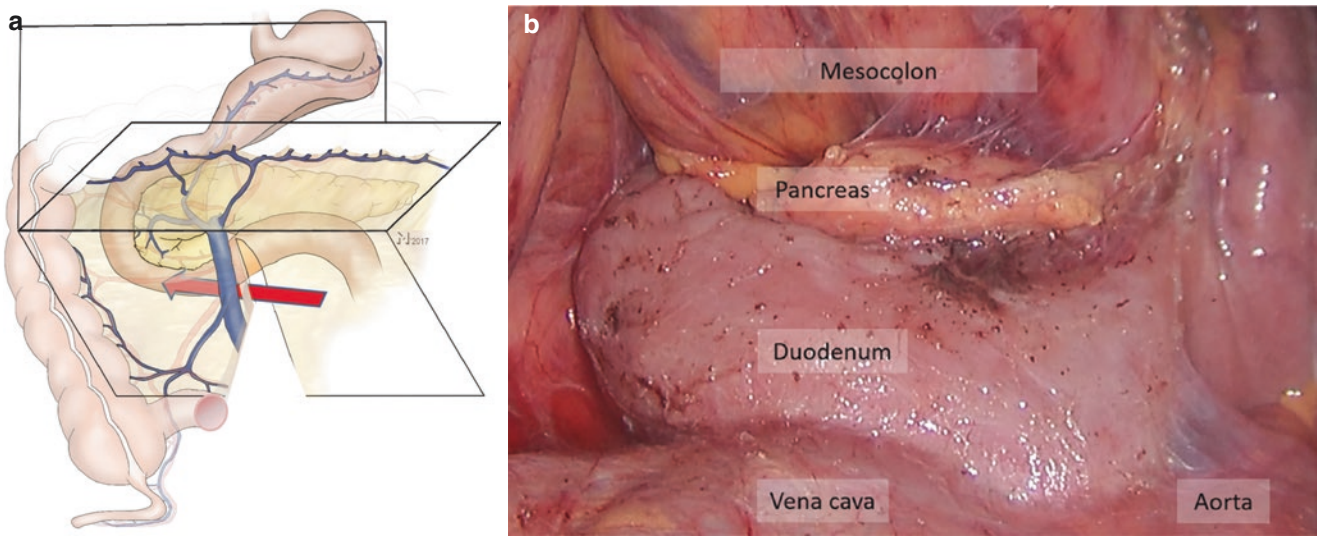

Fig. 37.9 Step 1 of the retrofascial uncinate first approach for CME with central ligation. (**a**) Dissection starts at the duodeno-jejunal flexure [51]. (**b**) Critical view 1: The third portion of the duodenum and uncinate process are visible. (Courtesy of Dr. Stefan Benz)

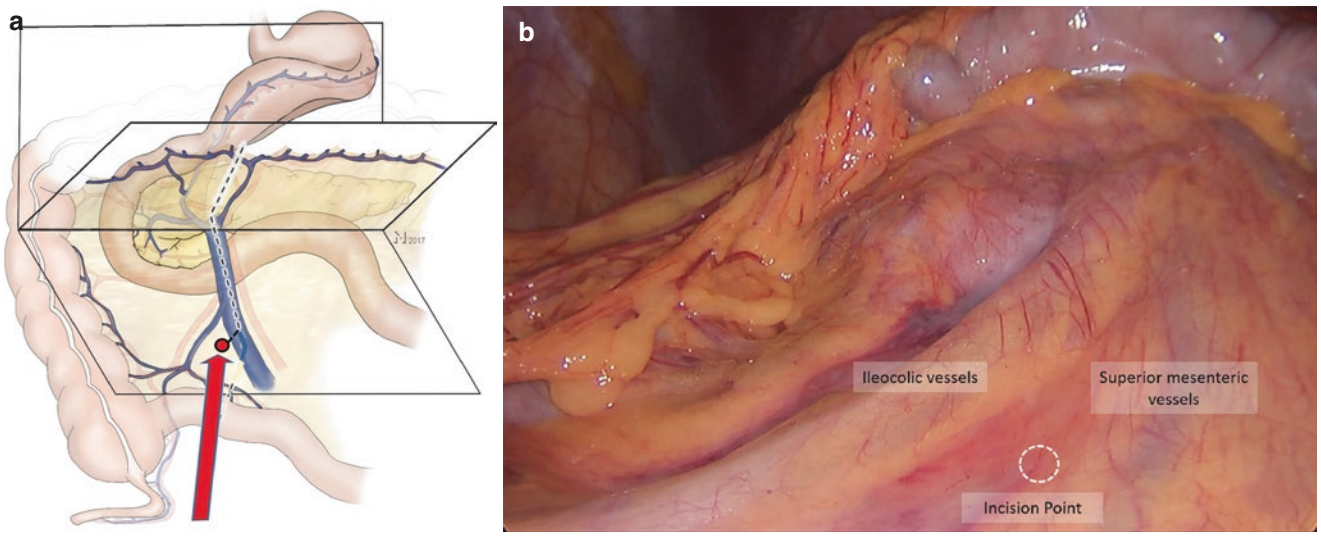

Fig. 37.10 Step 2 of the retrofascial uncinate first approach for CME with central ligation. (**a**) Incision point between the ileocolic and mesenteric vessels [51]. (**b**) Critical view 2: The incision point is highlighted after placing tension on the ileocolic pedicle. (Courtesy of Dr. Stefan Benz)

ascending mesocolon. The right ureter and gonadal vessels are separated from the mesocolon. Cranially the hepatic flexure is usually reached, and Toldt's fascia is incised along the lower border of the duodenum and the anterior surface of the uncinate process is separated from mesocolon (Critical view 1: Figs. 37.9b and 37.8).

Step 2 The small bowel is repositioned to the left, and the ileocolic vessels are placed on tension. A V-shaped configuration between the ileocolic and the superior mesenteric vessel can be identified (Critical view 2: Figs. 37.10a, b and 37.8).

Step 3 The peritoneum is incised approximately 3 cm distal to the ileocolic root, between the ileocolic and superior mesenteric vessels. The dorsal dissection plane is entered and the pancreatic head and the duodenum can be clearly identified. The dissection is continued in the direction of the SMV, which should be dissected to about 180–270° of its circumference. The incision line along the edge of the mesenteric root up to the root of the transverse mesocolon is marked with monopolar cautery. Dissection along the SMV is extended superiorly and 360° dissection of ICV at its confluence with the SMV is carried out (Critical view 3: Fig. 37.8). The ICV is then divided.

Step 4 The ICA is identified crossing either anterior or posterior to the SMV and is dissected entirely 360° at least at the level of the SMV (Critical view 4: Fig. 37.8). In most patients the SMA can be readily identified during this dissection, and all lymphatic tissue on the right side of the SMA is resected. After division of the ICA, the SMV is dissected toward the GCT which is usually the major vein running into the SMV from the right side and cranial to the ICV.

Step 5 Following the principle that the pages of the open-book model should be dissected before vessels are divided, the mesogastric page is now separated from the mesocolic page. Thus, the stomach is retracted cranially, and the gastrocolic ligament is incised approximately 5 cm to the left of the midline, in this way preserving the gastro-omental arcade. The slightly left-sided incision is important because the lesser sac is usually obliterated on the right side of the middle colic vessel which is located approximately in the midline. The lesser sac is entered and the dorsal aspect of the stomach is visualized (Critical view 5: Fig. 37.8).

Step 6 The gastrocolic ligament is divided in a medial to lateral fashion. The vessels running into the omentum need to be transected. Dorsal to these vessels, the avascular plane between the transverse mesocolon and the dorsal mesogastrium (containing the gastroepiploic vessels and infrapyloric lymph nodes) is identified and dissected. This plane crosses the second part of the duodenum and can be followed laterally toward the hepatic flexure and merges with the previously completed step 1. The separation of mesocolon and mesogastrium creates a sulcus, and the colic veins (usually the SRCV) in the mesocolon and the RGEV in the mesogastrium can be identified merging at the base of this sulcus (Critical view 6: Fig. 37.11a, b and 37.12). Because the SRCV often runs outside this axis, excessive tension will result in major bleeding (bleeding point).

Step 7 The operation continues inferior to the mesocolon. The mesocolon is retracted cranially and the transverse mesocolon is incised directly anterior to the SMV. The mesocolon is then divided stepwise from cranial to caudal, dissecting the origin of the right branch of the middle colic artery which is usually found at the base. The origin of the right branch is mobilized 360° ensuring the preservation of the integrity of the left branch (Critical view 7, Fig. 37.8). The vessel is divided, and the middle colic vein is only divided if it impedes adequate lymphadenectomy.

Step 8 The anterior surface of the trunk of Henle is exposed, and all the veins that merge with it from the mesocolon can be divided including the SRCV/RCV. The gastroepiploic vein can usually be identified and must be preserved, as well as the ASPDV. Central dissection is now complete (Critical view 8: Fig. 37.12a, b).

Step 9 The lateral attachments of the right colon can be divided. If extracorporeal anastomosis is planned, the specimen can be exteriorized at this time. If intracorporeal anastomosis is performed, the colon and the terminal ileum are divided. Care must be taken to preserve the ileocolic lymphatic drainage.

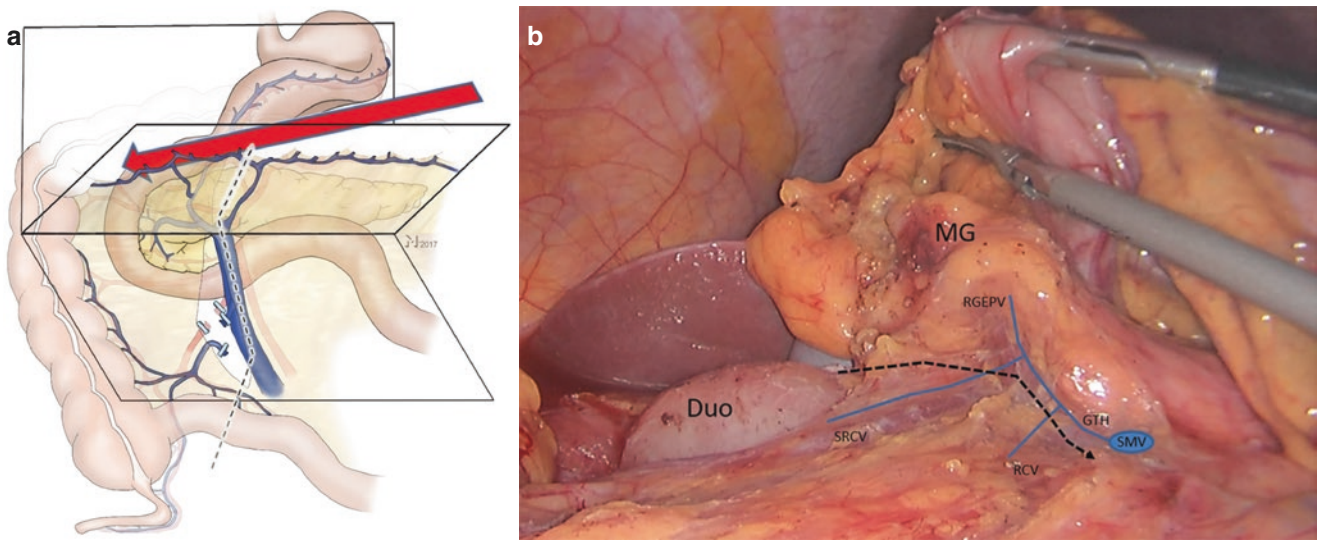

Fig. 37.11 Step 6 of the retrofascial uncinate first approach for CME with central ligation. (**a**) Dissection of the mesogastrium from the mesocolon [51]. (**b**) Critical view 6: The lesser sac is dissected; the sulcus between the mesogastrium and mesocolon is visible. (Courtesy of Dr. Stefan Benz)

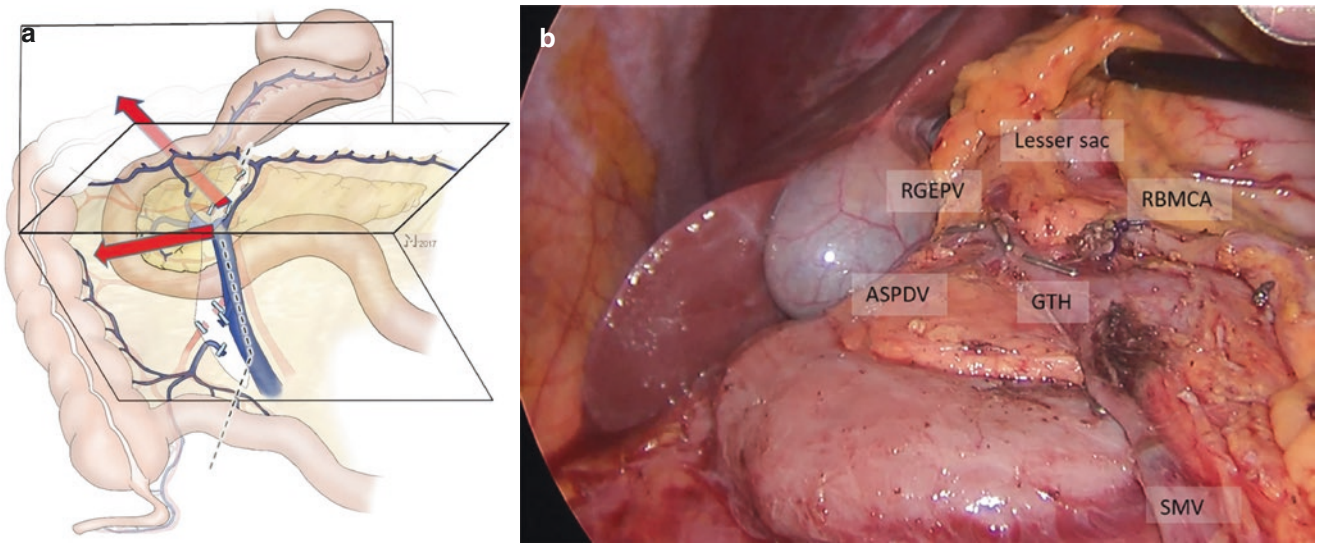

Fig. 37.12 Step 8 of the retrofascial uncinate first approach for CME with central ligation. (**a**) The remainder of the mesocolon is dissected by dividing the colic branches of the GCT while preserving the RGEV and ASPDV [51]. (**b**) Critical view 8: Completed CME with central ligation. (Courtesy of Dr. Stefan Benz)

Lateral to Medial Approach

This alternative approach is preferred in the event the base of the ileocolic pedicle is difficult to identify. The white line of Toldt's is incised along the right gutter, and the embryological plane between the right mesocolon and Gerota's fascia is dissected sharply, taking care to avoid injury to the right ureter, kidney, and right gonadal vessels. This dissection is extended medially toward the duodenum. The base of the ileocolic pedicle is exposed and dissected with exposure of the SMV and dissection of the lymphatic tissue on SMV. The ileocolic pedicle is dissected at its base followed by sharp dissection along the SMV up to the root of the middle colic vessels. After dissection of all lymphatic tissue at the base of the middle colic pedicle, with skeletonization of each branch, arterial and venous ligation is performed based on tumor location. The transverse colon is retracted caudally, and the gastrocolic ligament is divided along the right gastroepiploic vessels.

Cranial to Caudal Approach

This approach has been increasingly adopted in Asia and proposes early and easy access to and exposure of the pancreas, GCT and SMV [52]. With this approach, the omental bursa is opened with exposure of the GCT using the right gastroepiploic vessel and superior (accessory) right colic vein as landmark. After dividing the latter, the SMV and middle colic vein are identified and the latter is divided at its root. Complete dissection of the lymphatic tissue along the SMV proceeds in a cranial to caudal direction. In addition, the middle colic artery is dissected and the MCA or its right branch is divided at its base. The transverse colon is then pulled ventrally and dissection of lymphatic tissue continues along the SMV in a cranial-caudal approach. The ileocolic and right colic vessels are dissected and divided at their origin, and the ascending and transverse mesocolon is dissected off Gerota's fascia, the retroperitoneum, pancreatic head, and duodenum using a medial approach.

MIS CME for Left Colon Cancer with D3 Dissection

A medial to lateral approach to the sigmoid mesentery is preferred. The medial aspect of the sigmoid mesocolon is incised just above the level of the sacral promontory, and medial to lateral mobilization of the mesocolon is carried out sharply through the avascular plane as during standard medial to lateral approach for proctectomy. The IMA is elevated and skeletonized at its base, with dissection of the entire lymphatic and areolar tissue at its root. Care is taken to avoid injury to the superior hypogastric plexus at the level of the aortic bifurcation and the left ureter and gonadal vessels during medial to lateral mesocolic dissection. Following D3 dissection, the principles of tumor-specific CME are subsequently followed with respect to extent of colonic mobilization and division of the IMA or left colic artery, based on tumor location. For proximal left colon tumors, the left colic artery may be divided at its origin, and the root of the IMA and superior rectal artery

are preserved if anastomosis to the distal sigmoid is contemplated. If the entire sigmoid colon is to be resected, as for mid-left sided, sigmoid, and rectosigmoid tumors, the IMA is ligated at its origin on the aorta. In either situation, the IMV is typically divided just inferior to the border of the pancreas, which will allow the proximal colon to rotate inferiorly, when combined with complete mobilization of the splenic flexure. The ligament of Treitz serves as the landmark to identify the IMV. It is important to ensure that there is no arterial branch in the tissues adjacent to the IMV prior to dividing the IMV, as occasionally the dominant arterial flow from the left branch of the middle colic artery runs at the root of the mesentery. If this artery is inadvertently divided, arterial flow to the proximal colonic conduit may be compromised. The left mesocolon is dissected away from Gerota's fascia, the lesser sac is entered, and the root of the transverse mesocolon is freed from the inferior border of the pancreas. The splenic flexure can also be mobilized using the medial to lateral approach. Once completed, the lateral attachments of the left colon are taken down as is the splenocolic ligament. Omentectomy is completed just below the gastroepiploic vessels with preservation of the left gastroepiploic vessels, unless infiltrated by tumor.

Short-Term Outcomes of CME

In a 2019 systematic review of studies comparing outcomes between CME and non-CME resections for right and left colon cancer, two of three eligible studies demonstrated longer operative time with CME [14]. The pooled perioperative morbidity rate among 6 studies was 22.5% vs 19.6% in CME vs NCME groups. The majority of older institutional reports include no information regarding the occurrence of intraoperative adverse events during CME dissection.

The more recent Danish Colorectal Cancer Group (DCCG) published short-term outcomes from 529 patients who underwent CME/D3 for stage I–III colon cancer at a single institution between 2008 and 2013, soon after a short implementation period, and were performed or supervised by a "specialist." A laparoscopic approach was attempted in 48.8% of cases with a 19.9% conversion rate. This is the only study documenting a higher rate of intraoperative organ injury with CME relative to a non-CME historical cohort (9.1% vs 3.6%) with injuries including splenic and SMV injuries [42].

In the Japanese JCOG0404 laparoscopic vs open RCT comparing 521 open to 527 laparoscopic CME + D3 for stage II/III for right- and left-sided cancer, the conversion rate was 5.4%, with longer OR time and a higher, albeit not significant, rate of intraoperative organ injury in the CME group (3.6% vs 1.7%). Intraoperative events included injuries to the small bowel and rectum, arterial supply, portal vein, bladder and ureter, portal vein and gonadal vein, and gastrocolic trunk [41].

In a recent interim analysis of 3-year outcomes of a prospective non-randomized trial comparing 220 CME with 110 non-CME open colon cancer resections, no difference in perioperative complications was noted between the groups. However lower blood loss, faster resolution of ileus, and shorter length of hospital stay were noted in the CME group [23]. These differences likely reflect the vast experience of Japanese surgeons with D3 dissection that preceded the description of CME/CVL by Hohneberger et al. in 2009 by at least a decade [10]. As reflected by three ongoing Chinese RCT's evaluating CME vs D2/D3 dissection, D3 dissection has also been embraced by Chinese surgeons.

There are limited data on the learning curve required for CME. Melich et al. described excellent lymph node harvest, low rate of major complications (3.6%), and no conversion during their initial 81 laparoscopic CME cases with central ligation. However, OR time only decreased from 250 minutes to under 200 minutes after 81 cases completed over 3 years [40].

With respect to complications specific to CME, the most concerning is increased risk of vascular injury to the SMV and its tributaries and the roots of the ICA, RCA, and MCA that need to be dissected in order to achieve adequate D3 lymphadenectomy. Inadvertent ligation of the SMV or tributaries of the GCT can lead to bowel ischemia and necrosis. The risk of injury is likely highest for surgeons early along their learning curve, who must gain extensive understanding of the vascular anatomy around the Trunk of Henle and SMV. The risk of vascular injury is difficult to estimate. Freund et al. reported a 1.6% injury rate over 159 open and 145 CME cases performed for right colon cancer over a 10-year period [53]. The mechanism of injury was attributed to errors related to misperception and lack of understanding of variations in the venous and arterial branches at the root of the mesentery and avulsion of the middle colic vein due to excessive traction.

Other potential injuries related to CME includes organ injury, chyle leak from extensive nodal dissection, severe diarrhea from injury of the superior mesenteric plexus, and genitourinary dysfunction during left-sided dissection near the IMA (injury to the inferior mesenteric plexus and superior hypogastric plexus). As mentioned in the section on MIS CME + D2/D3, there are no documented additional procedural risks when performing CME using laparoscopic or robotic assistance when performed by experienced high-volume surgeons [22].

Long-Term Outcomes of CME with D3 Dissection

In a recent 2019 pooled analysis of eligible studies comparing long-term oncologic outcomes between CME and NCME resections, five studies demonstrated no differences in 3- or 5-year overall survival (OS), and one study demonstrated a lower 5-year cancer-specific survival (CSS) in the CME + D3 vs CME + D1/D2 [14, 54]. Four studies demonstrated higher disease-free survival (DFS) or cancer-specific survival (CSS) with CME [26, 55–57], although interpretation of results was limited given historical biases, significant heterogeneity in study design, procedures performed, extent of lymphadenectomy (D1, D2, D3/CVL), and pathologic assessment of CME specimens. The authors concluded that the limited quality of the evidence did not consistently support the oncologic superiority of CME.

In their 2009 seminal article reporting on outcomes from 1329 consecutive patients with stage I–III CRC from the ERCRC registry, Hohenberger et al. reported that adoption of a standardized approach for CME with central ligation resulted in a decrease in 5-year locoregional recurrence rate (6.5–3.6%) and improvement in 5-year cancer-related survival (82.1–89.1%) between the 1978–1984 and 1995–2002 time periods [10]. It is important to note that only 5.6% of patients received adjuvant chemotherapy in that timeframe. The results from the updated 1978–2014 ERCRC registry by the same authors were contrasted between the pre-CME, CME development, implementation, and CME practice time periods. The authors documented a rise in achievement of ≥12 lymph node harvest from 84.8% to 100% and R0 resection rate from 97% to 100%. Significant reduction in the 5-year locoregional recurrence rate (14.8–4.1%) and improvement in 5-year CSS (61.7–80.9%) and 5-year OS (53.1–68.6%) was reported among stage III patients between 1978 and 2009, in the background of increased use of adjuvant chemotherapy (0–79%) between 1978 and 2014 [55].

While this oncologic benefit was likely confounded by historical changes in adjuvant therapies, this survival advantage was confirmed in a population-based study by the DCCG [23]. The Danish 2008–2011 dataset compared 364 CME performed at a single specialized center to 1031 non-CME performed at 3 other centers and demonstrated a higher 4-year DFS in the CME group, especially for stage I/II stages [26]. In the 2008–2013 dataset for right colectomy, 256 CME from the same specialized center were compared with 813 non-CME cases from 3 other centers in Denmark. The 5.2-year recurrence rate for stage I–III colon cancer was significantly lower in the CME vs non-CME group (9.7% vs 17.9%) [43].

Another cohort study of 189 consecutive patients with stage I–II colon cancer treated with CME + D3 at one hospital vs CME + D2 at 3 other institutions between 2007 and 2008 demonstrated significant improvement of 3-year OS (88.1% vs 79%) and DFS (82.1% vs 74.3%) in the CME + D3 group [56].

Finally, a smaller institutional study comparing 45 CME with a historical control group of 58 patients treated with non-CME resections for right colon cancer also demonstrated that CME was associated with a significantly lower local recurrence rate (0% vs 20.6%) and higher 5-year CSS in stage III patients [50], despite the fact that similar portion of patients underwent adjuvant chemotherapy (47% vs 43% in CME vs NCME).

Much of the criticism of the above studies relate to flaws in study designs and reliance on historical cohorts as control groups. In several of the above studies, NCME procedures were localized at hospitals that never adopted CME and compared with CME performed at a single specialized institution, which introduces significant bias [26, 43, 56]. In addition, two studies reported inexplicably high rates of local/locoregional recurrence in the historical NCME cohort (14.8% and 20.6%) [55, 57], which raises concerns about baseline surgical techniques and outcomes [14]. Finally, the majority of these studies did not report the use of quality indicators to demonstrate/validate the adequacy of CME resections, other than the number of lymph nodes. As a result, the extent/quality of CME and D2 vs D3 dissection could not be validated [18, 43, 54–57].

With respect to more recent studies, interim analysis of an ongoing prospective non-randomized double blind trial comparing outcomes of 220 vs 110 patients who underwent open CME + D3 vs non-CME for right and left colon cancer, respectively, demonstrated improved 3-year local recurrence-free survival in stage II and III cases but no differences in OS or DFS [23]. Long-term outcomes form the ongoing COLD trial (multicenter randomized trial comparing mostly laparoscopic D2 vs D3 dissection), which so far demonstrated an equivalent number of lymph nodes harvested in each group among the first 100 patients accrued, will provide more insight regarding long-term outcomes of CME with D3 dissection [29]. Three other RCTs are currently underway in China to evaluate long-term outcome of laparoscopic CME + D2 vs CME+D3 for right colon cancer (RELARC, SLRC trials) [29, 58] and right- and left-sided cancer (LCME) [29].

Few groups in the USA have published their experience with CME + D3 dissection. Sammour et al. recently reported their short-term results with laparoscopic and robotic CME + D3 performed in 141 patients with right colon cancer (including 98 stage II/III patients) with favorable anatomy and in whom D3 dissection was preferred based on preopera-

tive staging [40]. Relative to a CME + D2 cohort of 56 patients performed during the same time period, no significant difference in short-term outcomes were identified with the exception of a higher median number of lymph node retrieved with CME + D3 (31 vs 27) although the number of positive nodes did not differ between the groups. It was not possible to determine the incidence of centrally positive nodes in this study since nodal stations are not routinely recorded on pathological analysis in the USA, nor is the level of vascular ligation based on mesenteric and pedicle length between the vascular tie and the tumor and/or bowel wall recorded.

In the USA, American cancer societies including American Society of Clinical Oncology (ASCO), the American College of Surgeons Commission on Cancer (ACS CoC), and National Collaborative Cancer Network (NCCN) have endorsed the recommendation that a minimum of 12 lymph nodes be used as a quality indicator for colorectal cancer resections, along with the oncologic principles of high ligation and negative margins. There are no guidelines or expectations regarding the optimal distribution of lymph nodes to be harvested relative to major vascular pedicles, or expected amount of mesentery to be removed. In sum, these recommendations could be translated to mean that CME with D2 lymphadenectomy is considered standard of care, with consideration for selective D3 lymphadenectomy based on preoperative detection of suspicious central lymph nodes in select patients.

It has become essential when designing prospective trials to evaluate outcomes of D2 versus D3 resection during CME for colon cancer, for the surgical community to standardize anatomic definitions, surgical principles and procedural milestones, as well as quality indicators of CME specimen assessment. As for mesorectal specimen grading, colon mesentery specimen grading should be externally validated using pathological parameters with high interrater agreement. Studies evaluating the safety and oncologic outcomes of CME will need to define the exact parameters of the operation, especially with respect to extent of lymphadenectomy, using standardized video-based assessment of procedures and review of intraoperative photographs highlighting prespecified anatomic landmarks.

With respect to adoption of CME + D2/D3 resection, it is hoped that based on the evidence presented in this chapter, and in light of the emerging evidence from well-designed ongoing trials, surgeons will become engaged and eager to reflect on their own surgical techniques when performing colectomy for cancer and strive to optimize CME + D2 dissection. CME + D3 resection can be considered in select cases, although at present there are no definitive data to support its use.

Conclusions

Although the published evidence supports completion of CME for colon cancer based on global improvement in surgical quality, prognostic and survival advantage provided by higher lymph node counts achieved, routine D3 lymphadenectomy for stage II/III colon cancers remains highly controversial, especially given the lack of direct and high-level evidence demonstrating long-term oncologic benefits. While in experienced hands, CME + D3 has an acceptable risk profile; when applied to right colectomy in particular, it requires thorough knowledge of the anatomy of the superior mesenteric vessels and their tributaries. These are technically challenging procedures with added risk of organ and vascular injury during the early learning curve. Recently, laparoscopic and robotic approaches for CME + D3 dissection have been increasingly described, with acceptable conversion rates, improved short-term results, and non-inferior oncologic outcomes in experienced hands and at high volume centers. Several ongoing prospective observational and randomized trials are currently underway to evaluate the oncologic impact of CME + D2/D3 resection in stage II/III disease. Unlike older trials, these trials incorporate video-based standardized assessment of the quality of CME resections, as well as standardized pathologic assessment of quality indicators for CME specimens using photodocumentation. Until then, the current evidence only supports selective use of CME + D3 for tumors with high risk for lymph node metastasis, based on preoperative imaging, tumor location, and/or clinical T stage. The same published evidence however should serve as a reminder to the surgical community of the importance of adopting CME + D2 dissection and adopting procedural and pathological quality assessment measures.

References

1. Wibe A, Moller B, Norstein J, et al. A national strategic change in treatment policy for rectal cancer: implementation of TME as routine treatment in Norway: a national audit. DCR. 2002;45:857–66.
2. Martling AL, Holm T, Rutqvist LE, Moran BJ, Heald RJ, Cedemark B. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. Lancet. 2000;356:93–6.
3. Kapiteijin E, Van De Velde CJ. European trials with TME. Sem Surg Oncol. 2000;19:350–7.
4. Enker WE, Laffer UT, Block GE. Enhanced survival of patients with colon and rectal cancer is based upon wide anatomic resection. Ann Surg. 1979;190:350–60.
5. Le Voyer TE, Sigurdson ER, Hanlon AL, Mayer RJ, Macdonald JS, Catalano PJ, Haller DG. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. J Clin Oncol. 2003;21(15):2912–9.

6. Chen SL, Bilchik AJ. More extensive nodal dissection improves survival for stages I to III of colon cancer: a population-based study. Ann Surg. 2006;244(4):602–10.
7. Kotake K, Honjo S, Sugihara K, Hashiguchi Y, Kato T, Kodaira S, Muto T, Koyama Y. Number of lymph nodes retrieved is an important determinant of survival of patients with stage II and stage III colorectal cancer. Jpn J Clin Oncol. 2012;42(1):29–35.
8. Jamieson JK, Dobson FJ. The lymphatics of the colon. Ann Surg. 1909;50:1077–90.
9. Ishiguro M, Higashi T, Watanabe T, Sugihara K, Japanese Society for Cancer of the Colon and Rectum Guideline Committee. Changes in colorectal cancer care in Japan before and after guideline publication: a nationwide survey about D3 lymph node dissection and adjuvant chemotherapy. J Am Coll Surg. 2014;218(5):969–77.
10. Hohenberger W, Weber K, Matzel K, Papadopolos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation – technical notes and outcome. Colorectal Dis. 2009;11:354–64.
11. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, et al. Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. Int J Clin Oncol. 2012;17(1):1–29.
12. Hashiguchi Y, Muro K, Saito Y, Ito Y, Ajioka Y, Hamaguchi T, Hasegawa K, Hotta K, Ishida H, Ishiguro M, Ishihara S, Kanemitsu Y, Kinugasa Y, Murofushi K, Nakajima TE, Oka S, Tanaka T, Taniguchi H, Tsuji A, Uehara K, Ueno H, Yamanaka T, Yamazaki K, Yoshida M, Yoshino T, Itabashi M, Sakamaki K, Sano K, Shimada Y, Tanaka S, Uetake H, Yamaguchi S, Yamaguchi N, Kobayashi H, Matsuda K, Kotake K, Sugihara K. Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol. 2020;25(1):1–42.
13. Japanese Society for Cancer of the Colon and Rectum. Japanese classification of colorectal, appendiceal, and anal carcinoma, third, English edn. Tokyo: Kanehara & CO., Ltd.; 2019.
14. Alhassan N, Yang M, Wong-Chong N, Liberman AS, Charlebois P, Stein B, Fried GM, Lee L. Comparison between conventional colectomy and complete mesocolic excision for colon cancer: a systematic review and pooled analysis : a review of CME versus conventional colectomies. Surg Endosc. 2019;33(1):8–18.
15. Iwatate M, Sano Y, Tanaka S, Kudo SE, Saito S, Matsuda T, Wada Y, Fujii T, Ikematsu H, Uraoka T, Kobayashi N, Nakamura H, Hotta K, Horimatsu T, Sakamoto N, Fu KI, Tsuruta O, Kawano H, Kashida H, Takeuchi Y, Machida H, Kusaka T, Yoshida N, Ichiro H, Terai T, Yamano H, Nakajima T, Sakamoto T, Yamaguchi T, Tamai N, Nakano N, Hayashi N, Oka S, Ishikawa H, Murakami Y, Yoshida S, Saito Y. Japan NBI Expert Team (JNET).Validation study for development of the Japan NBI Expert Team classification of colorectal lesions. Dig Endosc. 2018;642–651(28):30.
16. Saitoh Y, Obara T, Watari J, Nomura M, Taruishi M, Orii Y, Taniguchi M, Ayabe T, Ashida T, Kohgo Y. Invasion depth diagnosis of depressed type early colorectal cancers by combined use of videoendoscopy and chromoendoscopy. Gastrointest Endosc. 1998;48:362–370 29.
17. Watari J, Saitoh Y, Obara T, Fujiki T, Taniguchi M, Nomura M, Ayabe T, Ohta T, Orii T, Kohgo Y. Early nonpolypoid colo- rectal cancer: radiographic diagnosis of depth of invasion. Radiology. 1997;205:67–74.
18. West NP, Hohenberger W, Weber K, Perrakis A, Finan PJ, Quirke P. Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. J Clin Oncol. 2010;28(2):272–8.
19. Kataoka K, Beppu N, Shiozawa M, Ikeda M, Tomita N, Kobayashi H, Sugihara K, Ceelen W. Colorectal cancer treated by resection and extended lymphadenectomy: patterns of spread in left- and right-sided tumours. Br J Surg. 2020;107:1070.
20. Kobayashi H, West NP, Takahashi K, Perrakis A, Weber K, Hohenberger W, Quirke P, Sugihara K. Quality of surgery for stage III colon cancer: comparison between England, Germany, and Japan. Ann Surg Oncol. 2014;21 Suppl 3:S398–404.
21. West NP, Kobayashi H, Takahashi K, Perrakis A, Weber K, Hohenberger W, Sugihara K, Quirke P. Understanding optimal colonic cancer surgery: comparison of Japanese D3 resection and European complete mesocolic excision with central vascular ligation. J Clin Oncol. 2012;30(15):1763–9.
22. Søndenaa K, Quirke P, Hohenberger W, Sugihara K, Kobayashi H, Kessler H, Brown G, Tudyka V, D'Hoore A, Kennedy RH, West NP, Kim SH, Heald R, Storli KE, Nesbakken A, Moran B. The rationale behind complete mesocolic excision (CME) and a central vascular ligation for colon cancer in open and laparoscopic surgery: proceedings of a consensus conference. Int J Color Dis. 2014;29(4):419–28.
23. Gao Z, Wang C, Cui Y, Shen Z, Jiang K, Shen D, Wang Y, Zhan S, Guo P, Yang X, Liu F, Shen K, Liang B, Yin M, Xie Q, Wang Y, Wang S, Ye Y. Efficacy and safety of complete mesocolic excision in patients with colon cancer: three-year results from a prospective, nonrandomized, double-blind, controlled trial. Ann Surg. 2020;271(3):519–26.
24. Nakajima K, Inomata M, Akagi T, Etoh T, Sugihara K, Watanabe M, Yamamoto S, Katayama H, Moriya Y, Kitano S. Quality control by photo documentation for evaluation of laparoscopic and open colectomy with D3 resection for stage II/III colorectal cancer: Japan Clinical Oncology Group Study JCOG 0404. Jpn J Clin Oncol. 2014;44(9):799–806.
25. West NP, Morris EJ, Rotimi O, Cairns A, Finan PJ, Quirke P. Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study. Lancet Oncol. 2008;9(9):857–65.
26. Bertelsen CA, Neuenschwander AU, Jansen JE, Wilhelmsen M, Kirkegaard-Klitbo A, Tenma JR, Bols B, Ingeholm P, Rasmussen LA, Jepsen LV, Iversen ER, Kristensen B, Gögenur I, Danish Colorectal Cancer Group. Disease-free survival after complete mesocolic excision compared with conventional colon cancer surgery: a retrospective, population-based study. Lancet Oncol. 2015;16(2):161–8.
27. Bertelsen CA, Kirkegaard-Klitbo A, Nielsen M, Leotta SM, Daisuke F, Gögenur I. Pattern of colon cancer lymph node metastases in patients undergoing central mesocolic lymph node excision: a systematic review. Dis Colon Rectum. 2016;59(12):1209–21.
28. Liang JT, Lai HS, Huang J, Sun CT. Long-term oncologic results of laparoscopic D3 lymphadenectomy with complete mesocolic excision for right-sided colon cancer with clinically positive lymph nodes. Surg Endosc. 2015;29(8):2394–401.
29. Karachun A, Panaiotti L, Chernikovskiy I, Achkasov S, Gevorkyan Y, Savanovich N, Sharygin G, Markushin L, Sushkov O, Aleshin D, Shakhmatov D, Nazarov I, Muratov I, Maynovskaya O, Olkina A, Lankov T, Ovchinnikova T, Kharagezov D, Kaymakchi D, Milakin A, Petrov A. Short-term outcomes of a multicentre randomized clinical trial comparing D2 versus D3 lymph node dissection for colonic cancer (COLD trial). Br J Surg. 2020;107(5):499–508.
30. Willaert W, Cosyns S, Ceelen W. Biology-based surgery: the extent of lymphadenectomy in cancer of the colon. Eur Surg Res. 2018;59(5–6):371–9.
31. Klein CA. Parallel progression of primary tumours and metastases. Nat Rev Cancer. 2009;9(4):302–12.
32. Fisher B. Biological research in the evolution of cancer surgery: a personal perspective. Cancer Res. 2008;68(24):10007–20.
33. Naxerova K, Reiter JG, Brachtel E, Lennerz JK, van de Wetering M, Rowan A, Cai T, Clevers H, Swanton C, Nowak MA, Elledge SJ, Jain RK. Origins of lymphatic and distant metastases in human colorectal cancer. Science. 2017;357(6346):55–60.

34. Kawada H, Kurita N, Nakamura F, Kawamura J, Hasegawa S, Kotake K, Sugihara K, Fukuhara S, Sakai Y. Incorporation of apical lymph node status into the seventh edition of the TNM classification improves prediction of prognosis in stage III colonic cancer. Br J Surg. 2014;101(9):1143–52.
35. Kang J, Hur H, Min BS, Kim NK, Lee KY. Prognostic impact of inferior mesenteric artery lymph node metastasis in colorectal cancer. Ann Surg Oncol. 2011;18(3):704–10.
36. Hida J, Yasutomi M, Maruyama T, Fujimoto K, Nakajima A, Uchida T, Wakano T, Tokoro T, Kubo R, Shindo K, Hida J, Yasutomi M, Maruyama T, Fujimoto K, Nakajima A, Uchida T, Wakano T, Tokoro T, Kubo R, Shindo K. Indication for using high ligation of the inferior mesenteric artery in rectal cancer surgery. Examination of nodal metastases by the clearing method. Dis Colon Rectum. 1998;41(8):984–7.
37. Sun Y, Chi P, Lin H, Lu X, Huang Y, Xu Z, Huang S, Wang X. Inferior mesenteric artery lymph node metastasis in rectal cancer treated with neoadjuvant chemoradiotherapy: incidence, prediction and prognostic impact. Eur J Surg Oncol. 2017;43(1):85–91.
38. Kuzu MA, İsmail E, Çelik S, Şahin MF, Güner MA, Hohenberger W, Açar Hİ. Variations in the vascular anatomy of the right colon and implications for right-sided colon surgery. Dis Colon Rectum. 2017;60(3):290–8.
39. Lee SJ, Park SC, Kim MJ, Sohn DK, Oh JH. Vascular anatomy in laparoscopic colectomy for right colon cancer. Dis Colon Rectum. 2016;59(8):718–24.
40. Melich G, Jeong DH, Hur H, Baik SH, Faria J, Kim NK, Min BS. Laparoscopic right hemicolectomy with complete mesocolic excision provides acceptable perioperative outcomes but is lengthy--analysis of learning curves for a novice minimally invasive surgeon. Can J Surg. 2014;57(5):331–6.
41. Yamamoto S, Inomata M, Katayama H, Mizusawa J, Etoh T, Konishi F, Sugihara K, Watanabe M, Moriya Y, Kitano S, Japan Clinical Oncology Group Colorectal Cancer Study Group. Short-term surgical outcomes from a randomized controlled trial to evaluate laparoscopic and open D3 dissection for stage II/III colon cancer: Japan Clinical Oncology Group Study JCOG 0404. Ann Surg. 2014;260(1):23–30.
42. Bertelsen CA, Neuenschwander AU, Jansen JE, Kirkegaard-Klitbo A, Tenma JR, Wilhelmsen M, Rasmussen LA, Jepsen LV, Kristensen B, Gögenur I, Copenhagen Complete Mesocolic Excision Study (COMES), Danish Colorectal Cancer Group (DCCG). Short-term outcomes after complete mesocolic excision compared with 'conventional' colonic cancer surgery. Br J Surg. 2016;103(5):581–9.
43. Bertelsen CA, Neuenschwander AU, Jansen JE, Tenma JR, Wilhelmsen M, Kirkegaard-Klitbo A, Iversen ER, Bols B, Ingeholm P, Rasmussen LA, Jepsen LV, Born PW, Kristensen B, Kleif J. 5-year outcome after complete mesocolic excision for right-sided colon cancer: a population-based cohort study. Lancet Oncol. 2019;20(11):1556–65.
44. Athanasiou CD, Markides GA, Kotb A, Jia X, Gonsalves S, Miskovic D. Open compared with laparoscopic complete mesocolic excision with central lymphadenectomy for colon cancer: a systematic review and meta-analysis. Color Dis. 2016;18(7):O224–35.
45. West NP, Kennedy RH, Magro T, Luglio G, Sala S, Jenkins JT, Quirke P. Morphometric analysis and lymph node yield in laparoscopic complete mesocolic excision performed by supervised trainees. Br J Surg. 2014;101(11):1460–7.
46. Kitano S, Inomata M, Mizusawa J, Katayama H, Watanabe M, Yamamoto S, Ito M, Saito S, Fujii S, Konishi F, Saida Y, Hasegawa H, Akagi T, Sugihara K, Yamaguchi T, Masaki T, Fukunaga Y, Murata K, Okajima M, Moriya Y, Shimada Y. Survival outcomes following laparoscopic versus open D3 dissection for stage II or III colon cancer (JCOG0404): a phase 3, randomised controlled trial. Lancet Gastroenterol Hepatol. 2017;2(4):261–8.
47. Sammour T, Malakorn S, Thampy R, Kaur H, Bednarski BK, Messick CA, Taggart M, Chang GJ, You YN. Selective central vascular ligation (D3 lymphadenectomy) in patients undergoing minimally invasive complete mesocolic excision for colon cancer: optimizing the risk-benefit equation. Color Dis. 2020;22(1):53–61.
48. Yang Y, Malakorn S, Zafar SN, Nickerson TP, Sandhu L, Chang GJ. Superior mesenteric vein-first approach to robotic complete mesocolic excision for right colectomy: technique and preliminary outcomes. Dis Colon Rectum. 2019;62(7):894–7.
49. Hameed I, Aggarwal P, Weiser MR. Robotic extended right hemicolectomy with complete mesocolic excision and D3 lymph node dissection. Ann Surg Oncol. 2019;26(12):3990–1.
50. Spinoglio G, Bianchi PP, Marano A, Priora F, Lenti LM, Ravazzoni F, Petz W, Borin S, Ribero D, Formisano G, Bertani E. Robotic versus laparoscopic right colectomy with complete mesocolic excision for the treatment of colon cancer: perioperative outcomes and 5-year survival in a consecutive series of 202 patients. Ann Surg Oncol. 2018;25(12):3580–6.
51. Strey CW, Wullstein C, Adamina M, Agha A, Aselmann H, Becker T, Grützmann R, Kneist W, Maak M, Mann B, Moesta KT, Runkel N, Schafmayer C, Türler A, Wedel T, Benz S. Laparoscopic right hemicolectomy with CME: standardization using the "critical view" concept. Surg Endosc. 2018;32(12):5021–30.
52. Matsuda T, Iwasaki T, Mitsutsuji M, Hirata K, Maekawa Y, Tanaka T, Shimada E, Kakeji Y. Cranial-to-caudal approach for radical lymph node dissection along the surgical trunk in laparoscopic right hemicolectomy. Surg Endosc. 2015;29(4):1001.
53. Freund MR, Edden Y, Reissman P, Dagan A. Iatrogenic superior mesenteric vein injury: the perils of high ligation. Int J Color Dis. 2016;31(9):1649–51.
54. Ishihara S, Otani K, Yasuda K, Nishikawa T, Tanaka T, Tanaka J, Kiyomatsu T, Kawai K, Hata K, Nozawa H, Kazama S, Yamaguchi H, Sunami E, Kitayama J, Sugihara K, Watanabe T. Prognostic impact of lymph node dissection is different for male and female colon cancer patients: a propensity score analysis in a multicenter retrospective study. Int J Color Dis. 2016;31(6):1149–55.
55. Merkel S, Weber K, Matzel KE, Agaimy A, Gohl J, Hohenberger W. Prognosis of patients with colonic carcinoma before, during and after implementation of complete mesocolic excision. Br J Surg. 2016;103:1220–9.
56. Storli KE, Søndenaa K, Furnes B, Nesvik I, Gudlaugsson E, Bukholm I, Eide GE. Short term results of complete (D3) vs. standard (D2) mesenteric excision in colon cancer shows improved outcome of complete mesenteric excision in patients with TNM stages I-II. Tech Coloproctol. 2014;18(6):557–64.
57. Galizia G, Lieto E, De Vita F, Ferraraccio F, Zamboli A, Mabilia A, Auricchio A, Castellano P, Napolitano V, Orditura M. Is complete mesocolic excision with central vascular ligation safe and effective in the surgical treatment of right-sided colon cancers? A prospective study. Int J Color Dis. 2014;29(1):89–97.
58. Lu JY, Xu L, Xue HD, Zhou WX, Xu T, Qiu HZ, Wu B, Lin GL, Xiao Y. The Radical Extent of lymphadenectomy – D2 dissection versus complete mesocolic excision of LAparoscopic Right Colectomy for right-sided colon cancer (RELARC) trial: study protocol for a randomized controlled trial. Trials. 2016;17(1):582.

Part IV

Benign Colorectal Disease

Colonic Diverticular Disease

38

Jason F. Hall and Willem A. Bemelman

Key Concepts

- Our understanding of the pathophysiology of diverticular disease is evolving.
- Many behavioral and environmental factors may influence the development of diverticular disease.
- Some patients with early uncomplicated diverticulitis can be treated without antibiotics.
- The decision to perform elective surgery after several episodes of recurrent uncomplicated diverticulitis should be individualized.
- The decision to perform elective surgery after successful non-operative management of a diverticular abscess should be individualized.
- Laparoscopic lavage can be employed in some patients with Hinchey III diverticulitis.
- Minimally invasive surgery is an acceptable option for managing diverticulitis and its complications.

Introduction

Diverticular disease of the colon is one of the most commonly diagnosed gastrointestinal conditions [1, 2]. Symptomatic diverticular disease represents a spectrum of disease ranging from mild abdominal symptoms to free perforation with peritonitis and sepsis. In the past few decades, there has been renewed enthusiasm for research in this area, and many practice patterns have been challenged. Presentations of diverticulitis are stratified into complicated or uncomplicated diverticulitis.

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Complicated disease includes diverticulitis associated with free perforation, fistula, abscess, stricture, or obstruction. Uncomplicated diverticulitis is defined as diverticulitis which is not associated with any of the aforementioned features. Microperforation with small amounts of contained extraluminal gas, in the absence of a systemic inflammatory response, is considered uncomplicated diverticulitis [3]. Symptomatic uncomplicated diverticular disease (SUDD) is defined as diverticulosis associated with chronic abdominal pain. These patients do not have clinically overt colitis [4].

This chapter focuses on the pathophysiology, evaluation, and treatment of left-sided colonic diverticulitis. Diverticular hemorrhage is associated with diverticulosis and not diverticulitis. The management of diverticular bleeding is covered in the chapter on lower gastrointestinal bleeding.

Epidemiology

The prevalence of diverticula-related illness has risen in the United States over the past few decades [5, 6]. A recent report utilizing information from the National Inpatient Sample (NIS) suggested that the rate of hospitalization for diverticulitis increased from 74.1/100,000 in the year 2000 to 96.0/100,000 in 2008 [1]. Peery recently examined data from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey. In 2010, there were more than 2.7 million discharges in the ambulatory setting associated with a diagnosis of diverticular disease. In 2012 there were >340,000 emergency department visits for diverticulitis [7]. More recent data revealed that in 2014, there were 1.92 million patients diagnosed with diverticular disease in the ambulatory setting [2]. The estimated aggregate national cost of caring for patients with diverticular disease in the emergency setting was $1.6 billion in 2013 [8].

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Histology and Pathology

Many of the microscopic features of diverticulitis include thickening of the lamina propria, mucin depletion, and Paneth cell hyperplasia. Crypt abscesses and ulceration are also observed in some cases [9]. Many of the histologic features are similar to those associated with inflammatory bowel disease [10]. Hinchey developed pathologic criteria to classify the severity of diverticular disease. This classification has been used and is divided into Stages I–IV [11]. Stage I includes patients with diverticulitis and a pericolic abscess. Stage II represents patients with distant abscesses such as a pelvic or retroperitoneal. Stage III and IV are patients with purulent and feculent peritonitis, respectively. A number of attempts have been made to extend the Hinchey criteria to preoperative staging based on CT scan [12].

Role of Fiber

A number of authors have postulated that diverticular disease is related to fiber deficiency. Painter and Burkitt studied colonic transit times and fiber contents in patients in Uganda and the United Kingdom. Patients with a higher fiber intake had more frequent bowel movements, faster colonic transit times, and larger stool volumes. They postulated that a progressively more processed diet removes a large source of fiber from the Western diet [13]. These observations are confounded by a number of factors, including differing life expectancies in industrialized and non-industrialized countries [14]. It is interesting to note that as non-industrialized societies have adopted a more Western diet, a number of authors have noted an increasing prevalence of diverticular disease [15].

A number of studies have examined dietary factors in large patient populations with and without diverticular disease and found an inverse association between incidence and fiber intake [16, 17]. The relative risks associated with fruit and vegetable fiber intake were 0.62 and 0.55, respectively [16]. Fiber found in fruits and vegetables conferred the most protective effect (compared with fiber from cereal) and a high intake of fat and red meat increased the incidence of diverticular disease.

Manousos et al. [17] compared individuals who ate a vegetarian diet to those who predominantly ate meat. The risk of developing diverticular disease was 50-fold greater in meat eaters. In a more recent cohort study of 47,228 male health professionals, popcorn, nut, and seed consumption were inversely correlated with diverticulosis or diverticular complications. This study refutes the adage that "nuts, corn, seeds and popcorn" cause diverticulitis and should be avoided in patients who have had an attack of diverticulitis [18].

Recent data has examined the association between eating a "Western" diet (high in red meat, refined grains, and high-fat dairy) and the risk of developing diverticulitis. In a study of men from the Health Professionals Follow-Up Study, Western diet was associated with an increased risk of diverticulitis when compared to a "prudent approach" (high in fruits, vegetables, and whole grains). Men who had the highest consumption of a Western diet had a multivariate hazard ratio of 1.55 (95% CI: 1.20–1.99) for diverticulitis compared to men in the lowest quintile. The authors suggested that this association was related primarily to the intake of less fiber and more red meat [19].

Another group demonstrated a similar pattern when they studied 907 incident cases of diverticulitis. The cohort was divided into patients with low- and high-risk lifestyles. The components of a low-risk lifestyle are an average red meat intake (<51 g per day), dietary fiber intake in the top 40% of the cohort (about 23 g per day), approximately 2 hours of exercise weekly, normal BMI, and never smoked. These authors demonstrated an inverse linear relationship between the number of low-risk lifestyle factors and the incidence of diverticulitis (p for trend <0.001). Although there were numerous contributors to the lower risk of disease, it appears that fiber has an important role to play in the pathogenesis of this disease [20].

Pathophysiology

Genetics

The progression of normal colonic architecture to diverticulosis and subsequent diverticulitis is not well understood. Multiple lines of evidence suggest that this progression is multifactorial and may involve diet, the microbiome, lifestyle, and genetics [21, 22].

A hereditary basis for diverticular disease was suggested by a number of sources. Hall demonstrated that a family history of diverticular disease is associated with a higher risk of recurrence in patients with an incident case of diverticulitis [23]. Two large, twin studies compared the risk of diverticular disease in monozygotic and dizygotic twins. The risk of developing diverticular disease in a twin pair was significantly higher among monozygotic as opposed to dizygotic twins. These authors estimated that heritability accounted for 40–50% of the risk for diverticular disease [24, 25].

Although these clinical observations have been important in establishing a hereditary predisposition to the disease, localization of a specific gene is still in flux. A recent genome-wide association study identified several gene variants (COLQ, ARHGAP15, and FAM155A) that may contribute to diverticular disease [26]. Many of these genes are thought to influence important cellular functions such as

regulation of immunity, cell adhesion, membrane transport, intestinal motility, and immunity [21].

Other authors have detected several single-nucleotide polymorphisms in the TNFSF15 gene in a cohort of patients with diverticular disease who required surgery [27]. Variations in this gene have also been implicated in the pathogenesis of Crohn's disease [28]. Coble used whole exome sequencing to examine genes that are associated with early onset diverticulitis. LAMB4, a gene localized to the colonic myenteric plexus, was found to alter the function of the enteric nervous system and was proposed as a potential contributor to early onset diverticular disease [29].

Microbiome

The human gastrointestinal tract contains a variety of microorganisms, which harbor approximately 10^{12} to 10^{14} genes. The size of this genome is estimated to be at least 100 times larger than the size of our own genome [30]. The aggregate of these varied microorganisms is referred to as the microbiome. Several authors have postulated that an altered microbiome could influence the pathogenesis of diverticulitis [31].

The human metabolism and inflammatory response can be influenced by genetic information outside our genome. However, insights into the influence of microorganisms on gastrointestinal function and diverticular disease are in their infancy and rely on extrapolation from other disease states. Patients with obesity, colon cancer, irritable bowel syndrome, and inflammatory bowel disease have all been proposed to have altered microbiomes [31–34].

There have been a few small studies that examined the role of the microbiome in the pathogenesis of diverticular disease. There is some evidence that patients with diverticular disease have lower levels of bacteria that metabolize fiber into short-chain fatty acids (SCFA) [35]. SCFA are thought to increase the production of antimicrobial and mucus peptides in the gut. In this way they help to regulate intestinal barrier function and cell proliferation [36].

Other authors have demonstrated that patients who had colonic resections for diverticulitis had higher levels of *Bifidobacterium* when compared to patients with colon cancer or IBD [37]. Another group compared the microbiome of patients with diverticulitis undergoing colonoscopy to asymptomatic controls. They found that the diversity of *Proteobacteria* was higher in patients with diverticulitis [38]. Other studies have demonstrated lower levels of Clostridial organisms in patients with a history of diverticulitis when compared to controls with asymptomatic diverticulosis [39, 40].

The fecal microbiome appears to be important to normal gut function. Its role in the pathogenesis of diverticular disease is still to be determined. It is not clear whether the aforementioned changes are causal or simply associated with the development of the disease.

Risk Factors for Disease

Age

Diverticular disease tends to affect patients during middle age; the incidence rises from 5% at age 40% to 80% by age 80 [3]. Historically, diverticulitis in patients under the age of 50 years was thought to be more virulent and associated with more complications [3]. More contemporary data suggests that young age is not associated with worse clinical outcomes.

Younger patients do have higher recurrence rates compared with older patients. However, younger patients do not seem to have more complicated recurrences [41–43]. This observation is bolstered by data from multiple national databases and systematic reviews, which demonstrate that younger patients are more likely to require repeat hospitalization for diverticulitis, but are not more likely to undergo emergency surgery [44–46].

Sex

Diverticulitis is more common in men. Previous estimates suggest between a 3:2 and 3:1 male-to-female ratio [47]. Others have reported that patients with symptomatic diverticular disease under the age of 65 tend to be male. Hall demonstrated that younger male patients may present with more severe CT findings of diverticulitis than female patients [48]. Etzioni reported that women are at higher risk of treatment failure when managed as outpatients [49]. A similar pattern was noted in a paper examining recurrence of diverticulitis in the National Health Service (United Kingdom) [44].

Physical Activity

Several studies have examined the effect of exercise on the development of diverticular disease [50, 51]. The risk of developing diverticular disease and levels of physical activity appeared to be inversely related. This difference persisted even when the authors adjusted for differences in dietary fiber intake. These findings were later replicated in 2009. Strate demonstrated that men who had >57.4 metabolic equivalent hours per week (MET-h/week) had a RR of 0.75 for diverticulitis and 0.54 for bleeding, as compared with men in the lowest quintile (< or = 8.2 MET-h/week). Vigorous activity appeared to be particularly important and was inversely related to diverticulitis (multivariable RR, 0.66; 95% CI, 0.51–0.86). Nonvigorous activity was not associated with a similar benefit [52].

Smoking

Although the association between smoking and diverticular disease was once considered controversial, more recent data suggests a strong association. One large case-control study demonstrated that smokers had three times the risk of developing complications from diverticular disease compared to nonsmokers [53]. Aune performed a meta-analysis of 5 studies examining 6076 cases of diverticular disease. Current smokers had a much higher incidence of diverticular disease when compared to former smokers and ever smokers. The relative risk associated with developing a complication of diverticular disease (abscess or perforation) was 2.54 for current smokers and 1.83 for ever smokers [54].

Non-steroidal Anti-inflammatory Agents

The use of non-steroidal anti-inflammatory (NSAID) agents has been associated with the development of multiple gastrointestinal complications. A number of cohort studies have consistently demonstrated an association between NSAID use and diverticular disease [55–58]. While the health professionals' follow-up study showed an increased incidence of uncomplicated diverticular disease in patients who used NSAIDs compared with their asymptomatic counterparts, additional studies have also noted an increased risk of complicated diverticulitis with NSAID use [59]. A retrospective study by Corder demonstrated a 23% higher risk of perforating diverticulitis in patients who took NSAIDs regularly compared with patients with diverticular disease who did not take NSAIDs [60]. An additional study of hospitalized patients reported chronic NSAID use to be much higher in patients admitted with diverticular disease than the population as a whole. In addition these patients were four times more likely to develop perforated diverticulitis than patients with no history of NSAID use [61].

Obesity

A number of retrospective case series have noted increased rates of obesity in patients with diverticulitis, particularly patients under the age of 40 [62–64]. In addition, two prospective cohort studies (the Health Professionals Follow-up Study and a Swedish study) have shown an association between body mass index (BMI) and diverticular disease [65–67]. A prospective cohort from the Nurses' health study demonstrated that women who gained ≥20 kg had a 73% increased risk of diverticulitis (95% CI, 27–136%) compared to women who maintained the same weight from age 18 years to the present [68].

Aune examined the role of obesity in a meta-analysis of five studies. They found that the relative risk for an incident episode of diverticulitis was 1.31 for each 5 unit increase in BMI. Similarly, they found that the relative risk for a diverticular complication was 1.20 for each 5 unit increase in BMI [69].

Clinical Manifestations and Physical Findings

Differential Diagnosis

The differential diagnosis for suspected diverticular disease includes appendicitis, bowel obstruction, ruptured aortic aneurysm, colorectal cancer, ischemic colitis, pyelonephritis, gynecologic disease, inflammatory bowel disease, and irritable bowel syndrome. Other diagnoses that should be entertained include endometriosis, tubo-ovarian abscess, pelvic inflammatory disease, ureteral calculi, volvulus, stercoral ulcer, and ovarian torsion. Modern cross-sectional imaging is often helpful in diagnosing many of these clinical entities. An important diagnosis to exclude on initial presentation is colorectal cancer.

History and Physical Examination

Patients with acute diverticulitis typically present with left-sided abdominal pain, fever, and leukocytosis. Physical findings include left lower quadrant tenderness on examination. Patients with free perforation will typically present with diffuse peritonitis and signs of systemic toxicity. When there is a significant phlegmon involving the colon, an abdominal mass may be palpable or appreciated on rectal or pelvic exam. Many patients present with some degree of abdominal distention. Right-sided tenderness can be a presentation in patients who have a redundant sigmoid colon that extends to the right side of the abdomen. Free perforation is associated with diffuse abdominal pain, sometimes referred pain in the shoulder, and shortness of breath.

Many patients often describe changes in their bowel habits such as constipation, or an alteration in stool caliber. Rectal bleeding rarely occurs as a presentation of acute diverticulitis. If present, rectal bleeding is more suggestive of ischemic colitis or inflammatory bowel disease. In complicated presentations, an inflammatory phlegmon can be associated with a small or large bowel obstruction. Patients with an associated obstruction will present with abdominal distention and sometimes nausea and vomiting.

Patients with fistulas may have minimal abdominal complaints and often present initially to a urologist or gynecologist. Colovesical fistulas may present with pneumaturia, pyuria, or fecaluria, while patients with colovaginal fistulas present with vaginal discharge, vaginal air, or stool per vagina.

A number of patients with "chronic" or atypical diverticular disease will present with pain as their predominant symptom in the absence of other physical findings. The pain is typically persistent and boring, and remains constant over long periods of time. It does not tend to be "crampy" in nature as in patients with irritable bowel syndrome, but is difficult to distinguish from this entity [70]. Recently, symptomatic uncomplicated diverticular disease (SUDD) has been used to describe this group of patients. Many patients with SUDD have continuing symptoms and quality of life limitations even after recovery from an acute episode of diverticulitis. Often, there are no imaging findings which correlate with their symptoms [71].

Diagnostic Evaluation

Most laboratory tests are not terribly helpful in the evaluation of acute diverticulitis. Many patients with acute diverticulitis present with leukocytosis. Patients with colovesical fistulas may have an abnormal urinalysis and/or a urine culture with enteric organisms. C-reactive protein (CRP), procalcitonin, and fecal calprotectin have been considered as potential adjuncts in assessing diverticulitis severity [72–74]. In multiple case series, CRP has been examined as a marker of complicated diverticulitis. Much of the available data is limited as the series are small and the suggested cutoff values vary [75–79].

In one study, CRP >150 mg/L significantly discriminated acute uncomplicated from complicated diverticulitis. This study also examined the use of CRP and CT imaging findings. A CRP >150 mg/L and free fluid on CT scan were associated with increased mortality [80]. Another recent study used procalcitonin levels to discriminate between patients with uncomplicated and complicated disease [72]. Although laboratory testing may play an important predictive role in the future, evidence supporting its routine use is limited at present.

Although a number of different modalities have been used to evaluate patients with suspected diverticular disease, computed tomography has emerged as the study of choice. Flat and upright plain films of the abdomen are commonly obtained in the evaluation of the patient with acute abdominal pain to exclude obstruction or free intraperitoneal air. In patients with diverticular disease, the findings of plain films tend to be nonspecific [81]. Ultrasound has not gained wide acceptance in the United States. Contrast enemas are seldom currently used in the evaluation and management of diverticulitis. Water-soluble contrast studies may be useful when an obstructing stricture is suspected.

A CT scan is usually the most useful test in the evaluation of patients with acute abdominal pain. CT findings associated with diverticulitis were first described over 30 years ago. These signs included the presence of diverticula, pericolic fat stranding, colonic wall thickening more than 4 mm, and abscess formation [73]. CT has the ability to stage the severity of disease and may provide a road map for percutaneous drainage of an associated abscess. CT has the added advantage of detecting other intraperitoneal findings including hepatic abscesses, pylephlebitis, small bowel obstruction, colonic strictures/obstruction, and colovesical fistulas.

The first system for classifying the severity of diverticulitis on CT findings to guide clinical management was proposed by Ambrosetti. CT findings consistent with mild diverticulitis included localized wall thickening (>5 mm) and inflammation of the pericolic fat. Severe CT findings were the combination of localized wall thickening and inflammation of the pericolic fat with abscess, extraluminal air, or extraluminal contrast. When the natural history of patients with diverticulitis was stratified by these CT criteria, the authors found that patients with severe CT findings underwent operative intervention more frequently than those patients with mild findings (33% vs. 15%). Patients under 50 years of age with severe findings on CT scan were more likely to have recurrence or complications [74].

In a prospectively collected dataset, patients with findings of severe diverticulitis on CT scan during an index attack treated with antibiotics were more likely to have recurrent attacks of diverticulitis, when compared to patients with mild diverticulitis (39% vs. 14%) [75]. Poletti explored CT and demographic predictors for nonoperative treatment failure in 312 patients with a first episode of left-sided diverticulitis and concluded that the presence of an abscess or extraluminal air >5 cm in diameter was a significant predictor of treatment failure [76].

CT findings which are relevant to clinical management were reclassified based on the Hinchey classification system**.** In grade 0, there is colonic wall thickening but not pericolonic fat stranding. Grade 1a consists of wall thickening and pericolonic fat stranding, while grade 1b includes pericolonic or mesocolic abscess. Patients with grade 2 disease have distant intra-abdominal or pelvic abscesses. Patients with grade 3 and grade 4 disease have purulent and fecal peritonitis, respectively. CT is somewhat limited in distinguishing between patients with grade 3 and grade 4 disease, as purulent and fecal peritonitis often cannot be distinguished on imaging [77].

Kaiser found that disease severity using the modified CT Hinchey classification system correlated with postoperative morbidity and mortality. This group also found that the CT stage correlated with recurrence in patients managed nonoperatively. The presence of a diverticulitis with an associated abscess was one particular factor highly associated with an increased risk of failed nonoperative management [78].

Endoscopic Evaluation

Endoscopic evaluation of the colon is typically recommended following an acute episode of diverticulitis. This

approach is generally advocated to exclude the presence of a malignancy or an alternative diagnosis such as ischemic colitis or inflammatory bowel disease. In actual practice, finding a malignancy is rare. Bryan evaluated 307 patients with flexible sigmoidoscopy (20%) or colonoscopy (80%) following an acute episode of diverticulitis. They found only two patients with colorectal carcinomas [82]. These findings were mirrored by Lau. Of 319 patients who underwent endoscopic evaluation, 26% had polyps (9 polyps >1 cm) and 2.8% were found to have colorectal cancer [83].

Patients with the highest prevalence of malignancy diagnosed after an acute presentation of apparent diverticulitis are those with complicated diverticular disease. A recent systematic review demonstrated that the incidence of malignancy was 7.9% in patients following an attack of complicated diverticulitis and 1.3% following an attack of uncomplicated diverticulitis [84]. Sharma found that the risk of malignancy was 11% in patients with complicated diverticulitis versus 0.7% in those with uncomplicated diverticulitis [85]. A recently published meta-analysis examining 17 studies and 3296 patients demonstrated that the pooled prevalence of colorectal cancer in all patients with diverticulitis was 2.1% (95% CI 1.5–3.1%). In patients with uncomplicated acute diverticulitis, the prevalence of colorectal carcinoma was 0·5 (0·2–1·2) percent [59].

Endoscopic procedures (flexible sigmoidoscopy and colonoscopy) are generally not advocated during an acute episode of diverticulitis. A delay of 6 weeks following resolution of symptoms is typically recommended. This approach is encouraged in order to avoid potential conversion of a sealed microperforation into a free perforation [60]. This position has been questioned by other groups who have demonstrated that colonoscopy during an acute episode of diverticulitis can be safe. However, when colonoscopy is performed in the acute setting, a significant number of the procedures cannot be completed [61, 86].

Cystoscopy or cystography have been used to identify suspected colovesical fistulas associated with diverticulitis. However, in the CT era, the presence of air in the urinary bladder in the absence of instrumentation may be considered diagnostic [87].

Management of Diverticulitis

Acute Uncomplicated Diverticulitis

The number of patients that are admitted for diverticulitis is rising, particularly in the young [1, 88]. Ten percent of these patients develop complications requiring additional management [89]. The vast majority of patients with CT confirmed uncomplicated diverticulitis can be managed without the need for surgery. A number of areas of controversy still exist as new data continues to emerge that influences medical practice.

Antibiotics

Two large randomized trials performed in immunocompetent and stable patients questioned the use of antibiotics for the treatment of uncomplicated diverticulitis (DIABOLO and AVOD). In DIABOLO, a proportion of patients with small abscesses were included. In both trials, there were no differences with respect to development of complicated diverticulitis in the short or long term, nor in rates of recurrent diverticulitis based on antibiotic usage [90–92]. Antibiotic-related complications were reported up to 8% in the DIABOLO trial. Although the aforementioned trials provide level I evidence for non-antibiotic treatment of uncomplicated diverticulitis, there is still not broad agreement in actual practice. The combined SAGES/EAES guideline failed to achieve consensus [93]. The 2020 ASCRS guidelines for the treatment of left-sided diverticulitis are in press and recommend that "selected patients with uncomplicated diverticulitis can be treated without antibiotics/"

Ambulatory Management

Most patients with uncomplicated diverticulitis can be treated in an outpatient setting [94]. General practitioners successfully treat many patients without hospitalization, with low rates of readmission (7%). These patients rarely require percutaneous drainage, and outpatient management is associated with considerable costs savings. Patient selection is paramount. Outpatient treatment candidates should be hemodynamically stable and generally healthy appearing and without major comorbidities or immunosuppression [94, 95].

Dietary Changes

Dietary changes have been applied as non-surgical management of acute uncomplicated diverticulitis. There is little data that suggests that a change in dietary approach can alter the course of diverticulitis. For this reason, the patients should be allowed to have a normal diet as tolerated [96, 97].

Management of Acute Complicated Diverticulitis

Complicated diverticulitis is defined as acute diverticulitis associated with fistula, free perforation, abscess, and/or large bowel obstruction.

Diverticular Abscesses (Hinchey Stages Ib and II)

Literature on the management of diverticular abscesses is difficult to interpret because of significant selection bias. Smaller abscesses (<3 cm) are predominantly treated with antibiotics only, while larger abscesses are treated with percutaneous drainage or even surgery. The failure rates of management of abscesses are therefore difficult to compare.

A recent large multicenter observational study including 447 patients demonstrated a significantly higher rate of treatment failure in the percutaneous drainage group compared to antibiotic treatment (36% vs 24%, $p = 0.013$). In this study, there were more complications in the subgroup of patients with a large or distant abscess (Hinchey 2) [98]. However, the majority of smaller abscesses were treated with antibiotics and the larger ones with percutaneous drainage.

In a systematic review of 7653 patients treated with antibiotics, the overall recurrence rate was 25.5%; in patients treated with percutaneous drainage, the recurrence rate was 15% [99]. Although the optimal role of percutaneous drainage is not completely clear, it may be considered in patients with a diverticular abscess larger than 3 centimeters. Other patients may initially be treated with antibiotics, as may be patients with an abscess inaccessible for percutaneous drainage. Emergent surgery is appropriate for patients who do not respond to standard non-surgical treatments [100–103].

Hinchey Stage III Diverticulitis

Nonoperative Management

Hinchey III diverticulitis is suspected when the CT scan shows free air and free fluid. It is important to tailor the management of perforated diverticulitis toward the patient's clinical condition and CT images. If the patient is clinically stable and without fever, hemodynamic changes, or toxicity, an attempt at antibiotic therapy should be considered. CT scan with the addition of rectal contrast to oral/IV contrast administration can rule out an overt connection between the bowel lumen and the peritoneal cavity (Hinchey IV). There are four case series indicating that in select patients with CT diagnosed perforated diverticulitis, nonoperative management is effective in the majority [104–107].

Laparoscopic Lavage

There have been three randomized trials and numerous cohort studies looking at the efficacy of laparoscopic lavage compared to resectional surgery. In all three trials, the surgical approach was not uniform and the trials examined different primary outcomes [108–110]. In the LOLA trial, the primary outcome was a composite of morbidity and mortality. The primary outcome in the SCANDIV trial was the rate of severe postoperative complications at 90 days (Clavien-Dindo >3a). The DILALA trial compared reoperation rates within 12 months of surgery [108–111].

The LOLA trial was closed early by the data monitoring board because an interim analysis demonstrated an increased rates of serious short-term adverse events in the lavage group (39% vs. 19%, $p = 0.04$) [112]. In addition, the laparoscopic lavage required more surgical re-interventions (20% vs. 7%, $p = 0.12$) and had more abscesses that required drainage (20% vs. 0%, $p = 0.002$). The composite endpoint of morbidity/mortality was comparable between the laparoscopic lavage and sigmoid resection groups at 12 months (67% vs. 60%, $p = 0.58$). Interestingly, 52% of patients in the laparoscopic lavage group did not require any acute or elective surgical intervention, and 74% of patients never required a stoma [112].

In the SCANDIV trial, there was no difference in the rate of severe complications between the groups at 90 days. These results remained consistent at 1 year after surgery [110, 113]. The laparoscopic lavage group had a higher rates of deep surgical site infection (32% vs. 13%, $p = 0.006$) and unplanned reoperation (27% vs. 10%, $p = 0.01$). There were lower rates of superficial wound infection (1% vs. 17%, $p = 0.001$) and stoma formation (14% vs. 42%, $p < 0.001$) in the laparoscopic lavage group. Four patients undergoing laparoscopic lavage were ultimately found to have colon adenocarcinoma.

In the DILALA trial, there was no difference in the rate of early re-interventions (30 days) between the laparoscopic lavage and Hartmann groups (13.2% vs. 17.1%, $p = 0.67$). When long-term results were assessed, the laparoscopic lavage group had a 45% reduction in the risk of undergoing of reoperation within 24 months of surgery [109, 114].

A number of meta-analyses have been performed to summarize the evidence surrounding this technique. Laparoscopic lavage was associated with initial success rate in three out of four patients; similarly, ~3/4 of patients remain stoma free at 1 year. Secondary surgery appears to be necessary in one out of four because of ongoing complaints, who then most often undergo laparoscopic resection. Laparoscopic lavage, however, was associated with a significantly increased risk of intra-abdominal abscess, peritonitis, and future emergency reoperation [108, 110, 111, 115, 116]. Figure 38.1 shows the different outcomes of the three trials at 1 year.

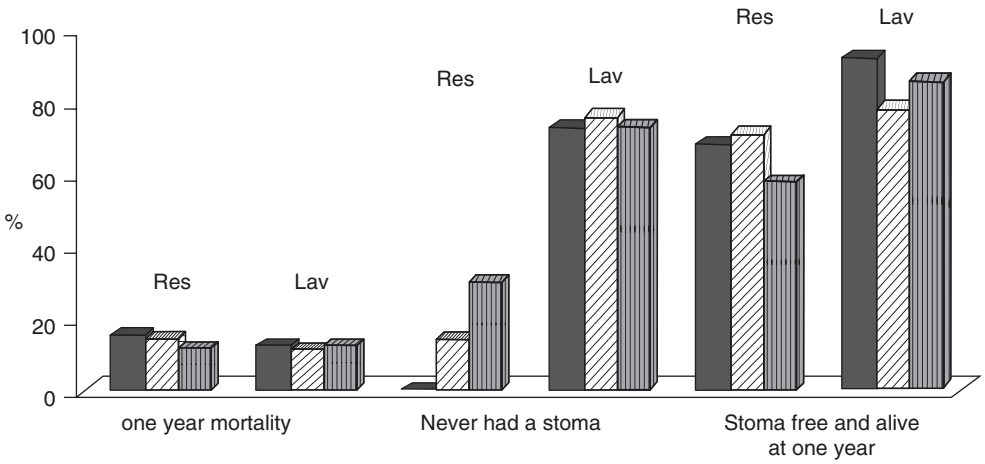

Fig. 38.1 Shows the different outcomes of the three trials at 1 year. (■) DILALA trial [111, 115], LOLA trial [117], (■) SCANDIV trial [110, 116]

The trade-off with lavage is a higher initial re-intervention rate, but overall morbidity and mortality at 1 year and the need for subsequent intervention is similar to resectional surgery. Lavage has been shown to be more cost-effective [118].

Technique: Diagnostic Laparoscopy and Laparoscopic Lavage

During diagnostic laparoscopy, it is important to examine and irrigate the whole peritoneal cavity. When purulent peritonitis is noted, the abdominal cavity is extensively lavaged until the return is clear. Fibrinous exudate may be evacuated if it can be readily removed without damaging the small bowel. The whole peritoneal cavity must be inspected, in particular the pelvis, to ensure there is not an underlying feculent peritonitis. If necessary, the inflammatory mass should be elevated to ensure there is not fecal contamination hidden deep in the pelvis.

Omentum covering the inflamed sigmoid should be carefully removed, but left alone if densely adherent. Laparoscopic lavage for purulent peritonitis is usually effective if the initial diverticular perforation is sealed. Early failure of laparoscopic lavage can be caused by misdiagnosed Hinchey IV diverticulitis or perforated colorectal cancer. Both are conditions that require sigmoid colectomy. Endoscopic insufflation enables detection of a patent perforation.

Hinchey IV Diverticulitis

Hinchey stage IV perforation is characterized by the presence of feculent peritonitis. Resection of the perforated segment is imperative to control sepsis. Segmental resection has been extensively studied in both Hinchey III as well as Hinchey IV perforations. It is important note that in the acute setting, formal mesenteric resection is not necessary unless there is concern for malignancy. If malignancy is suspected, then oncologic resection with high ligation is suggested.

Table 38.1 Randomized trials comparing sigmoidectomy with anastomosis to Hartmann's procedure for Hinchey III and IV perforated diverticulitis (cumulative at 1 year)

	n	Stoma closure		Overall morbidity	
	PA/HP	PA (%)	HP (%)	PA (%)	HP (%)
Oberkoffler [119]	32/30	90	57	84	80
Binda [120]	34/56	65	60	40	69
Bridoux [121]	50/52	96	65	47	48
Lambrichts [122]	64/66	95	72	40	56

In hemodynamically stable and immunocompetent patients, it has been shown that anastomosis after sigmoid colectomy +/− diverting loop ileostomy is safe and associated with a much higher rate of subsequent stoma reversal (Tables 38.1, 38.2, and 38.3). If a definitive anastomosis is to be performed, then a proper diverticular resection should be undertaken to minimize recurrence (see below); if a Hartmann procedure is chosen, only the perforated segment needs be initially resected. When the colostomy is taken down after full recovery of the patient, a proper completion sigmoidectomy can be performed.

Chronic Diverticular Disease

Chronic Uncomplicated Disease

Traditionally, elective sigmoid resection was recommended after the second episode of diverticulitis [124–126]. However, complications of diverticulitis are most likely to occur with a first episode and prophylactic surgery to prevent complicated disease is not justified [23, 127, 128]. Therefore, the decision to perform surgery should be a shared one, which weighs the potential improvement in quality of life against the risks of surgery. The decision for surgery should be individualized, based on severity of symptoms and interference with overall

Table 38.2 Cohort studies comparing sigmoidectomy with anastomosis to Hartmann's procedure for Hinchey III and IV perforated diverticulitis

	N	MR* (%) p<0.0001	MB (%)	MB reversal* (%) p = 0.005	SSI (%)	SSI deep* (%) p = 0.003	Hernia (%)	ReOK (%)	Stoma closure (%)
PA	529	7.9	49	13.5	28	3	11	6	86
HP	366	19.5	41	28.5	29	12	10	16	68

PA Primary anastomosis, *HP* Hartmann's procedure [123]

Table 38.3 Inclusion and exclusion criteria of the trials

	Age limit	Steroids	Pelvic radiotherapy	Dementia	Hemodynamically unstable
Oberkoffler [119]	Not mentioned				
Binda [120]	<18 yrs	–	–	–	–
Bridoux [121]	<18 yrs	–	–	+	+
Lambrichts [122]	<18 >85 yrs	>20 mg	+	+	+

quality of life. Patients should have CT confirmation of the diagnosis of acute diverticulitis, as symptoms from irritable bowel syndrome may mimic ongoing inflammation or recurrent attacks. A randomized study comparing optimal conservative management versus surgery for ongoing complaints or recurrent attacks showed superior quality of life with surgery, despite a relatively high complication rate (DIRECT trial) [129].

The Young

Younger patients do not appear to have more virulent disease than their older counterparts. However, the younger patients have a higher lifetime risk of developing recurrent disease owing to the greater number of remaining years at risk [130]. The relative risk of having an emergent operation in the younger cohort was slightly higher in a systematic review (7.3% vs. 4.9%) [131]. However, this may represent a more aggressive approach to this cohort or a higher rate of misdiagnosis (e.g., appendicitis), rather than the nature of disease.

The Immunocompromised

Complicated diverticulitis may be more aggressive in immunocompromised patients, with a higher incidence of free perforation [132, 133]. However, overall, the incidence of complicated diverticulitis is only slightly higher (1%) in this cohort [134]. The same individualized assessment and approach toward elective resection after an acute episode of diverticulitis appears appropriate.

Fistula

Complicated diverticular disease can be associated with fistulas to adjacent organs. Diverticular fistulas typically form when a diverticular abscess decompresses through a nearby viscus. Colovesical fistulas are characterized by pneumaturia, fecaluria, and recurrent urinary tract infections. Cross-sectional imaging revealing air in the bladder or a urinary culture with a multiple gut microorganism is usually diagnostic in patients with diverticulitis. Colovesical fistulas may also be identified on cystoscopy. Most patients who are medically fit should be offered surgery to avoid recurrent urosepsis.

Colovaginal fistulas typically arise in patients who have had prior hysterectomies. Most patients will complain of passing gas or stool per vagina. Cross-sectional imaging typically is sufficient for diagnosis. Most patients with a significant colovaginal fistula will desire repair because of the associated distressing symptoms and drainage.

Colocutaneous fistula usually results from a longstanding abscess which drains though the abdominal wall. Initially, these can be managed expectantly. As with other fistulas, patients with significant symptoms usually will require or wish to have an elective operation.

Obstruction

Diverticulitis-related obstructions should be treated surgically. Colonic stenting is generally not successful in benign conditions. It is important to differentiate diverticular stricture from colorectal cancer, owing to the need for oncologic resection in the latter circumstance.

Technical Aspects of Surgery

Approach

Three randomized trials and three meta-analyses have evaluated the application of laparoscopy to sigmoid colectomy for diverticulitis. Two of them showed superiority of the laparoscopic approach compared to open surgery [135–138].

Laparoscopy within an enhanced recovery after surgery program is usually the preferred approach in suitable cases and is associated with earlier recovery and less complications [139]. Pfannenstiel incisions are associated with low incisional hernia rates [140]. In emergency surgery, the evidence is accumulating that a laparoscopic approach may also be of benefit [141].

Transection Margins

Most literature regarding the extent of resection is based on retrospective data and is not very robust. The distal margin of the sigmoidectomy should be the proximal rectum. Colorectal as opposed to colocolic anastomoses have a lower frequency of recurrent disease [142–146]. The proximal margin of the sigmoidectomy should be chosen where the bowel is not diseased, as evidenced by the absence of bowel wall thickening. The presence of diverticula per se should not guide the proximal margin of resection.

Inferior Mesenteric Artery Preservation

If there is suspicion of malignancy, an oncologic resection should be done with appropriate proximal ligation of the inferior mesenteric vessels. In cases where malignancy is not suspected, an extensive mesenteric resection is not necessary. One randomized trial showed improved intestinal function when the mesentery is preserved [147]. Another study reported a lower radiological and clinical leak rate [148]. Both systematic reviews and cohort studies have reported that leak rates are either lower or the same with vessel preserving surgery [149–154]. High pedicle ligation seems therefore warranted in cases where cancer cannot be excluded, whereas IMA preservation may otherwise be beneficial.

Splenic Flexure Mobilization

Routine splenic flexure mobilization has not been tested in a systematic way. Nonetheless, creation of a tension-free, well-vascularized anastomosis is desired. In many cases, mobilization of the flexure is necessary to achieve a tension-free anastomosis. The few studies on this topic suggest that splenic flexure mobilization should be done on an individualized basis, depending on the anatomy, disease extent, and the need for additional length to create a tension-free anastomosis [155, 156]. One study suggested that splenic flexure mobilization is associated with increased risk of superficial surgical site infections (10.6% vs. 8.4%, $p < 0.0002$) [157].

Ureteral Stents

Available evidence suggests that routine ureteral stenting in surgery for diverticular disease is associated with a longer operative time, longer length of stay, and higher costs [158–160]. Analysis of the protective impact of ureteral stents against ureteral injury in the literature is always confounded by selection bias, as higher-risk patients are more likely to receive stents. As such, comparable rates of injury in stent vs no stent groups may actually be evidence to support their efficacy. A selective approach appears appropriate.

Anastomotic Leak Testing

Anastomotic leak testing may be simply performed by instilling air transanally while submerging the anastomosis under saline in the pelvis (air bubble test). A positive result identifies patients at higher risk of having a clinical leak [161, 162]. This allows the surgeon to repair or revise and then retest the anastomosis [163]. A randomized trial comparing leak testing versus no leak testing in 145 colorectal anastomoses showed that leak testing significantly reduced the incidence of postoperative clinical and radiological leaks [164].

Right-Sided Diverticulitis

There are distinct differences between left- and right-sided diverticulitis. While left-sided diverticula consist of a protrusion of the mucosa through the bowel wall and are by definition false diverticula, the right-sided diverticula are most often true diverticula consisting of all layers of the bowel wall. They are more common in Asia [3]. The scarce literature on right-sided diverticulitis suggests that right-sided diverticulitis is less often associated with a complicated course. The management of complicated diverticulitis, be it left- or right-sided, is generally similar [165, 166].

Conclusion

Colonic diverticular disease is associated with a wide spectrum of presentations and treatment options. While many of the current treatment methods have been in use for the greater part of a century, new approaches to treatment continue to evolve. The initial goal of therapy is to control inflammation and infection, if present. Increasingly, attenuation of the inflammatory response itself will become a target of medical therapy. Individualized assessment is the key to surgical decision-making.

References

1. Wheat CL, Strate LL. Trends in hospitalization for diverticulitis and diverticular bleeding in the United States from 2000 to 2010. Clin Gastroenterol Hepatol. 2016;14:96–103.e1.
2. Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL, Jensen ET, Shaheen NJ, Barritt AS, Lieber SR, Kochar B, Barnes EL, Fan YC, Pate V, Galanko J, Baron TH, Sandler RS. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2018. Gastroenterology. 2019;156:254–72.e11.
3. Hall J, Hammerich K, Roberts P. New paradigms in the management of diverticular disease. Curr Probl Surg. 2010;47:680–735.
4. Rezapour M, Ali S, Stollman N. Diverticular disease: an update on pathogenesis and management. Gut Liver. 2018;12:125–32.
5. Heise CP. Epidemiology and pathogenesis of diverticular disease. J Gastrointest Surg. 2008;12:1309–11.
6. Ricciardi R, Baxter NN, Read TE, Marcello PW, Hall J, Roberts PL. Is the decline in the surgical treatment for diverticulitis associated with an increase in complicated diverticulitis? Dis Colon Rectum. 2009;52:1558–63.
7. Peery AF, Crockett SD, Barritt AS, Dellon ES, Eluri S, Gangarosa LM, Jensen ET, Lund JL, Pasricha S, Runge T, Schmidt M, Shaheen NJ, Sandler RS. Burden of gastrointestinal, liver, and pancreatic diseases in the United States. Gastroenterology. 2015;149:1731–41.e3.
8. Bollom A, Austrie J, Hirsch W, Nee J, Friedlander D, Ellingson K, Cheng V, Lembo A. Emergency department burden of diverticulitis in the USA, 2006–2013. Dig Dis Sci. 2017;62:2694–703.
9. A Brian West, NDSG. The pathology of diverticulitis. J Clin Gastroenterol. 2008;42(10):1137–8.
10. Goldstein NS, Leon-Armin C, Mani A. Crohn's colitis-like changes in sigmoid diverticulitis specimens is usually an idiosyncratic inflammatory response to the diverticulosis rather than Crohn's colitis. Am J Surg Pathol. 2000;24(5):668–75.
11. Hinchey EJ, Schaal PG, Richards GK. Treatment of perforated diverticular disease of the colon. Adv Surg. 1978;12:85–109.
12. Wasvary H, Turfah F, Kadro O, Beauregard W. Same hospitalization resection for acute diverticulitis. Am Surg. 1999;65:632–5; discussion 6.
13. Painter NS, Burkitt DP. Diverticular disease of the colon: a deficiency disease of Western civilization. Br Med J. 1971;2:450–4.
14. Commane DM, Arasaradnam RP, Mills S, Mathers JC, Bradburn M. Diet, ageing and genetic factors in the pathogenesis of diverticular disease. World J Gastroenterol. 2009;15:2479–88.
15. Kiguli-Malwadde E, Kasozi H. Diverticular disease of the colon in Kampala, Uganda. Afr Health Sci. 2002;2:29–32.
16. Aldoori WH, Giovannucci EL, Rimm EB, Wing AL, Trichopoulos DV, Willett WC. A prospective study of diet and the risk of symptomatic diverticular disease in men. Am J Clin Nutr. 1994;60:757–64.
17. Manousos O, Day NE, Tzonou A, Papadimitriou C, Kapetanakis A, Polychronopoulou-Trichopoulou A, Trichopoulos D. Diet and other factors in the aetiology of diverticulosis: an epidemiological study in Greece. Gut. 1985;26:544–9.
18. Strate LL, Liu YL, Syngal S, Aldoori WH, Giovannucci EL. Nut, corn, and popcorn consumption and the incidence of diverticular disease. JAMA. 2008;300:907–14.
19. Strate LL, Keeley BR, Cao Y, Wu K, Giovannucci EL, Chan AT. Western dietary pattern increases, and prudent dietary pattern decreases, risk of incident diverticulitis in a prospective Cohort study. Gastroenterology. 2017;152:1023–30.e2.
20. Liu PH, Cao Y, Keeley BR, Tam I, Wu K, Strate LL, Giovannucci EL, Chan AT. Adherence to a healthy lifestyle is associated with a lower risk of diverticulitis among men. Am J Gastroenterol. 2017;112:1868–76.
21. Strate LL, Morris AM. Epidemiology, Pathophysiology, and Treatment of Diverticulitis. Gastroenterology. 2019;156:1282−+.
22. Schafmayer C, Harrison JW, Buch S, Lange C, Reichert MC, Hofer P, Cossais F, Kupcinskas J, von Schonfels W, Schniewind B, Kruis W, Tepel J, Zobel M, Rosendahl J, Jacobi T, Walther-Berends A, Schroeder M, Vogel I, Sergeev P, Boedeker H, Hinrichsen H, Volk A, Erk JU, Burmeister G, Hendricks A, Hinz S, Wolff S, Bottner M, Wood AR, Tyrrell J, Beaumont RN, Langheinrich M, Kucharzik T, Brezina S, Huber-Schonauer U, Pietsch L, Noack LS, Brosch M, Herrmann A, Thangapandi RV, Schimming HW, Zeissig S, Palm S, Focke G, Andreasson A, Schmidt PT, Weitz J, Krawczak M, Volzke H, Leeb G, Michl P, Lieb W, Grutzmann R, Franke A, Lammert F, Becker T, Kupcinskas L, D'Amato M, Wedel T, Datz C, Gsur A, Weedon MN, Hampe J. Genome-wide association analysis of diverticular disease points towards neuromuscular, connective tissue and epithelial pathomechanisms. Gut. 2019;68:854–65.
23. Hall JF, Roberts PL, Ricciardi R, Read T, Scheirey C, Wald C, Marcello PW, Schoetz DJ. Long-term follow-up after an initial episode of diverticulitis: what are the predictors of recurrence? Dis Colon Rectum. 2011;54:283–8.
24. Granlund J, Svensson T, Olen O, Hjern F, Pedersen NL, Magnusson PK, Schmidt PT. The genetic influence on diverticular disease–a twin study. Aliment Pharmacol Ther. 2012;35:1103–7.
25. Strate LL, Erichsen R, Baron JA, Mortensen J, Pedersen JK, Riis AH, Christensen K, Sorensen HT. Heritability and familial aggregation of diverticular disease: a population-based study of twins and siblings. Gastroenterology. 2013;144:736−+.
26. Sigurdsson S, Alexandersson KF, Sulem P, Feenstra B, Gudmundsdottir S, Halldorsson GH, Olafsson S, Sigurdsson A, Rafnar T, Thorgeirsson T, Sorensen E, Nordholm-Carstensen A, Burcharth J, Andersen J, Jorgensen HS, Possfelt-Moller E, Ullum H, Thorleifsson G, Masson G, Thorsteinsdottir U, Melbye M, Gudbjartsson DF, Stefansson T, Jonsdottir I, Stefansson K. Sequence variants in ARHGAP15, COLQ and FAM155A associate with diverticular disease and diverticulitis. Nat Commun. 2017;8:15789.
27. Connelly TM, Berg AS, Hegarty JP, Deiling S, Brinton D, Poritz LS, Koltun WA. The TNFSF15 gene single nucleotide polymorphism rs7848647 is associated with surgical diverticulitis. Ann Surg. 2014;259:1132–7.
28. Connelly TM, Choi CS, Berg AS, Harris L 3rd, Coble J, Koltun WA. Diverticulitis and Crohn's disease have distinct but overlapping tumor necrosis superfamily 15 haplotypes. J Surg Res. 2017;214:262–9.
29. Coble JL, Sheldon KE, Yue F, Salameh TJ, Harris LR III, Deiling S, Ruggiero FM, Eshelman MA, Yochum GS, Koltun WA, Gerhard GS, Broach JR. Identification of a rare LAMB4 variant associated with familial diverticulitis through exome sequencing. Hum Mol Genet. 2017;26:3212–20.
30. Gill SR, Pop M, DeBoy RT, Eckburg PB, Turnbaugh PJ, Samuel BS, Gordon JI, Relman DA, Fraser-Liggett CM, Nelson KE. Metagenomic analysis of the human distal gut microbiome. Science. 2006;312(5778):1355–9.
31. Daniels L, Philipszoon LE, Boermeester MA. A hypothesis: important role for gut microbiota in the etiopathogenesis of diverticular disease. Dis Colon Rectum. 2014;57:539–43.
32. Strate LL. Lifestyle factors and the course of diverticular disease. Digest Dis (Basel, Switzerland). 2012;30:35–45.
33. Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterol. 2012;143(4):913–6.e7.

34. Backhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U S A. 2004;101:15718–23.
35. Barbara G, Scaioli E, Barbaro MR, Biagi E, Laghi L, Cremon C, Marasco G, Colecchia A, Picone G, Salfi N, Capozzi F, Brigidi P, Festi D. Gut microbiota, metabolome and immune signatures in patients with uncomplicated diverticular disease. Gut. 2017;66:1252–61.
36. Koh A, De Vadder F, Kovatcheva-Datchary P, Backhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell. 2016;165:1332–45.
37. Gueimonde M, Ouwehand A, Huhtinen H, Salminen E, Salminen S. Qualitative and quantitative analyses of the bifidobacterial microbiota in the colonic mucosa of patients with colorectal cancer, diverticulitis and inflammatory bowel disease. World J Gastroenterol. 2007;13:3985–9.
38. Daniels L, Budding AE, de Korte N, Eck A, Bogaards JA, Stockmann HB, Consten EC, Savelkoul PH, Boermeester MA. Fecal microbiome analysis as a diagnostic test for diverticulitis. Eur J Clin Microbiol Infect Dis. 2014;33:1927–36.
39. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci U S A. 2007;104:13780–5.
40. Gevers D, Kugathasan S, Denson LA, Vazquez-Baeza Y, Van Treuren W, Ren B, Schwager E, Knights D, Song SJ, Yassour M, Morgan XC, Kostic AD, Luo C, Gonzalez A, McDonald D, Haberman Y, Walters T, Baker S, Rosh J, Stephens M, Heyman M, Markowitz J, Baldassano R, Griffiths A, Sylvester F, Mack D, Kim S, Crandall W, Hyams J, Huttenhower C, Knight R, Xavier RJ. The treatment-naive microbiome in new-onset Crohn's disease. Cell Host Microbe. 2014;15:382–92.
41. Li D, de Mestral C, Baxter NN, McLeod RS, Moineddin R, Wilton AS, Nathens AB. Risk of readmission and emergency surgery following nonoperative management of colonic diverticulitis: a population-based analysis. Ann Surg. 2014;260:423–30; discussion 30–1.
42. Katz LH, Guy DD, Lahat A, Gafter-Gvili A, Bar-Meir S. Diverticulitis in the young is not more aggressive than in the elderly, but it tends to recur more often: systematic review and meta-analysis. J Gastroenterol Hepatol. 2013;28:1274–81.
43. van de Wall BJ, Draaisma WA, van Iersel JJ, Consten EC, Wiezer MJ, Broeders IA. Elective resection for ongoing diverticular disease significantly improves quality of life. Dig Surg. 2013;30:190–7.
44. El-Sayed C, Radley S, Mytton J, Evison F, Ward ST. Risk of recurrent disease and surgery following an admission for acute diverticulitis. Dis Colon Rectum. 2018;61:382–9.
45. Mathews SN, Lamm R, Yang J, Kang L, Telem D, Pryor AD, Talamini M, Genua J. Factors associated with repeated health resource utilization in patients with diverticulitis. J Gastrointest Surg. 2017;21:112–20.
46. Hupfeld L, Burcharth J, Pommergaard HC, Rosenberg J. Risk factors for recurrence after acute colonic diverticulitis: a systematic review. Int J Color Dis. 2017;32:611–22.
47. Parks TG. Natural history of diverticular disease of colon. A review of 521 cases. Br Med J. 1969;4:639–&.
48. Hall JF, Roberts PL, Ricciardi R, Marcello PW, Scheirey C, Wald C, Scholz FJ, Schoetz D. Colonic diverticulitis: does age predict severity of disease on CT imaging? Dis Colon Rectum. 2010;53(2):121–5.
49. Etzioni DA, Chiu VY, Cannom RR, Burchette RJ, Haigh PI, Abbas MA. Outpatient treatment of acute diverticulitis: rates and predictors of failure. Dis Colon Rectum. 2010;53:861–5.
50. Aldoori WH, Giovannucci EL, Rimm EB, Wing AL, Trichopoulos DV, Willett WC. A prospective study of diet and the risk of symptomatic diverticular disease in men. Am J Clin Nutr. 1994;60(5):757–64.
51. Heaton KW, Thompson WG. Exercise and diverticular disease. BMJ. 1995;310(6990):1332.
52. Strate LL, Liu YL, Aldoori WH, Giovannucci EL. Physical activity decreases diverticular complications. Am J Gastroenterol. 2009;104:1221–30.
53. Papagrigoriadis S, Macey L, Bourantas N, Rennie JA. Smoking may be associated with complications in diverticular disease. Br J Surg. 1999;86(7):923–6.
54. Aune D, Sen A, Leitzmann MF, Tonstad S, Norat T, Vatten LJ. Tobacco smoking and the risk of diverticular disease – a systematic review and meta-analysis of prospective studies. Color Dis. 2017;19:621–33.
55. Kvasnovsky CL, Papagrigoriadis S, Bjarnason I. Increased diverticular complications with nonsteriodal anti-inflammatory drugs and other medications: a systematic review and meta-analysis. Color Dis. 2014;16:O189–96.
56. Aldoori WH, Giovannucci EL, Rimm EB, Wing AL, Willett WC. Use of acetaminophen and nonsteroidal anti-inflammatory drugs: a prospective study and the risk of symptomatic diverticular disease in men. Arch Fam Med. 1998;7:255–60.
57. Humes DJ, Fleming KM, Spiller RC, West J. Concurrent drug use and the risk of perforated colonic diverticular disease: a population-based case-control study. Gut. 2011;60:219–24.
58. Strate LL, Liu YL, Huang ES, Giovannucci EL, Chan AT. Use of aspirin or nonsteroidal anti-inflammatory drugs increases risk for diverticulitis and diverticular bleeding. Gastroenterology. 2011;140:1427–33.
59. Rottier SJ, van Dijk ST, Unlu C, van Geloven AAW, Schreurs WH, Boermeester MA. Complicated disease course in initially computed tomography-proven uncomplicated acute diverticulitis. Surg Infect (Larchmt). 2019;20(6):453–9.
60. Lahat A, Yanai H, Sakhnini E, Menachem Y, Bar-Meir S. Role of colonoscopy in patients with persistent acute diverticulitis. World J Gastroenterol. 2008;14:2763–6.
61. Lahat A, Yanai H, Menachem Y, Avidan B, Bar-Meir S. The feasibility and risk of early colonoscopy in acute diverticulitis: a prospective controlled study. Endoscopy. 2007;39:521–4.
62. Sheth AA, Longo W, Floch MH. Diverticular disease and diverticulitis. Am J Gastroenterol. 2008;103(6):1550–6.
63. Dobbins C, DeFontgalland D, Duthie G, Wattchow DA. The relationship of obesity to the complications of diverticular disease. Colorectal Dis. 2006;8(1):37–40.
64. Zaidi E, Daly B. CT and clinical features of acute diverticulitis in an urban U.S. population: rising frequency in young, obese adults. JR Am J Roentgenol. 2006;187(3):689–94.
65. Aldoori WH, Giovannucci EL, Rimm EB, Wing AL, Trichopoulos DV, Willett WC. A prospective study of alcohol, smoking, caffeine, and the risk of symptomatic diverticular disease in men. Ann Epidemiol. 1995;5(3):221–8.
66. Strate LL, Liu YL, Aldoori WH, Syngal S, Giovannucci EL. Obesity increases the risks of diverticulitis and diverticular bleeding. Gastroenterology. 2009;136:115–22.e1.
67. Rosemar A, Angerås U, Rosengren A. Body mass index and diverticular disease: a 28-year follow-up study in men. Dis Colon Rectum. 2008;51(4):450–5.
68. Ma W, Jovani M, Liu PH, Nguyen LH, Cao Y, Tam I, Wu K, Giovannucci EL, Strate LL, Chan AT. Association between obesity and weight change and rsk of diverticulitis in women. Gastroenterology. 2018;155, 58:–66.e4.
69. Aune D, Sen A, Leitzmann MF, Norat T, Tonstad S, Vatten LJ. Body mass index and physical activity and the risk of diver-

ticular disease: a systematic review and meta-analysis of prospective studies. Eur J Nutr. 2017;56:2423–38.
70. Horgan AF, McConnell EJ, Wolff BG, The S, Paterson C. Atypical diverticular disease. Dis Colon Rectum. 2001;44(9):1315–8.
71. Rezapour M, Ali S, Stollman N. Diverticular disease: an udate on pathogenesis and management. Gut Liver. 2018;12(2):125–32.
72. Jeger V, Pop R, Forudastan F, Barras JP, Zuber M, Piso RJ. Is there a role for procalcitonin in differentiating uncomplicated and complicated diverticulitis in order to reduce antibiotic therapy? A prospective diagnostic cohort study. Swiss Med Weekly. 2017;147:w14555.
73. Kiewiet JJ, Andeweg CS, Laurell H, Daniels L, Lameris W, Reitsma JB, Hendriks JC, Bleichrodt RP, van Goor H, Boermeester MA. External validation of two tools for the clinical diagnosis of acute diverticulitis without imaging. Digest Liver Dis. 2014;46:119–24.
74. Tursi A, Elisei W, Picchio M, Brandimarte G. Increased faecal calprotectin predicts recurrence of colonic diverticulitis. Int J Color Dis. 2014;29:931–5.
75. Hogan J, Sehgal R, Murphy D, O'Leary P, Coffey JC. Do inflammatory indices play a role in distinguishing between uncomplicated and complicated diverticulitis? Dig Surg. 2017;34:7–11.
76. Kechagias A, Rautio T, Kechagias G, Makela J. The role of C-reactive protein in the prediction of the clinical severity of acute diverticulitis. Am Surg. 2014;80:391–5.
77. Kechagias A, Rautio T, Makela J. The early C-reactive protein trend does not hve a role in monitoring acute diverticulitis progression. Chirurgia (Bucharest, Romania : 1990). 2016;111:43–7.
78. Makela JT, Klintrup K, Rautio T. The role of low CRP values in the prediction of the development of acute diverticulitis. Int J Color Dis. 2016;31:23–7.
79. Nizri E, Spring S, Ben-Yehuda A, Khatib M, Klausner J, Greenberg R. C-reactive protein as a marker of complicated diverticulitis in patients on anti-inflammatory medications. Tech Coloproctol. 2014;18:145–9.
80. Makela JT, Klintrup K, Takala H, Rautio T. The role of C-reactive protein in prediction of the severity of acute diverticulitis in an emergency unit. Scand J Gastroenterol. 2015;50:536–41.
81. Rosen MP, Sands DZ, Longmaid HE, Reynolds KF, Wagner M, Raptopoulos V. Impact of abdominal CT on the management of patients presenting to the emergency department with acute abdominal pain. AJR Am J Roentgenol. 2000;174(5):1391–6.
82. van de Wall BJ, Reuling EM, Consten EC, van Grinsven JH, Schwartz MP, Broeders IA, Draaisma WA. Endoscopic evaluation of the colon after an episode of diverticulitis: a call for a more selective approach. Int J Color Dis. 2012;27:1145–50.
83. Lau KC, Spilsbury K, Farooque Y, Kariyawasam SB, Owen RG, Wallace MH, Makin GB. Is colonoscopy still mandatory after a CT diagnosis of left-sided diverticulitis: can colorectal cancer be confidently excluded? Dis Colon Rectum. 2011;54:1265–70.
84. Meyer J, Orci LA, Combescure C, Balaphas A, Morel P, Buchs NC, Ris F. Risk of colorectal cancer in patients with acute diverticulitis: a systematic review and meta-analysis of observational studies. Clin Gastroenterol Hepatol. 2019;17:1448–56.e17.
85. Sharma PV, Eglinton T, Hider P, Frizelle F. Systematic review and meta-analysis of the role of routine colonic evaluation after radiologically confirmed acute diverticulitis. Ann Surg. 2014;259:263–72.
86. Sakhnini E, Lahat A, Melzer E, Apter S, Simon C, Natour M, Bardan E, Bar-Meir S. Early colonoscopy in patients with acute diverticulitis: results of a prospective pilot study. Endoscopy. 2004;36:504–7.
87. Touzios JG, Dozois EJ. Diverticulosis and acute diverticulitis. Gastroenterol Clin N Am. 2009;38:513–25.
88. Binda GA, Mataloni F, Bruzzone M, Carabotti M, Cirocchi R, Nascimbeni R, Gambassi G, Amato A, Vettoretto N, Pinnarelli L, Cuomo R, Annibale B. Trends in hospital admission for acute diverticulitis in Italy from 2008 to 2015. Tech Coloproctol. 2018;22:597–604.
89. Bolkenstein HE, van Dijk ST, Consten ECJ, Heggelman BGF, Hoeks CMA, Broeders I, Boermeester MA, Draaisma WA. Conservative treatment in diverticulitis patients with pericolic extraluminal air and the role of antibiotic treatment. J Gastrointest Sur. 2019;23(11):2269–76.
90. Chabok A, Pahlman L, Hjern F, Haapaniemi S, Smedh K. Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. Br J Surg. 2012;99:532–9.
91. Daniels L, Ünlü Ç, de Korte N, van Dieren S, Stockmann HB, Vrouenraets BC, Consten EC, van der Hoeven JA, Eijsbouts QA, Faneyte IF, Bemelman WA, Dijkgraaf MG, Boermeester MA, Dutch Diverticular Disease (3D) Collaborative Study Group. Randomized clinical trial of observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis. Br J Surg.
92. van Dijk ST, Daniels L, Unlu C, de Korte N, van Dieren S, Stockmann HB, Vrouenraets BC, Consten EC, van der Hoeven JA, Eijsbouts QA, Faneyte IF, Bemelman WA, Dijkgraaf MG, Boermeester MA. Long-term effects of omitting antibiotics in uncomplicated acute diverticulitis. Am J Gastroenterol. 2018;113:1045–52.
93. Francis NK, Sylla P, Abou-Khalil M, Arolfo S, Berler D, Curtis NJ, Dolejs SC, Garfinkle R, Gorter-Stam M, Hashimoto DA, Hassinger TE, CJL M, Pucher PH, Schuermans V, Arezzo A, Agresta F, Antoniou SA, Arulampalam T, Boutros M, Bouvy N, Campbell K, Francone T, Haggerty SP, Hedrick TL, Stefanidis D, Truitt MS, Kelly J, Ket H, Dunkin BJ, Pietrabissa A. EAES and SAGES 2018 consensus conference on acute diverticulitis management: evidence-based recommendations for clinical practice. Surg Endosc. 2019;33:2726–41.
94. Biondo S, Golda T, Kreisler E, Espin E, Vallribera F, Oteiza F, Codina-Cazador A, Pujadas M, Flor B. Outpatient versus hospitalization management for uncomplicated diverticulitis: a prospective, multicenter randomized clinical trial (DIVER Trial). Ann Surg. 2014;259:38–44.
95. van Dijk ST, Bos K, de Boer MGJ, Draaisma WA, van Enst WA, Felt RJF, Klarenbeek BR, Otte JA, Puylaert J, van Geloven AAW, Boermeester MA. A systematic review and meta-analysis of outpatient treatment for acute diverticulitis. Int J Color Dis. 2018;33:505–12.
96. van de Wall BJ, Draaisma WA, van Iersel JJ, van der Kaaij R, Consten EC, Broeders IA. Dietary restrictions for acute diverticulitis: evidence-based or expert opinion? Int J Color Dis. 2013;28:1287–93.
97. Stam MA, Draaisma WA, van de Wall BJ, Bolkenstein HE, Consten EC, Broeders IA. An unrestricted diet for uncomplicated diverticulitis is safe: results of a prospective diverticulitis diet study. Color Dis. 2017;19:372–7.
98. Lambrichts DPV, Bolkenstein HE, van der Does D, Dieleman D, Crolla R, Dekker JWT, van Duijvendijk P, Gerhards MF, Nienhuijs SW, Menon AG, de Graaf EJR, Consten ECJ, Draaisma WA, Broeders I, Bemelman WA, Lange JF. Multicentre study of non-surgical management of diverticulitis with abscess formation. Br J Surg. 2019;106:458–66.
99. Gregersen R, Mortensen LQ, Burcharth J, Pommergaard HC, Rosenberg J. Treatment of patients with acute colonic diverticulitis complicated by abscess formation: a systematic review. Int J Surg. 2016:35.
100. Vennix S, Morton DG, Hahnloser D, Lange JF, Bemelman WA. Systematic review of evidence and consensus on diverticuli-

tis: an analysis of national and international guidelines. Color Dis. 2014;16:866–78.
101. Brandt D, Gervaz P, Durmishi Y, Platon A, Morel P, Poletti PA. Percutaneous CT scan-guided drainage vs. antibiotherapy alone for Hinchey II diverticulitis: a case-control study. Dis Colon Rectum. 2006;49:1533–8.
102. Kumar RR, Kim JT, Haukoos JS, Macias LH, Dixon MR, Stamos MJ, Konyalian VR. Factors affecting the successful management of intra-abdominal abscesses with antibiotics and the need for percutaneous drainage. Dis Colon Rectum. 2006;49:183–9.
103. Ambrosetti P, Chautems R, Soravia C, Peiris-Waser N, Terrier F. Long-term outcome of mesocolic and pelvic diverticular abscesses of the left colon: a prospective study of 73 cases. Dis Colon Rectum. 2005;48:787–91.
104. Costi R, Cauchy F, Le Bian A, Honart JF, Creuze N, Smadja C. Challenging a classic myth: pneumoperitoneum associated with acute diverticulitis is not an indication for open or laparoscopic emergency surgery in hemodynamically stable patients. A 10-year experience with a nonoperative treatment. Surg Endosc. 2012;26:2061–71.
105. Dharmarajan S, Hunt SR, Birnbaum EH, Fleshman JW, Mutch MG. The efficacy of nonoperative management of aute complicated diverticulitis. Dis Colon Rectum. 2011;54:663–71.
106. Sallinen VJ, Mentula PJ, Leppaniemi AK. Nonoperative management of perforated diverticulitis with extraluminal air is safe and effective in selected patients. Dis Colon Rectum. 2014;57:875–81.
107. Titos-Garcia A, Aranda-Narvaez JM, Romacho-Lopez L, Gonzalez-Sanchez AJ, Cabrera-Serna I, Santoyo-Santoyo J. Nonoperative management of perforated acute diverticulitis with extraluminal air: results and risk factors of failure. Int J Color Dis. 2017;32:1503–7.
108. Vennix S, Musters G, Mulder I, Swank H, Consten E, Belgers E, Geloven A, Gerhards M, Govaert M, Grevenstein W, Hoofwijk A, Kruyt P, Nienhuijs S, Boermeester M, Vermeulen J, Dieren S, Lange J, Bemelman W. Laparoscopic peritoneal lavage or sigmoidectomy for perforated diverticulitis with purulent peritonitis: a multicentre, parallel-group, randomised, open-label trial. Lancet (London, England). 2015; https://doi.org/10.1016/S0140-6736(15)61168-0.
109. Angenete E, Thornell A, Burcharth J, Pommergaard H, Skullman S, Bisgaard T, Jess P, Läckberg Z, Matthiessen P, Heath J, Rosenberg J, Haglind E. Laparoscopic lavage is feasible and safe for the treatment of perforated diverticulitis with purulent peritonitis: the first results from the randomized controlled trial DILALA. Ann Surg. 2017; https://doi.org/10.1097/SLA.0000000000001061.
110. Schultz J, Yaqub S, Wallon C, Blecic L, Forsmo H, Folkesson J, Buchwald P, Körner H, Dahl F, Øresland T. Laparoscopic lavage vs primary resection for acute perforated diverticulitis: the SCANDIV randomized clinical trial. JAMA. 2015; https://doi.org/10.1001/jama.2015.12076.
111. Thornell A, Angenete E, Bisgaard T, Bock D, Burcharth J, Heath J, Pommergaard H, Rosenberg J, Stilling N, Skullman S, Haglind E. Laparoscopic lavage for perforated diverticulitis with purulent peritonitis: a randomized trial. Ann Intern Med. 2016; https://doi.org/10.7326/M15-1210.
112. Vennix S, Musters GD, Mulder IM, Swank HA, Consten EC, Belgers EH, van Geloven AA, Gerhards MF, Govaert MJ, van Grevenstein WM, Hoofwijk AG, Kruyt PM, Nienhuijs SW, Boermeester MA, Vermeulen J, van Dieren S, Lange JF, Bemelman WA. Laparoscopic peritoneal lavage or sigmoidectomy for perforated diverticulitis with purulent peritonitis: a multicentre, parallel-group, randomised, open-label trial. Lancet. 2015;386:1269–77.
113. Schultz J, Wallon C, Blecic L, Forsmo H, Folkesson J, Buchwald P, Korner H, Dahl F, Oresland T, Yaqub S. One-year results of the SCANDIV randomized clinical trial of laparoscopic lavage versus primary resection for acute perforated diverticulitis. Br J Surg. 2017; https://doi.org/10.1002/bjs.10567.
114. Kohl A, Rosenberg J, Bock D, Bisgaard T, Skullman S, Thornell A, Gehrman J, Angenete E, Haglind E. Two-year results of the randomized clinical trial DILALA comparing laparoscopic lavage with resection as treatment for perforated diverticulitis. Br J Surg. 2018;105:1128–34.
115. Angenete E, Bock D, Rosenberg J, Haglind E. Laparoscopic lavage is superior to colon resection for perforated purulent diverticulitis-a meta-analysis. Int J Color Dis. 2017;32:163–9.
116. Schultz JK, Wallon C, Blecic L, Forsmo HM, Folkesson J, Buchwald P, Kørner H, Dahl FA, Øresland T, Yaqub S. One-year results of the SCANDIV randomized clinical trial of laparoscopic lavage versus primary resection for acute perforated diverticulitis. Br J Surg. 2017;104:1382–92.
117. Vennix S, Musters G, Swank H, Mulder I, Consten E, Boermeester M, Dieren S, Lange J, Bemelman W. Laparoscopic peritoneal lavage or sigmoidectomy for generalized peritonitis due to perforated diverticulitis; results: of a multicenter randomised trial (the ladies trial). Surg Endosc Other Interv Tech. 2015; https://doi.org/10.1007/s00464-015-4135-8.
118. Vennix S, Dieren S, Opmeer B, Lange J, Bemelman W. Cost analysis of laparoscopic lavage compared with sigmoid resection for perforated diverticulitis in the Ladies trial. Br J Surg. 2017; https://doi.org/10.1002/bjs.10329.
119. Oberkofler CE, Rickenbacher A, Raptis DA, Lehmann K, Villiger P, Buchli C, Grieder F, Gelpke H, Decurtins M, Tempia-Caliera AA, Demartines N, Hahnloser D, Clavien P-A, Breitenstein S. A multicenter randomized clinical trial of primary anastomosis or Hartmann's procedure for perforated left colonic diverticulitis with purulent or fecal peritonitis. Ann Surg. 2012;256:819–27.
120. Binda GA, Karas JR, Serventi A, Sokmen S, Amato A, Hydo L, Bergamaschi R. Primary anastomosis vs nonrestorative resection for perforated diverticulitis with peritonitis: a prematurely terminated randomized controlled trial. Color Dis. 2012;14:1403–10.
121. Bridoux V, Regimbeau J, Ouaissi M, Mathonnet M, Mauvais F, Houivet E, Schwarz L, Mege D, Sielezneff I, Sabbagh C, Tuech J-J. Hartmann's procedure or primary anastomosis for generalized peritonitis due to perforated diverticulitis: a prospective multicenter randomized trial (DIVERTI). J Am Coll Surg. 2017; https://doi.org/10.1016/j.jamcollsurg.2017.09.004.
122. Lambrichts DPV, Vennix S, Musters GD, Mulder IM, Swank HA, Hoofwijk AGM, Belgers EHJ, Stockmann H, Eijsbouts QAJ, Gerhards MF, van Wagensveld BA, van Geloven AAW, Crolla R, Nienhuijs SW, Govaert M, di Saverio S, D'Hoore AJL, Consten ECJ, van Grevenstein WMU, Pierik R, Kruyt PM, van der Hoeven JB, Steup WH, Catena F, Konsten JM, Vermeulen J, van Dieren S, Bemelman WA, Lange JF. Hartmann's procedure versus sigmoidectomy with primary anastomosis for perforated diverticulitis with purulent or faecal peritonitis (LADIES): a multicentre, parallel-group, randomised, open-label, superiority trial. Lancet Gastroenterol Hepatol. 2019;4:599–610.
123. Gachabayov M, Oberkofler CE, Tuech JJ, Hahnloser D, Bergamaschi R. Resection with primary anastomosis vs nonrestorative resection for perforated diverticulitis with peritonitis: a systematic review and meta-analysis. Color Dis. 2018;20:753–70.
124. Kohler L, Sauerland S, Neugebauer E. Diagnosis and treatment of diverticular disease: results of a consensus development conference. The Scientific Committee of the European Association for Endoscopic Surgery. Surg Endosc. 1999;13:430–6.
125. Wong WD, Wexner SD, Lowry A, Vernava A 3rd, Burnstein M, Denstman F, Fazio V, Kerner B, Moore R, Oliver G, Peters W, Ross T, Senatore P, Simmang C. Practice parameters for the treatment of sigmoid diverticulitis–supporting documentation. The Standards Task Force. The American Society of Colon and Rectal Surgeons. Dis Colon Rectum. 2000;43:290–7.

126. Feingold D, Steele SR, Lee S, Kaiser A, Boushey R, Buie WD, Rafferty JF. Practice parameters for the treatment of sigmoid diverticulitis. Dis Colon Rectum. 2014;57:284–94.
127. Ritz JP, Lehmann KS, Frericks B, Stroux A, Buhr HJ, Holmer C. Outcome of patients with acute sigmoid diverticulitis: multivariate analysis of risk factors for free perforation. Surgery. 2011;149:606–13.
128. Haglund U, Hellberg R, Johnsen C, Hulten L. Complicated diverticular-disease of the sigmoid colon – analysis of short and long-term outcome in 392 patients. Ann Chir Gynaecol. 1979;68:41–6.
129. Wall B, Stam M, Draaisma W, Stellato R, Bemelman W, Boermeester M, Broeders I, Belgers E, Toorenvliet B, Prins H, Consten E. Surgery versus conservative management for recurrent and ongoing left-sided diverticulitis (DIRECT trial): an open-label, multicentre, randomised controlled trial. Lancet Gastroenterol Hepatol. 2017; https://doi.org/10.1016/S2468-1253%2816%2930109-1.
130. Rafferty J, Shellito P, Hyman NH, Buie WD. Practice parameters for sigmoid diverticulitis. Dis Colon Rectum. 2006;49:939–44.
131. van de Wall BJ, Poerink JA, Draaisma WA, Reitsma JB, Consten EC, Broeders IA. Diverticulitis in young versus elderly patients: a meta-analysis. Scand J Gastroenterol. 2013;48:643–51.
132. Biondo S, Borao JL, Kreisler E, Golda T, Millan M, Frago R, Fraccalvieri D, Guardiola J, Jaurrieta E. Recurrence and virulence of colonic diverticulitis in immunocompromised patients. Am J Surg. 2012;204:172–9.
133. Pourfarziani V, Mousavi-Nayeeni SM, Ghaheri H, Assari S, Saadat SH, Panahi F, Noorbala MH, Vasei A, Norouzi AR, Simforoosh N. The outcome of diverticulosis in kidney recipients with polycystic kidney disease. Transplant Proc. 2007;39:1054–6.
134. Oor JE, Atema JJ, Boermeester MA, Vrouenraets BC, Unlu C. A systematic review of complicated diverticulitis in post-transplant patients. J Gastrointest Surg. 2014;18:2038–46.
135. Gervaz P, Inan I, Perneger T, Schiffer E, Morel P. A prospective, randomized, single-blind comparison of laparoscopic versus open sigmoid colectomy for diverticulitis. Ann Surg. 2010;252:3–8.
136. Gervaz P, Mugnier-Konrad B, Morel P, Huber O, Inan I. Laparoscopic versus open sigmoid resection for diverticulitis: long-term results of a prospective, randomized trial. Surg Endosc Other Interv Tech. 2011;25:3373–8.
137. Klarenbeek BR, Veenhof AA, Bergamaschi R, van der Peet DL, van den Broek WT, de Lange ES, Bemelman WA, Heres P, Lacy AM, Engel AF, Cuesta MA. Laparoscopic sigmoid resection for diverticulitis decreases major morbidity rates: a randomized control trial short-term results of the sigma trial. Ann Surg. 2009;249:39–44.
138. Raue W, Paolucci V, Asperger W, Albrecht R, Buchler MW, Schwenk W. Laparoscopic sigmoid resection for diverticular disease has no advantages over open approach: midterm results of a randomized controlled trial. Langenbecks Arch Surg/Deutsche Gesellschaft fur Chirurgie. 2011;396:973–80.
139. Vlug MS, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF, Gerhards MF, van Wagensveld BA, van der Zaag ES, van Geloven AA, Sprangers MA, Cuesta MA, Bemelman WA. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). Ann Surg. 2011;254:868–75.
140. Bartels SA, Vlug MS, Hollmann MW, Dijkgraaf MG, Ubbink DT, Cense HA, van Wagensveld BA, Engel AF, Gerhards MF, Bemelman WA. Small bowel obstruction, incisional hernia and survival after laparoscopic and open colonic resection (LAFA study). Br J Surg. 2014;101:1153–9.
141. Vennix S, Lips DJ, Di Saverio S, van Wagensveld BA, Brokelman WJ, Gerhards MF, van Geloven AA, van Dieren S, Lange JF, Bemelman WA. Acute laparoscopic and open sigmoidectomy for perforated diverticulitis: a propensity score-matched cohort. Surg Endosc. 2016;30:3889–96.
142. Benn PL, Wolff BG, Ilstrup DM. Level of anastomosis and recurrent colonic diverticulitis. Am J Surg. 1986;151:269–71.
143. Bergamaschi R, Arnaud JP. Anastomosis level and specimen length in surgery for uncomplicated diverticulitis of the sigmoid. Surg Endosc. 1998;12:1149–51.
144. Bressan A, Marini L, Michelotto M, Frigo AC, Da Dalt G, Merigliano S, Polese L. Risk factors including the presence of inflammation at the resection margins for colorectal anastomotic stenosis following surgery for diverticular disease. Color Dis. 2018;20:923–30.
145. Thaler K, Baig MK, Berho M, Weiss EG, Nogueras JJ, Arnaud JP, Wexner SD, Bergamaschi R. Determinants of recurrence after sigmoid resection for uncomplicated diverticulitis. Dis Colon Rectum. 2003;46:385–8.
146. Wolff BG, Ready RL, MacCarty RL, Dozois RR, Beart RW Jr. Influence of sigmoid resection on progression of diverticular disease of the colon. Dis Colon Rectum. 1984;27:645–7.
147. Masoni L, Mari FS, Nigri G, Favi F, Gasparrini M, Dall'Oglio A, Pindozzi F, Pancaldi A, Brescia A. Preservation of the inferior mesenteric artery via laparoscopic sigmoid colectomy performed for diverticular disease: real benefit or technical challenge: a randomized controlled clinical trial. Surg Endosc. 2013;27:199–206.
148. Tocchi A, Mazzoni G, Fornasari V, Miccini M, Daddi G, Tagliacozzo S. Preservation of the inferior mesenteric artery in colorectal resection for complicated diverticular disease. Am J Surg. 2001;182:162–7.
149. Borchert DH, Schachtebeck M, Schoepe J, Federlein M, Bunse J, Gellert K, Burghardt J. Observational study on preservation of the superior rectal artery in sigmoid resection for diverticular disease. Int J Surg (London, England). 2015;21:45–50.
150. De Nardi P, Gazzetta P. Does inferior mesenteric artery ligation affect outcome in elective colonic resection for diverticular disease? ANZ J Surg. 2018;88:E778–e81.
151. Lehmann RK, Brounts LR, Johnson EK, Rizzo JA, Steele SR. Does sacrifice of the inferior mesenteric artery or superior rectal artery affect anastomotic leak following sigmoidectomy for diverticulitis? A retrospective review. Am J Surg. 2011;201:619–23.
152. Posabella A, Rotigliano N, Tampakis A, von Flue M, Fuglistaler I. Peripheral vs pedicle division in laparoscopic resection of sigmoid diverticulitis: a 10-year experience. Int J Color Dis. 2018;33:887–94.
153. Sohn M, Schlitt HJ, Hornung M, Zulke C, Hochrein A, Moser C, Agha A. Preservation of the superior rectal artery: influence of surgical technique on anastomotic healing and postoperative morbidity in laparoscopic sigmoidectomy for diverticular disease. Int J Color Dis. 2017;32:955–60.
154. Cirocchi R, Popivanov G, Binda GA, Henry BM, Tomaszewski KA, Davies RJ, Di Saverio S. Sigmoid resection for diverticular disease – to ligate or to preserve the inferior mesenteric artery? Results of a systematic review and meta-analysis. Colorectal Dis. 2019;21(6):623–31.
155. Schlussel AT, Wiseman JT, Kelly JF, Davids JS, Maykel JA, Sturrock PR, Sweeney WB, Alavi K. Location is everything: the role of splenic flexure mobilization during colon resection for diverticulitis. Int J Surg (London, England). 2017;40:124–9.
156. Simon T, Orangio GR, Ambroze WL, Armstrong DN, Schertzer ME, Choat D, Pennington EE. Factors associated with complications of open versus laparoscopic sigmoid resection for diverticulitis. JSLS. 2005;9:63–7.
157. Carlson RM, Roberts PL, Hall JF, Marcello PW, Schoetz DJ, Read TE, Ricciardi R. What are 30-day postoperative outcomes following splenic flexure mobilization during anterior resection? Tech Coloproctol. 2014;18:257–64.

158. Chiu AS, Jean RA, Gorecka J, Davis KA, Pei KY. Trends of ureteral stent usage in surgery for diverticulitis. J Surg Res. 2018;222:203–11.e3.
159. Speicher PJ, Goldsmith ZG, Nussbaum DP, Turley RS, Peterson AC, Mantyh CR. Ureteral stenting in laparoscopic colorectal surgery. J Surg Res. 2014;190:98–103.
160. Coakley KM, Kasten KR, Sims SM, Prasad T, Heniford BT, Davis BR. Prophylactic ureteral catheters for colectomy: a national surgical quality improvement program-based analysis. Dis Colon Rectum. 2018;61:84–8.
161. Wu Z, van de Haar RC, Sparreboom CL, Boersema GS, Li Z, Ji J, Jeekel J, Lange JF. Is the intraoperative air leak test effective in the prevention of colorectal anastomotic leakage? A systematic review and meta-analysis. Int J Color Dis. 2016;31:1409–17.
162. Ricciardi R, Roberts PL, Marcello PW, Hall JF, Read TE, Schoetz DJ. Anastomotic leak testing after colorectal resection what are the data? Arch Surg. 2009;144:407–11.
163. Daams F, Wu Z, Lahaye MJ, Jeekel J, Lange JF. Prediction and diagnosis of colorectal anastomotic leakage: a systematic review of literature. World J Gastrointest Surg. 2014;6:14–26.
164. Beard JD, Nicholson ML, Sayers RD, Lloyd D, Everson NW. Intraoperative air testing of colorectal anastomoses – a prospective, randomized trial. Br J Surg. 1990;77:1095–7.
165. Kim SH, Byun CG, Cha JW, Choi SH, Kho YT, Seo DY. Comparative study of the clinical features and treatment for right and left colonic diverticulitis. J Korean Soc Coloproctol. 2010;26:407–12.
166. Chung BH, Ha GW, Lee MR, Kim JH. TLE Management of colonic diverticulitis tailored to location and severity: comparison of the right and the left colon. Ann Coloproctol. 2016;32:228–33.

Large Bowel Obstruction

39

Daniel L. Feingold and Fergal J. Fleming

Key Concepts

- Perforation associated with obstructing colonic neoplasms may either be at the site of the tumor or the cecum based on the law of Laplace.
- Sigmoid volvulus is usually best treated with endoscopic detorsion followed by sigmoid resection.
- Cecal volvulus is typically best managed with urgent right hemicolectomy.
- Neostigmine is often successful in the management of acute colonic pseudo-obstruction.

Introduction

Large bowel obstruction (LBO), a relatively common entity in the practice of colorectal surgery, can be due to any number of underlying pathologies and may be challenging to manage (Table 39.1) The main causes of LBO reviewed in this chapter, colorectal cancer, volvulus, and acute colonic pseudo-obstruction, each have unique operative and nonoperative therapies available; it is important to determine what the ideal intervention is for each individual patient. Patients with LBO are typically older and have comorbidities that influence decision-making. These patients may present along a spectrum of clinical scenarios ranging from subacute, gradual derangements in bowel function that are evaluated in an outpatient setting to life-threatening, complete obstruction with ischemia and even perforation requiring emergency surgery.

Recognizing that a patient is at imminent risk for developing colonic ischemia or perforation requires clinical awareness and a recognition of the underlying etiology. Patients with a more subacute presentation should be counselled about symptoms to watch for that may signify acute worsening of their obstruction (e.g., worsening abdominal distension, clothes not fitting as they had previously, obstipation, abdominal pain, etc.) as these patients may progress to the point of needing emergency intervention and are at risk for worse outcomes. Obstructions due to a diverticular or inflammatory bowel disease stricture, a stercoral process, abdominal wall hernia, or extrinsic compression and obstructions in pediatric patients are not discussed in detail in this chapter.

Table 39.1 Differential diagnosis of large bowel obstruction

Intraluminal	Intramural	Extrinsic
Intussusception	Malignancy	Compressive mass
Impacted material	Colorectal cancer	Neoplasia
Feces (stercoral)	Inflammatory	Abscess
Foreign body	Diverticular disease	Cyst
Bezoar	Ulcerative colitis	Urinary retention
Gallstones	Crohn's disease	Pregnancy
Worms	Iatrogenic/trauma	Cysts
	Radiation	Pseudo-obstruction
	Anastomotic stricture	Volvulus
	Hematoma	Hernia
		Endometriosis
		Pancreatitis

Modified from Gore [77]

Pathophysiology

Bowel obstruction leads to proximal accumulation of gas and fluid, which in turn leads to distension of the gut. This accumulation causes increased intraluminal pressure and bowel distention, which leads to an intermittent increase in peristalsis, followed by a flaccid relaxation as the bowel obstruction persists. Intestinal stasis associated with obstruction facilitates bacterial and endotoxin translocation to the mesenteric lymph nodes and possibly the systemic circulation [1]. LBO

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can be classified according to whether it is deemed partial, complete, simple, or complicated. Partial obstruction indicates there is some liquid and/or gas getting through the obstructive process, while complete obstruction implies that there is no passage of fluid or gas. A simple obstruction suggests that the blood flow to the colon is preserved in the presence of either a partial or complete obstruction. A complicated obstruction suggests that there is compromise to visceral blood flow, leading to bowel wall edema, intestinal ischemia, and possibly bowel necrosis and perforation.

The clinical manifestations of a colon obstruction are related, in part, to the competency of the ileocecal valve. If the ileocecal valve is competent, which is the case in approximately 75% of patients, LBO will result in a closed loop obstruction which cannot decompress retrograde into the small bowel [2]. In this situation, both the afferent and efferent limbs of the colon are occluded, leading to a marked rise in intraluminal pressure; this can progress to impair the arterial blood flow to the bowel. Once ischemia commences, necrosis of the mucosal villi can occur within 4 hours and, if the pressure is not relieved, can progress to transmural infarction and ultimately perforation [3, 4].

Laplace's law states that the intraluminal pressure required to stretch the wall of a hollow tube is inversely proportional to the radius of the tube. As the cecum has the largest diameter of the colon, it requires the least amount of pressure to distend. The actual diameter that potentially puts the cecum at risk varies in the literature [2, 5]. In cases of chronic obstruction, the cecum may accommodate, without an imminent risk of perforation. Thus, the acuity of the presentation and the rapidity of cecal distention may be more important in determining the risk of perforation than the cecal size alone [6].

Clinical Presentation

A thoughtful history and directed physical examination can elicit the acuity of the presentation and help formulate a differential diagnosis. LBO can present acutely, with colic-like abdominal pain reflecting increased peristaltic activity. This can be followed by reduced peristaltic activity as the proximal bowel distends and relaxes so that the initially colicky pain transitions to a more constant pain. Markogiannakis reported on the clinical presentation of a series of 150 patients who presented with acute bowel obstruction. Cessation of flatus (90%), cessation of feces (80.6%), and abdominal distension (65%) were the most common symptoms and physical signs [7]. Vomiting tends to occur later in the clinical course of LBO compared to small bowel obstruction [3, 8]. Progression to bowel ischemia may be suggested by continuous abdominal pain, a tender irreducible mass in a hernia, fever, tachycardia, or signs of peritonitis with toxicity on physical examination. Bowel ischemia presentation can be quite insidious; a high index of suspicion should be maintained if there is clinical evidence of sepsis [8].

A complete blood count, renal profile, and electrolyte studies are appropriate first-line laboratory investigations for patients presenting with LBO. Marked electrolyte disturbances, especially with regard to potassium, can be present due to a combination of third-space losses, dehydration, sepsis, and duration of the obstructive process. An arterial blood gas may be a useful adjunct as a low arterial pH, low serum bicarbonate, and/or high lactic acid level may suggest intestinal ischemia; but the absence of these derangements does not exclude the presence of ischemia.

Initial Management

Irrespective of the underlying cause of the LBO, the tenets of LBO initial management are the same and involve bowel rest with appropriate fluid resuscitation. Patients are kept nil by mouth, and a nasogastric tube can be inserted to decompress the bowel. Nasogastric decompression can potentially reduce the risk of aspiration and provide symptomatic relief by decreasing the volume of gastrointestinal secretions in the proximal bowel. Fluid resuscitation with appropriate electrolyte repletion is required to address fluid and electrolyte losses from third spacing and lack of oral intake. Urine output should be monitored, and regular clinical assessment of fluid requirements should be undertaken in addition to laboratory tests to reassess electrolyte requirements.

Imaging

Imaging plays a crucial role in the evaluation of a patient with suspected LBO. In up to one third of cases where the working diagnosis following history and physical examination is LBO, no mechanical obstruction is found. Conversely, 20% of patients thought to have colonic pseudo-obstruction are actually found to have a mechanical LBO [3, 9]. Abdominal plain films are often the first imaging modality obtained. Supine and nondependent (upright or left lateral decubitus) radiographs can aid in the diagnosis of LBO and evaluate for pneumoperitoneum. Abdominal X-rays have a reported 84% sensitivity and 72% specificity in cases of suspected large bowel obstruction [1]. Normal colonic diameter ranges from 3 to 8 cm with the largest diameter in the cecum; the cecum is typically deemed dilated when its diameter exceeds ~9 cm in an acute presentation, and the remainder of the colon is considered dilated with a diameter greater than ~6 cm [2].

CT is often the imaging modality of choice for eliciting the cause of LBO, with a reported sensitivity and specificity of 96% and 93%, respectively [2, 10]. CT can also accurately

identify potential complications of LBO like pneumoperitoneum, pneumatosis, and portal venous gas. Pneumatosis indicates the breakdown of the mucosal integrity of the bowel wall, and while suggestive of intestinal ischemia, it is not pathognomonic, and this finding should be interpreted within the clinical context. The presence of free intraperitoneal air and/or portal venous gas is associated with a higher likelihood of transmural ischemia and necrosis than pneumatosis alone [11]. CT is the superior modality for the detection of intestinal perforation (95% sensitivity and 90% specificity) compared to plain film radiography (53% sensitivity and 53% specificity) and ultrasound (92% sensitivity and 53% specificity) [12, 13].

CT scanning is an integral modality for the assessment of a patient with possible malignant LBO; the two most common sites of obstruction due to colon cancer are the sigmoid colon and splenic flexure [14]. Meanwhile, the most common site of perforation in this setting is at the cecum reflecting Laplace's law, and perforation occurs in about 3–8% of these patients [15]. Typical imaging features of a malignant LBO include dilated large bowel with a transition point across a short segment of colonic thickening with a distally collapsed bowel. An obstructing tumor can often exhibit a shouldering appearance (Fig. 39.1) [2]. The remainder of the colon should also be assessed for synchronous lesions which occur in 2–7% of patients, although conventional CT scanning is not ideal for this purpose. Evidence of local invasion (e.g., into the bladder, small bowel loops, etc.) and metastatic disease should also be assessed as these can impact the therapeutic plan.

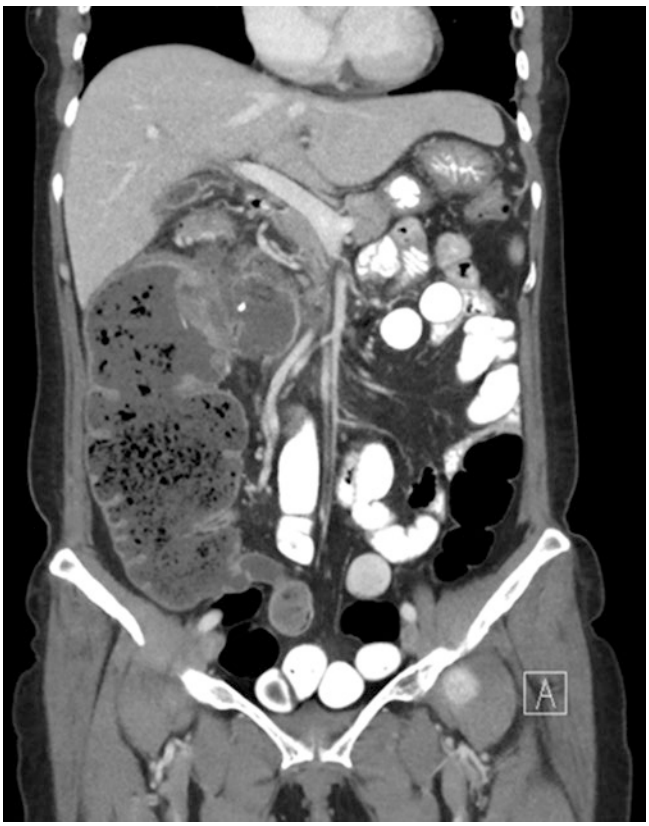

Fig. 39.1 CT scan displaying right colon dilation secondary to an obstructing transverse colon cancer. Note the competent ileocecal valve. (Courtesy of Daniel L. Feingold, MD)

While ultrasound can be as accurate as CT in determining the presence of LBO, CT is preferred where available as it provides more information regarding the likely etiology and can inform about relevant clinical factors as described above [16]. MR imaging is comparable to CT in assessing for bowel obstruction and ischemia [17] and is particularly useful in situations that call for omitting ionizing radiation. A water-soluble contrast enema has a 96% sensitivity and 98% specificity in diagnosing LBO but does not commonly elucidate the etiology of the process [18].

Malignant Large Bowel Obstruction

Malignant LBO occurs in up to 20% of patients with colorectal cancer and carries a significant morbidity and mortality. Multiple studies have shown a three- to fivefold higher rate of 30- and 90-day mortality when patients present acutely with colorectal cancer compared with an elective presentation [19, 20]. This reflects the fact that many of these patients are frail with medical comorbidities and present with obstruction often with concurrent sepsis and/or ischemia. Following resuscitation and nasogastric decompression, further management depends on the patient's response to resuscitation and clinical reassessment. Clinical decision-making should incorporate baseline patient medical comorbidities; relevant history; physical examination; presence of sepsis; tumor location (right versus left colon); radiological staging assessment (e.g., primary tumor resectability, presence of metastatic disease, etc.); feasibility of offering endoscopic stenting, if appropriate; and patient treatment goals.

Perforation

Perforation secondary to a colorectal cancer occurs in approximately 2.6–12% of cases [21]. Perforation can occur at the primary tumor site from tissue necrosis or proximal to the tumor due to ischemia related to dilation, most commonly at the cecum, which is referred to as a diastatic perforation [22]. This represents a surgical emergency as patients can rapidly progress to septic shock and multiorgan failure. With concomitant resuscitation underway, the surgical approach typically involves a laparotomy, washout, and identification of the obstructing mass. The site of perforation may be proximal to the obstruction. In some circumstances, damage control surgery principles

might need to be applied such as in hemodynamically unstable patients (e.g., septic shock requiring inotropic support, severe metabolic acidosis, hypothermia with coagulopathy, etc.) [12]. In such situations, the surgeon may limit the initial intervention to washout of the abdomen, placement of drains, and possibly a defunctioning ostomy and leaving the abdomen open with a plan for definitive resection once the patient's condition has stabilized. If the patient is hemodynamically stable, then the surgical procedure can address both the obstructing tumor and the proximal perforation, where applicable.

In the case of a right-sided tumor with perforation, an oncological right hemicolectomy with ileocolic anastomosis can be considered, though the increased rate of anastomotic leak in such situations (estimated at 3–15%) should be considered. A right hemicolectomy with ileostomy may be the safest approach in this situation as it avoids the potential risk of an anastomotic leak. In the scenario where there is a left-sided obstruction with perforation, an oncological resection with end colostomy should be considered with the proviso that the proximal colon appears viable with no concern for compromise of the cecum. In the situation where there is left-sided obstruction with a proximal colon perforation or concern for colon viability, a total abdominal colectomy should typically be performed.

Right-Sided Colonic Obstruction (Cecum to Distal Transverse Colon)

While the right colon's wide diameter and typical liquid contents render it less vulnerable to obstruction, right-sided cancers still account for approximately 30–40% of cases of malignant LBO [19, 20]. In contrast to left-sided LBO, oncological resection and anastomosis have been traditionally undertaken for right-sided LBO due to the perceived relative ease of the procedure and relatively low risk of anastomotic complications. However, contemporary studies should temper this perception. Mege reported on a prospective audit of 776 patients who presented with malignant LBO secondary to right-sided colon cancer; 92% had the primary tumor resected, and 82% had an anastomosis formed. The high postoperative mortality rate (10%) and anastomotic leak rate (14%) have been replicated in other studies [19, 20, 23]. While most patients will do well with resection and anastomosis, there is no robust data to guide the surgeon regarding which patient might be better served with resection with some form of ostomy (either end or covering loop). Surgeons' intraoperative judgment (including an assessment of intraoperative blood supply and tissue quality) remains integral to the decision-making pertaining to restoring intestinal continuity or creating an ostomy in these complex situations.

Left-Sided Colonic Obstruction (Splenic Flexure to Rectosigmoid)

There has been an evolution in the approach to managing LBO secondary to left-sided colorectal cancer (CRC) over the past 30 years. Creation of a loop colostomy had traditionally been the first stage of a two- or three-stage approach to LBO under these circumstances. Colostomy creation allows decompression of the colon with subsequent tumor resection (second stage) followed by colostomy closure (third stage). The downside of this approach is that the tumor is not resected at the time of the first surgery; several studies have shown equivalence in outcomes between patients undergoing defunctioning colostomy alone and primary tumor resection. A randomized, controlled trial comparing defunctioning loop colostomy and primary resection reported no significant differences in terms of morbidity rate or overall survival between the two approaches [24], a finding endorsed by a Cochrane systematic review [25]. Thus, one would advocate for oncological resection when feasible and reserve loop colostomy formation for very frail patients where an expeditious, palliative procedure to relieve the obstruction is required or in those with unresectable disease.

Surgical dogma has dictated that to undertake a primary anastomosis in the setting of colectomy for a left-sided LBO is too hazardous, as a combination of bowel wall edema and an unprepared colon made fashioning an anastomosis ill-advised. Hence, a Hartmann procedure with resection of the obstructing mass, stapling off the distal segment, and creation of an end colostomy has been one of the most common procedures performed in this setting. Intraoperative colonic irrigation or lavage was developed to address the concerns over anastomosis creation in the setting of an unprepared colon. The system can be accessed via an enterotomy or through the base of an amputated appendix to allow for decompression alone or decompression with antegrade, on-table lavage (OTL) of the colon. Lim randomized 49 patients with malignant left-sided LBO to either intraoperative colonic decompression alone or OTL [26]. There was a significant difference in time taken for OTL (31 minutes) versus that for decompression alone (13 minutes, $p = 0.005$). There was no significant difference in overall morbidity between the groups. In the decompression group, 2 of 25 patients developed an anastomotic leak (8%) requiring reoperation, but none (0/24) in the OTL group leaked. However, this difference was not statistically significant [26].

Segmental Versus Total Colectomy

An extended colectomy with either ileosigmoid anastomosis (subtotal colectomy) or ileorectal anastomosis (total colectomy) has been proposed as an alternative to segmental col-

ectomy and stoma creation as a way to avoid creating an anastomosis in a distended, stool-filled colon. This is a preferable approach in the presence of proximal colonic ischemia, cecal serosal tearing not amenable to primary repair, or a synchronous colon lesion. Multiple case series report outcomes after total colectomy and anastomosis with anastomotic leak rates of 0–10% and mortality rates of 0–11% [27, 28]. One major concern raised about this approach is that of medium- and long-term bowel function after a total colectomy and ileorectal anastomosis compared to that of patients undergoing a segmental colectomy. This question was addressed in the SCOTIA randomized trial where 91 patients with LBO were randomized to either segmental colectomy (SC) with or without on-table lavage (OTL) or subtotal colectomy (STC) [29]. No significant differences in anastomotic leak or overall mortality rates were observed between the SC and STC groups. However, patients in the STC group were significantly more likely to report increased bowel frequency (defined as ≥3 bowel motions per day) compared to the SC group (41% versus 9%, respectively, $p = 0.01$), and this difference persisted at 4-month follow-up [29].

Multiple prospective case series show that primary resection with anastomosis for malignant LBO can be performed with reported anastomotic leak rates of 2–12% [20, 30, 31] which is not dissimilar to outcomes reported after elective left-sided resections (2–8%) [28, 32–34]. However, it should be stressed that non-randomized studies are inherently subject to confounding bias, in that surgeons are more likely to fashion an anastomosis when intraoperative parameters are favorable (e.g., no or minimal contamination, healthy proximal colon, good mesenteric blood supply, negative leak test, etc.) in a physiologically stable patient and are more likely to divert when these factors were not present. The potentially disastrous consequences of an anastomotic leak in such a setting cannot be overstated and may lead to life-threatening sepsis and the inability to proceed with adjuvant chemotherapy in a timely fashion. Thus, risk stratification and surgical judgment are crucial in such cases. The Association of Coloproctology of Great Britain and Ireland (ACPGBI) Malignant LBO audit identified that patient age, American Society of Anesthesiologists (ASA) grade, operative urgency, and cancer stage were all significantly associated with in-hospital postoperative mortality [20].

To date, there is no randomized, controlled trial examining whether a diverting loop ostomy is efficacious after resection and anastomosis for malignant LBO. Kube reported the outcomes of 743 patients who underwent resection for malignant LBO; 58% had primary resection and anastomosis, 30% had a Hartmann procedure, and 12% had a primary resection and anastomosis with diverting loop ileostomy [35]. No significant differences were observed between groups who underwent primary anastomosis with or without a diverting ileostomy in terms of anastomotic leak rate (7% and 8%, respectively) or reoperation (5.6% and 5.7%, respectively).

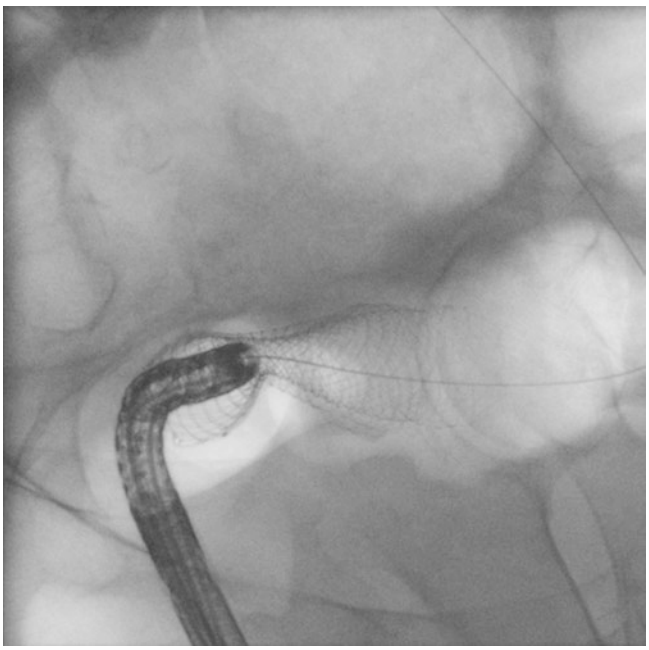

Fig. 39.2 Fluoroscopic image after deploying a self-expanding metallic stent over a guidewire. Note the waist in the mid-portion of the stent signifying the point of the obstructing cancer. (Courtesy of Daniel L. Feingold, MD)

As an alternative to operation, self-expanding metallic stents (SEMS) were originally developed to palliate obstructive symptoms from unresectable tumors or in patients deemed too frail to undergo surgical resection. SEMS involves the endoscopic deployment of a guidewire across the obstructing mass, often facilitated by fluoroscopy, followed by deployment of a stent delivery system (Fig. 39.2). The historically high rate of ostomy formation and morbidity associated with emergent resection for patients with malignant LBO led to studies exploring the deployment of SEMS in these patients to decompress the colon and to act as a bridge to a subsequent elective or semi-elective colonic resection, allowing time for patient optimization before surgery (Fig. 39.3a, b). Observational studies supported the concept that SEMS placement was associated with a reduction in stoma and morbidity rates compared to historical cohorts undergoing surgical resection [36]. However, concerns have been raised about possible tumor cell dissemination after stenting, especially in cases complicated by iatrogenic perforation (Fig. 39.4) [37].

To date there have been eight relatively small randomized, controlled trials comparing SEMS as a bridge to elective surgery compared to emergent surgery. Three of these trials were terminated prematurely due to a higher than anticipated event rate (two in the stenting arm and the third in the surgery arm). The Dutch Stent-In 2 trial was stopped when

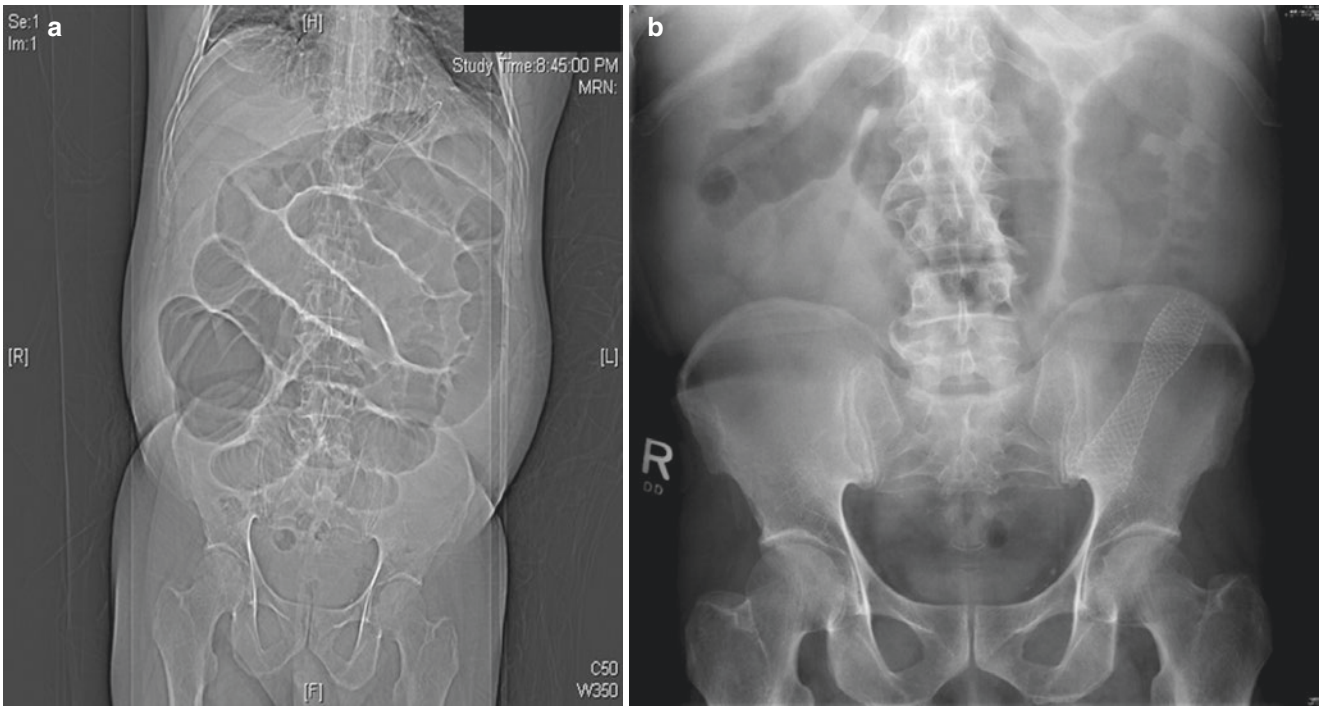

Fig. 39.3 (**a**) CT scan topogram demonstrating small bowel obstruction secondary to a large bowel obstruction in a patient with an obstructing left colon cancer with an incompetent ileocecal valve. (**b**) Abdominal radiograph demonstrating successful decompression after stenting. (Courtesy of Daniel L. Feingold, MD)

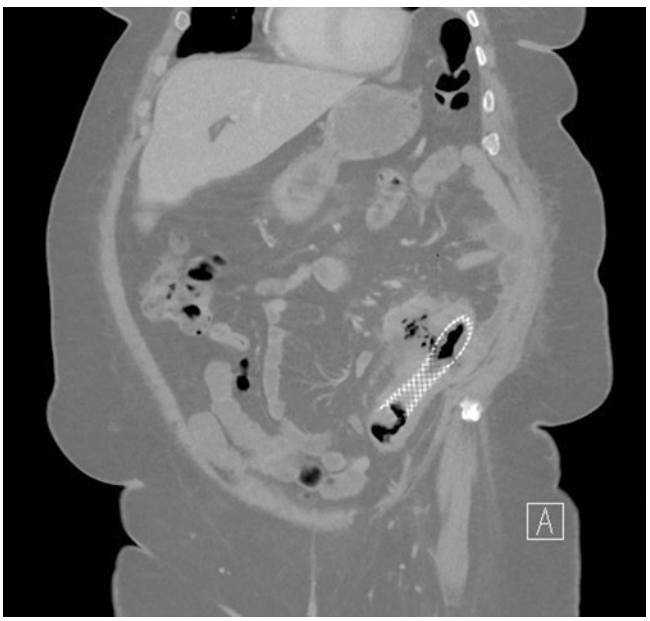

Fig. 39.4 Coronal CT scan image showing a left-sided stent with evidence of perforation. (Courtesy of Daniel L. Feingold, MD)

an interim analysis revealed a higher than anticipated morbidity rate in the SEMS arm, mainly driven by a high rate of perforation (13%) [38]. The relatively high rate of failure to pass a guidewire across the mass (17%) raised the question whether or not appropriate advanced endoscopic personnel were staffing the trial sites. A second randomized, controlled trial by Pirlet was closed early when an analysis found that the primary outcome of decreased ostomy rate was not achieved in the SEMS group compared to the straight-to-surgery group [39]; this was due to the low rate of successful stent deployment. These studies highlight the advanced endoscopic skill level required to safely and effectively deploy this intervention on a consistent basis. Meanwhile, Alcantara prematurely closed their randomized trial due to a high rate of morbidity in the emergent surgery arm [40]. Arezzo [41] undertook a meta-analysis of eight randomized, controlled trials comparing SEMS as a bridge to surgery to straight to emergent surgery (ES). 497 patients were included, and there was no significant difference in 60-day mortality between the SEMS arm (9.6%) and the ES arm (9.9%, RR = 0.99, $p = 0.97$). However, there was a significant difference in the temporary ostomy rate favoring the SEMS arm (33.9%) compared to the ES arm (51.4%, RR = 0.67, $p < 0.001$).

The United Kingdom-based CREST randomized, controlled trial, the largest to date, randomized 246 patients to SEMS as a bridge to surgery versus straight to emergent surgery and was published in abstract form in 2016 [42]. Stenting workshops were held prior to the trial to standardize technical aspects of SEMS deployment. There was no significant difference in 30-day mortality between the SEMS arm (5.3%) and the surgery arm (4.4%) though the overall

ostomy formation rates were markedly lower in the SEMS arm (45%) compared to the surgery arm (69%, $p < 0.001$).

Covered Versus Uncovered Stents

Uncovered stents were traditionally associated with increased rates of stent occlusion due to overgrowth through the stent interstices, while covered stents were thought to inhibit the rate of tumor ingrowth. However, covered stents may not anchor to the bowel well as effectively as an uncovered stent and may migrate more easily [43]. Mashar undertook a meta-analysis of a single randomized trial and nine observational studies comparing the outcomes of uncovered and covered stents. In this study, rates of successful stent deployment, perforation, and bleeding did not differ between the uncovered and covered stent groups, but the uncovered stent group was associated with a lower risk of tumor overgrowth (RR = 0.29, 95% CI 0.09–0.93, $p = 0.04$), decreased risk of stent migration (RR = 0.29, 95% CI 0.17–0.48, $p < 0.001$), and lower need for stent reinsertion (RR = 0.38, 95% CI 0.17–0.86, $p = 0.02$) [43].

Obstructing Rectal Cancer

It is rare for an extraperitoneal rectal cancer to cause LBO, and a locally advanced tumor is usually encountered. In this situation, emergent resection should be avoided, if possible, due to the higher risk of suboptimal surgical resection leading to poor oncological outcomes. Emergent management should focus on relieving the obstruction to facilitate appropriate clinical staging and neoadjuvant therapy followed by definitive surgical management in the form of a TME. SEMS placement in the extraperitoneal rectum is problematic due to the risk of stent migration and tenesmus [44]. A loop colostomy offers effective decompression under these circumstances but may compromise a future elective restorative procedure by damaging the marginal blood supply to the left colon. A loop ileostomy can be employed instead, though one must be circumspect about its use especially if the ileocecal valve is competent, as proximal colonic distension can persist.

Unresectable Disease

Approximately 10–15% of patients with malignant LBO may have unresectable disease at presentation due to local tumor infiltration [28] or metastatic disease or owing to a debilitated state such that it is not prudent to undertake an oncological resection. In the event there is no evidence of bowel ischemia or perforation, a diverting ostomy or a self-expanding metallic stent can be considered to effectively palliate.

Volvulus

Acute colonic volvulus (from the Latin *volvere* meaning to turn or twist) involves axial torsion of a redundant segment of the colon along its mesentery that results in a closed loop obstruction. Over time, the volvulized segment and the colon proximal to the volvulized segment can distend to the point of developing ischemia and perforation unless the patient experiences reduction of the volvulus either spontaneously or due to therapeutic intervention. While any mobile segment of the colon can volvulize, the condition most commonly occurs in the sigmoid colon (~60% of cases) and the cecum (~40% of cases). For unknown reasons, the twisting of sigmoid volvulus most commonly occurs in counterclockwise fashion, while cecal volvulus tends to twist in a clockwise direction. Volvulus of the transverse colon, splenic flexure, or other segments of the colon is rare.

Risk factors for developing colon volvulus include having amenable anatomy (e.g., redundant colon with a relatively narrow mesentery), constipation or colonic dysmotility, prior abdominal surgery, and prior volvulus. While sigmoid volvulus is more common in patients who are male, > 70 years of age, African American, diabetic, and institutionalized or have neuropsychiatric comorbidities, patients with cecal volvulus are typically younger and more likely female [45]. Colonic volvulus is relatively uncommon in the United States where only about 10–15% of large bowel obstructions and about 3–5% of all bowel obstructions are due to volvulus [45, 46]. In areas like Africa, the Middle East, India, Brazil, and South America (the so-called volvulus belt), volvulus is more endemic and may account for as many as 40% of bowel obstructions. The geographic variability in the incidence of volvulus is thought to be multifactorial and due in part to differences in diet, altitude, cultural factors, and certain kinds of infections [45].

Patients with volvulus often present with abdominal distension, decreased bowel function or obstipation, nausea, and abdominal pain. They may develop a secondary small bowel obstruction due to decompression of the colon through an incompetent ileocecal valve and can also present with vomiting. In cases where volvulus progresses to colonic ischemia and perforation, patients present with an abdominal catastrophe and sepsis. While patients presenting with signs and symptoms consistent with volvulus may have a differential diagnosis that includes the spectrum of etiologies for large bowel obstruction, imaging typically confirms the diagnosis. In emergency cases and cases where the imaging is not clear enough to establish the diagnosis, volvulus is confirmed at the time of exploration.

Given the constellation of symptoms and signs that patients can present with, abdominal radiographs and/or CT scan imaging are usually obtained as part of standard evaluation. Plain radiographs or CT topograms can demonstrate

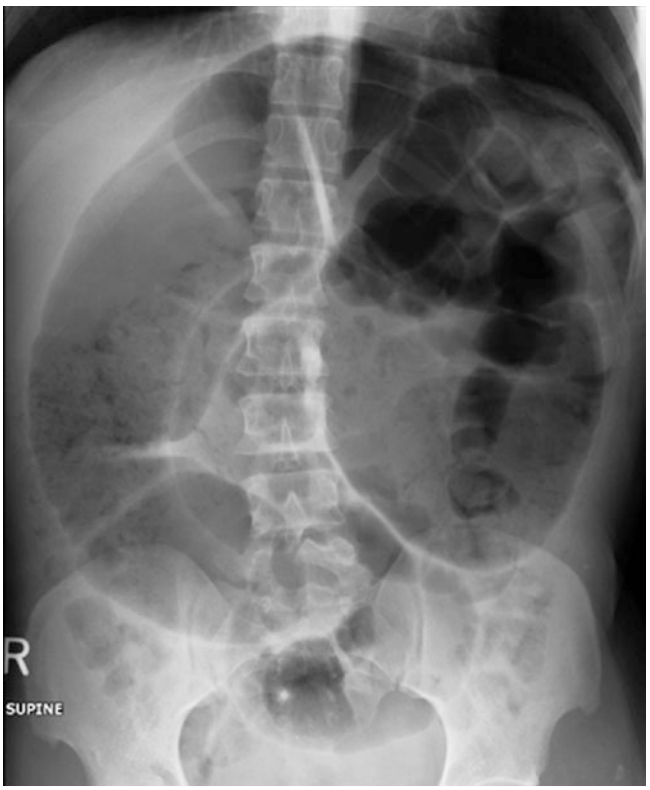

Fig. 39.5 Abdominal radiograph showing a typical sigmoid volvulus prior to decompression. (Courtesy of Daniel L. Feingold, MD)

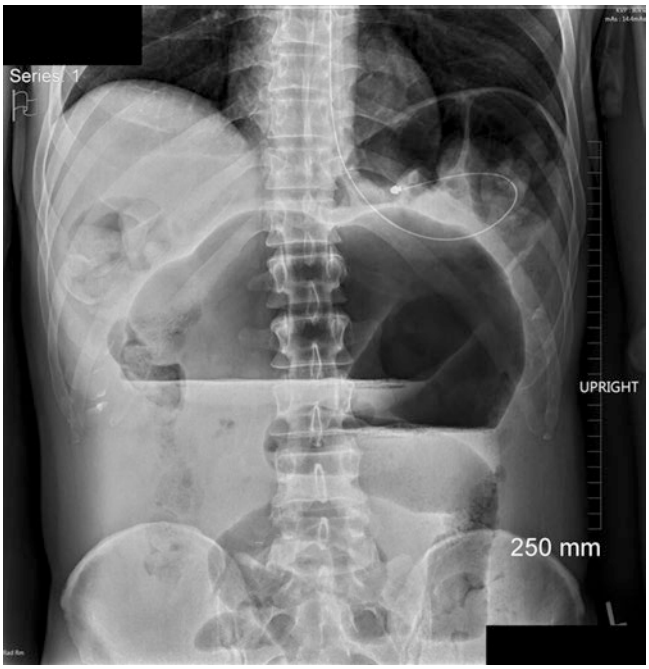

Fig. 39.6 Abdominal radiograph showing typical cecal volvulus. (Courtesy of Daniel L. Feingold, MD)

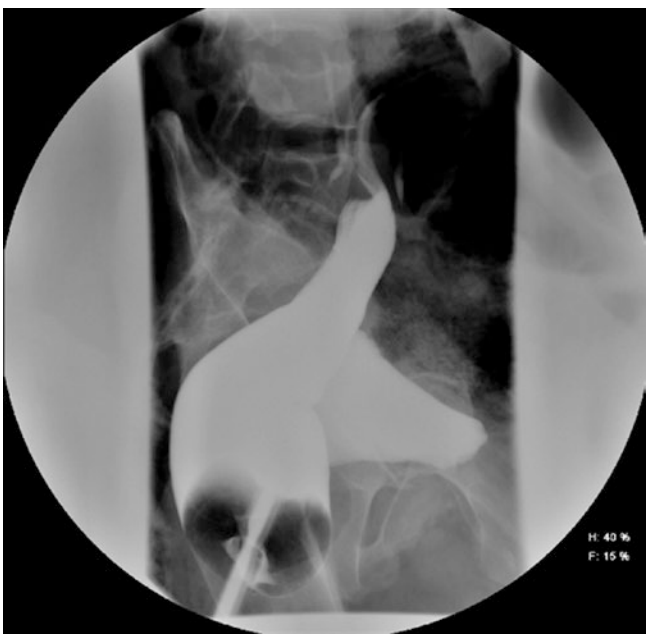

Fig. 39.7 Water-soluble contrast enema demonstrating a bird's beak sign from a sigmoid volvulus. (Courtesy of Daniel L. Feingold, MD)

classic findings consistent with volvulus such as a "coffee bean" or "bent inner tube" which describe the appearance of a massively dilated segment of volvulized colon (Figs. 39.5 and 39.6). The "northern exposure sign" describes the apex of the volvulized sigmoid loop cranial to the transverse colon. Water-soluble contrast enemas can reveal a "bird's beak" sign that reflects the tapering of the colon lumen due to the twisted distal limb of a sigmoid volvulus (Fig. 39.7). CT imaging may also reveal a "swirl" or "whirl" sign depicting the torsed mesenteric vessels due to the presence of a volvulus.

While historically plain radiographs and contrast enemas were used to investigate a possible volvulus, these modalities have effectively been supplanted by CT scanning with multiplanar reconstruction, which can diagnose volvulus with nearly 100% sensitivity and a specificity rate over 90% [47]. Importantly, CT imaging can also identify signs of complicated volvulus related to ischemia or perforation such as intravenous enhancement defects related to arterial occlusion, colon wall thickening related to venous occlusion, pneumatosis intestinalis, free peritoneal fluid, mesenteric or portal venous gas, and pneumoperitoneum. While CT scanning is the preferred modality to diagnose volvulus, depending on the degree of proximal bowel dilation, cross-sectional imaging can be challenging to interpret and may explain why some patients are not diagnosed until the time of exploration.

A cecal bascule is a rare entity distinct from volvulus in that there is no axial torsion across the mesenteric axis; in this situation, the caput of the cecum is displaced anteriorly and folds over the ascending colon closing off the cecum

[48]. In the setting of a competent ileocecal valve, this configuration can cause a closed loop obstruction. Cecal bascule may be demonstrated on cross-sectional imaging but is commonly diagnosed at the time of operative exploration. The evaluation and treatment for a patient with cecal bascule mirror those for cecal volvulus.

Another related anatomic variant that does not meet the criteria for volvulus, mobile cecum syndrome, is a poorly defined entity and postulated to be due to an embryologic abnormality whereby the lateral peritoneal attachments of the ascending colon are absent [49]. It is hypothesized that the resulting mobility of the cecum permits a degree of obstruction that can cause related symptoms. While the proposed treatment for this condition is laparoscopic cecopexy, it is not clear what the criteria are for intervening under these circumstances or what the outcomes are after cecopexy.

There is a paucity of high-quality or population-based evidence detailing the management of this condition. In practice, patients present or are referred in by primary care providers and gastroenterologists with episodic bloating, distension, and pain that resolve after an explosive, decompressive movement and with imaging demonstrating colon dilation but without evidence of volvulus. The concept of a "pre-volvulus" condition is not well described, and operative intervention under these circumstances, despite the insistence of patients or referring doctors, is not generally supported.

Sigmoid Volvulus

Nonoperative Methods for Devolvulizing a Sigmoid Volvulus

Patients with radiographic evidence of sigmoid volvulus without peritonitis, perforation, clinical instability, or sepsis are typically managed with an attempt at detorsion using endoscopy. Patients should be aware that procedures attempting to reduce a sigmoid volvulus risk failure as well as perforation. After obtaining appropriate consent, rigid proctoscopy can be performed at the bedside with the patient in the usual left decubitus position and without sedation. Proctoscopic detorsion is usually well tolerated. The rigid proctoscope is passed under direct visualization to the level of the torsion using air insufflation, as needed. The volvulized mucosa has a typical appearance one would expect from a twisting across the longitudinal axis of the colon which has been described as a pinwheel (Fig. 39.8). With continued insufflation and gentle manipulation of the colon lumen using the tip of the proctoscope, it is usually feasible to untwist the colon and intubate the more proximal sigmoid colon. Once the scope is advanced into what had been the volvulized segment of the colon, the window of the proctoscope is opened to vent the gas and liquid that had been trapped in the obstructed colon. The endoscopist should anticipate this maneuver to produce a dramatic decompression with efflux of the colon contents.

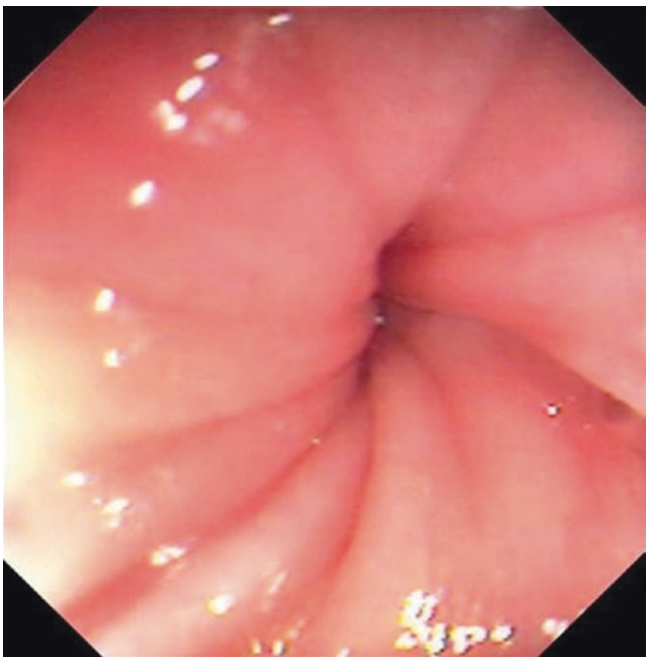

Fig. 39.8 Endoscopic appearance of the mucosa at the level of a sigmoid volvulus. Notice the classic pinwheel appearance of the mucosal folds

Upon successful intubation of the previously volvulized segment, the mucosa of the decompressed colon should be evaluated, and signs of ischemia should prompt a plan for colectomy. In the absence of concerning proctoscopic findings, a transrectal decompression tube should be placed not so much to allow for venting through the tube (this typically clogs with stool) but to stent the previously volvulized segment so that the volvulus does not recur immediately; this affords the patient the ability to continue to decompress and, depending on the individualized plan, to undergo a bowel preparation in anticipation of semi-elective colectomy in the following days. A semi-rigid chest tube passed through the proctoscope and sutured to the perianal skin can adequately function in this capacity. After an apparently successful detorsion, it may be helpful to obtain abdominal radiographs to document the location of the rectal tube and the degree of decompression, as well as to confirm the absence of free air (Fig. 39.9).

As an alternative to rigid proctoscopy or in uncommon cases where the level of the sigmoid volvulus is more proximal than the reach of a proctoscope, flexible sigmoidoscopy can be performed. This procedure may be performed with a water immersion technique or using gas insufflation, as needed, and the rectal tube that is passed is usually thinner and more flexible than rectal tubes that are passed through a proctoscope [50]. In some situations, fluoroscopic guidance

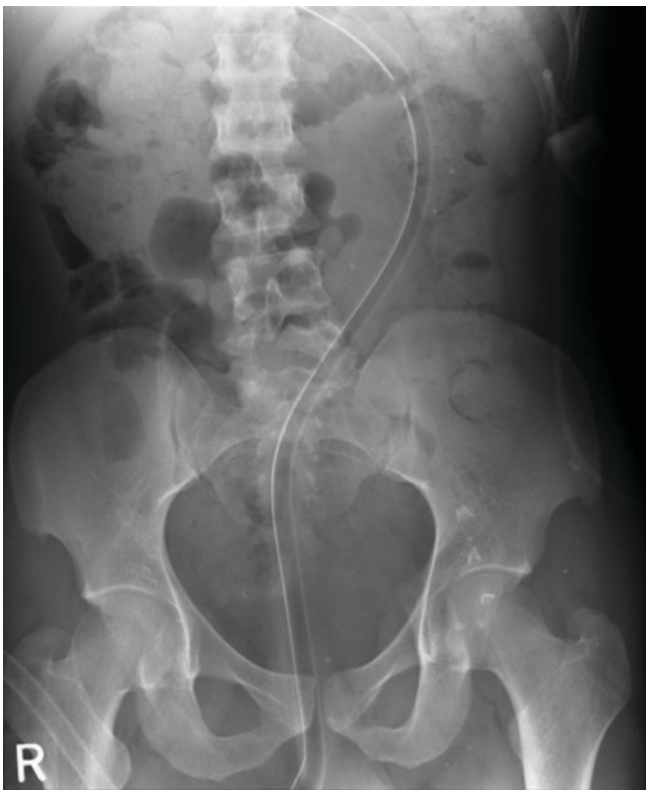

Fig. 39.9 Abdominal radiograph demonstrating the patient in Fig. 39.5 after successful proctoscopic detorsion and rectal tube insertion. (Courtesy of Daniel L. Feingold, MD)

can aid in successfully advancing the flexible scope under these circumstances. Nonoperative detorsion is relatively straightforward and is successful in 60–95% of cases and carries a low morbidity rate [51, 52]. Nonetheless, there is an estimated 3% mortality rate associated with detorsing a sigmoid volvulus which is considered to be a reflection of the patient population typical for volvulus rather than the actual procedure for reducing the volvulus [47].

After successful nonoperative detorsion, patients are observed as they decompress. In general, sigmoid colectomy should be considered after resolution of the acute phase of sigmoid volvulus, specifically in order to prevent recurrent volvulus [52]. The risk of recurrence after a first admission for sigmoid volvulus is estimated at 45–70% or even higher, depending on the length of follow-up, with a majority recurring within the first few months after successful nonoperative decompression [47, 51, 53, 54]. A common teaching and practice is to proceed with semi-elective resection during the same hospitalization, though patients may prefer to return on a more elective timeline, ideally soon after the index hospitalization [52]. Given that the sigmoid volvulus patient population is typically elderly with comorbidities, the decision to proceed with elective, interval sigmoidectomy under these circumstances should be individualized. In addition, it is important to consider the need for colonoscopy, or possibly CT colonography, prior to proceeding with colectomy in the non-emergent setting [55].

Surgery for Sigmoid Volvulus

Patients with evidence of perforation or concern for ischemia should be treated with broad-spectrum antibiotics and intravenous fluid resuscitation as the operating room is being mobilized and typically undergo exploratory laparotomy. Colon ischemia and peritonitis are the main risk factors for mortality related to volvulus; the mortality of volvulus presenting as an emergency may be as high as 33% or even higher [45, 47]. As with elective or semi-elective surgery for sigmoid volvulus, a laparoscopic approach may be utilized depending on the specific patient circumstances and the available expertise. However, even after endoscopic detorsion and decompression, the redundant sigmoid colon typically remains dilated to some degree and has a much larger diameter than a typical otherwise normal sigmoid colon. This anatomy can be difficult to negotiate within the domain of a laparoscopy, and the nature of the redundant colon is such that it usually prolapses out readily, if not spontaneously, through a relatively short midline laparotomy (Fig. 39.10). In addition, the splenic flexure does not typi-

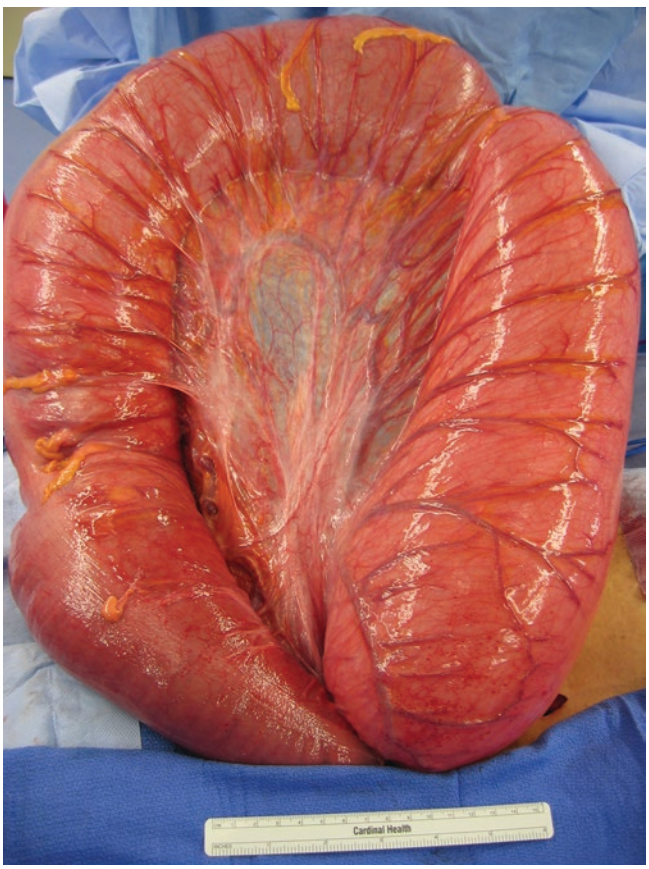

Fig. 39.10 Typical appearance of a sigmoid volvulus prolapsing through a laparotomy incision. (Courtesy of Daniel L. Feingold, MD)

cally need to be released for this operation, obviating the need for operative access to the left upper quadrant. Commonly there is fibrosis observed along the peritoneum overlying the mesocolon which is not thought to be a causative factor in volvulus, but rather a result of prior episodes. While it is relatively common to observe redundancy in other segments of the colon upon exploration, elongation in and of itself is not generally considered an indication for extended resection under these circumstances.

The most common operation performed for sigmoid volvulus is colectomy with the goal of resecting the redundant sigmoid colon in order to minimize the risk for recurrent volvulus [45, 46, 54]. In cases of cecal perforation complicating sigmoid volvulus, a subtotal colectomy is typically performed in order to address the different sites of pathology. Another indication for extended resection is when the colon proximal to the volvulized loop is ischemic due to the colonic obstruction; in these cases, the distribution of the ischemia is often patchy and diffuse, again requiring subtotal colectomy. In patients with sigmoid volvulus and concomitant megacolon, subtotal colectomy can effectively prevent recurrent volvulus at an otherwise retained segment of the colon [52].

The general recommendation for dealing with patients with a gangrenous, volvulized segment of the colon is to resect the loop without reducing the twist in order to try to prevent a load of potassium, bacteria, and endotoxin from entering the circulation and to minimize manipulation of the colon which can lead to perforation of the diseased segment. In practice, the anatomy of a volvulized segment folds the mesentery over itself, making it difficult to control coming across the mesentery without untwisting the colon, though modern-day energy devices are usually capable of coming across this thickness of tissue. While an oncologic operation with a nodal catch is not required under these circumstances, it is usually technically helpful to ligate the main mesenteric pedicle rather than repeatedly come through the mesentery closer to the colon wall. Meanwhile, an unwieldly sigmoid loop can impede dissecting the base of the mesentery and identifying the left ureter. The surgeon should be aware of these options, and it may be preferable to avoid dissecting near the retroperitoneum and use a mid-mesenteric plane of dissection. As with operations for other causes of large bowel obstruction, it may be helpful to decompress the colon in a controlled fashion to facilitate mobilization.

Once the diseased colon has been resected, a decision can be made regarding whether or not to restore bowel continuity. In emergency volvulus operations, the decision is based on individualized risk assessment and the clinical status of the patient. Ideally, patients will have been sited and marked for stoma location preoperatively. In semi-elective or elective operations for previously detorsed sigmoid volvulus, patients will commonly have an anastomosis created. It is common to have a wide diameter end of the colon coming down to the anastomosis which can be suboptimal when seating the anvil of an end-to-end mechanical stapler. In this situation, it may be particularly helpful to close the end of the colon with a linear stapler and perform a side-to-end Baker-type anastomosis.

Non-resectional operations that are alternatives to sigmoidectomy include simple operative detorsion alone, mesosigmoidoplasty, and sigmoidopexy [52]. These approaches spare the risk of morbidity related to stoma creation or creating an anastomosis but are associated with much higher rates of recurrent volvulus [45–47].

Another potential alternative option for treating patients with sigmoid volvulus is percutaneous endoscopic colostomy (PEC) or sigmoidopexy to restrict the mobility of the colon and reduce the risk of recurrent volvulus [56]. Patients considered to have a prohibitive operative risk or who otherwise decline to undergo abdominal surgery may be candidates for endoscopic fixation of the sigmoid colon to the anterior abdominal wall which is usually done under conscious sedation. This procedure can also be combined with laparoscopy to ensure proper alignment of the colon prior to fixation, to guide where along the length of the colon fixation is performed, and to decrease the risk of injury to nearby structures related to the endoscopic procedure [57]. While the approach is relatively straightforward and may even be performed at the time of endoscopic detorsion, there is no universally accepted PEC technique, and questions remain regarding how many points of fixation are used (typically one versus two) and when to remove the devices from the abdominal wall, as early removal has been associated with recurrent volvulus. Furthermore, although this approach is considered minimally invasive, minor and even major complications have been reported, ranging from infection or bleeding at the PEC site to peritonitis from PEC migration or dislodgement due to recurrent volvulus. Given that patients treated with PEC typically have significant comorbidities that preclude abdominal surgery, even minor complications related to an endoscopic procedure can have severe consequences. In reports of PEC that provide follow-up data, this particularly vulnerable patient population has a significantly high mortality rate after PEC from unrelated causes.

Cecal Volvulus

In contrast to sigmoid volvulus, the success of nonoperative detorsion of a cecal volvulus is low, and the general consensus is not to delay operation and risk ensuing ischemia, necrosis, and perforation. Patients diagnosed with cecal volvulus are considered to have a surgical emergency even in the absence of overt sepsis and are typically given broad-spectrum antibiotics and intravenous fluid resuscitation as the operating room is mobilized. As with cases of sigmoid

volvulus, the surgical approach, open versus laparoscopic, depends on the specific clinical circumstances and the available expertise; but the typical size of a cecal volvulus specimen is such that a meaningful extraction incision is usually unavoidable. In addition, as with a sigmoid volvulus, it can be difficult to laparoscopically negotiate the dilated, displaced, and elongated colon.

The most common operation performed to treat and prevent recurrent cecal volvulus is ileocolectomy with anastomosis [54]. In cases where creating an ileocolic anastomosis is considered too high risk, an end ileostomy with or without mucous fistula is performed. In certain circumstances, unstable patients may be resected, left in discontinuity, and brought back for a "second look" with possible anastomosis at that time. As with sigmoid volvulus, there are a number of non-resectional alternatives like simple detorsion alone, cecopexy, or cecostomy that may be considered in cases of cecal volvulus, but these approaches carry risks of morbidity including recurrent volvulus. While there is a role for individualizing the operative treatment in cases of volvulus, consideration of the risks and benefits will most commonly favor resection-based therapy [52, 55].

Ileosigmoid Knotting

While rare in the United States, this entity is more common in areas where volvulus is endemic, such as countries in the volvulus belt. Multiple configurations of knotting have been described, but all involve the ileum and sigmoid colon wrapping around each other in some fashion causing obstruction and frequently progressing to ischemia in one or both segments. This "double-loop" obstruction is associated with a poor prognosis, and patients present commonly with an abdominal catastrophe; the mortality in these cases can be as high as 73% [47, 58]. The diagnosis of ileosigmoid knotting can be made by cross-sectional imaging but is often made at the time of surgical exploration. The combination of imaging demonstrating sigmoid volvulus with a secondary small bowel obstruction and inability to reduce the sigmoid volvulus endoscopically may raise the suspicion of ileosigmoid knotting. Operative treatment depends on the specific anatomic variant encountered and often involves a double resection of the involved anatomy with or without restoration of bowel continuity depending on the anatomy and the circumstances.

Acute Colonic Pseudo-obstruction

Acute colonic pseudo-obstruction (ACPO) is generally considered to result from an imbalance or derangement of parasympathetic inhibition and/or sympathetic stimulation that impairs colonic motility leading to colon dilation in the absence of a mechanical source of obstruction. The prevailing hypothesis is that overall decreased parasympathetic tone in the area of the splenic flexure colon results in a relatively atonic segment that functions like an obstruction [59]. This condition may be referred to by a variety of terms including Ogilvie's syndrome, colonic ileus, acute megacolon, etc. The exact pathophysiologic mechanism underlying ACPO remains unclear, but the autonomic dysregulation involved is likely multifactorial and occurs most often in the setting of predisposing factors [59]. ACPO is rarely a primary diagnosis and is most commonly diagnosed in the setting of patients with some other active illness or state [60]. The dysregulation of the autonomic impulses in the enteric nervous system of the colon is likely part of a syndrome manifesting a more global process as described below [61].

While the exact incidence is unknown, ACPO is considered to be rare and is estimated to occur in 100 of every 100,000 admissions annually in the United States [62, 63]. Patients typically are elderly with medical comorbidities who have been hospitalized for an acute illness, nonoperative trauma, or metabolic disarray or are recovering from a recent surgery (including caesarean section). Many patients predisposed to developing ACPO are also maintained on medications that can affect colonic motility (e.g., opioids, calcium channel blockers, psychotropics, etc.), and these medications may be manipulated to facilitate treatment.

Patients who develop ACPO are typically already hospitalized, have severe or even massive colon dilation, and have symptoms and signs that may include abdominal distension, tympany, nausea, abdominal pain, decreased or absent bowel activity, or diarrhea. The degree of abdominal distension can cause respiratory symptoms by displacing the diaphragm. Right lower quadrant tenderness, signs of sepsis, or diffuse abdominal pain may signify ischemia with impending perforation.

While there is no universally accepted definition or criteria for diagnosing ACPO, patients in the appropriate clinical circumstances with imaging demonstrating a cecal diameter $\geq$ about 9 cm or other colonic segments $\geq$ about 6 cm may be classified as having ACPO. Radiologic imaging by way of abdominal radiographs or cross-sectional imaging typically demonstrates dilated, gas-filled colon with cecal dilation and with a transition to more normal colon in the area of the splenic flexure (Fig. 39.11). Interestingly, in this area of the colon (about where the midgut transitions to the hindgut), there is a transition in colonic innervation, supporting the concept of autonomic dysregulation as part of the underlying etiology of ACPO. When considering the diagnosis of ACPO, it is important to confirm there is no mechanical point of obstruction causing a large bowel obstruction (whether intrinsic or extrinsic to the colon) as these patients are treated according to a different algorithm. While it is usually possible to exclude a mechanical obstruction by reviewing CT scan imaging, in certain cases, it may be helpful to verify the anatomy by obtaining a water-soluble

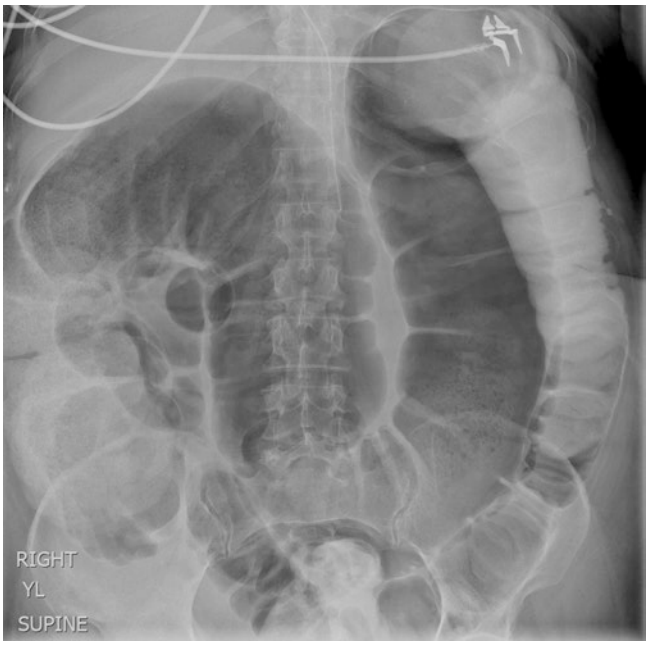

Fig. 39.11 A serial abdominal radiograph of a patient being treated for acute colonic pseudo-obstruction. Notice the dilated right and transverse colon and the relatively decompressed descending colon. Oral contrast has passed through the pseudo-obstructed colon. (Courtesy of Daniel L. Feingold, MD)

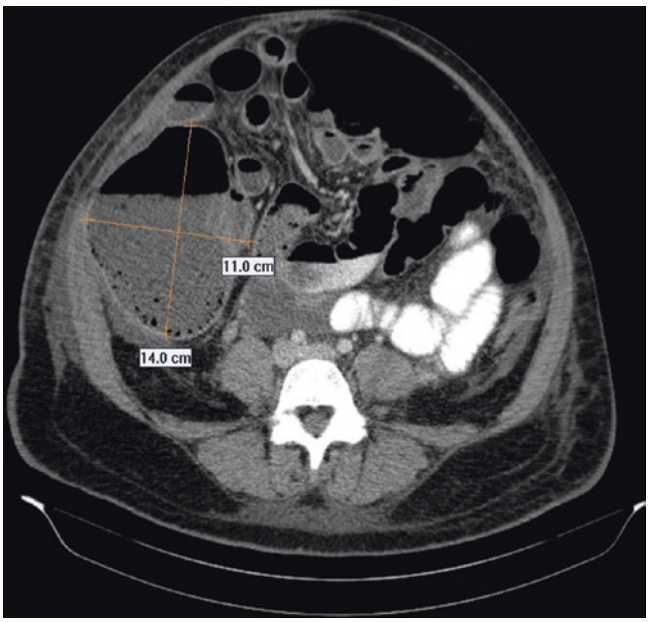

Fig. 39.12 Axial CT scan image measuring the cecal dimensions in the setting of acute colonic pseudo-obstruction. (Courtesy of Daniel L. Feingold, MD)

contrast enema study. Patients presenting with signs and symptoms consistent with ACPO carry a differential diagnosis similar to other etiologies of large bowel obstruction (Table 39.1). Toxic megacolon from an infectious source or from inflammatory bowel disease should also be considered in appropriate circumstances, as this can mimic the presentation and imaging seen in cases of ACPO. Cross-sectional imaging, as with cases of volvulus, can also reveal signs of colon ischemia that would prompt proceeding with surgery.

Medical Therapy

Patients who develop ACPO can progress to critical colonic distension, which increases the transmural pressure, resulting in ischemia from inadequate perfusion and, ultimately, perforation with peritonitis and even death. As with other etiologies of colon obstruction, the most common site of perforation is the cecum due to its increased diameter as compared to the rest of the colon as predicted by the law of Laplace [63]. The likelihood of experiencing these sequelae increases as the cecal diameter distends beyond about 10 cm and as the duration of distension approaches or exceeds about 6 days (Fig. 39.12) [51]. Although larger-diameter cecal dilation is associated with higher risk of perforation, the duration of distension and the acuity of how quickly the colon distends are important factors and contribute to perforation even in cases with less extreme degrees of dilation [64, 65]. The mortality rate associated with ACPO is higher in cases of perforation, ranges from about 10% to as high as 30–40%, and reflects the potential seriousness of the clinical entity as well as the population of patients prone to develop this unique form of large bowel obstruction [59, 60]. Early recognition and appropriate therapy to decompress the colon under the circumstances are important and clearly influence outcomes.

Patients with ACPO with complicating factors like ischemia, perforation, or signs of sepsis require urgent operation as discussed below. Otherwise, the initial management of a patient diagnosed with ACPO includes instituting bowel rest, eliminating or reducing potentially confounding or causative factors (e.g., narcotics and other medications that may influence colonic motility), encouraging ambulation and patient positioning to potentially facilitate colonic activity, correcting metabolic derangements, and decompressing the system with nasogastric and/or rectal tubes. In general, oral laxatives are contraindicated under these circumstances as these can increase intraluminal pressure [65]. This kind of supportive therapy is successful in resolving ACPO in 77–96% of patients [51]. Serial evaluations with physical examination, blood work, and imaging are important in order to determine the response to therapy and whether or not a patient requires escalation in treatment. The management of patients with ACPO usually requires coordinated, multidisciplinary care from medicine, gastroenterology, and surgery services. Patients who clinically worsen or fail to improve within about 48–72 hours of instituting medical therapy or who have cecal diameter of about 12 cm usually proceed with pharmacotherapy.

Pharmacotherapy

Neostigmine is the agent of choice for managing ACPO under these circumstances although it is *not FDA approved* for this indication. Neostigmine methylsulfate is a short-acting, competitive acetylcholinesterase inhibitor that reduces the breakdown of acetylcholine, effectively increasing the concentration of acetylcholine in the synaptic cleft (i.e., it is a parasympathomimetic agent). The efficacy of neostigmine supports, to some degree, the proposed pathogenesis of ACPO reviewed above. Placebo-controlled, double-blinded, randomized trials demonstrate that intravenous neostigmine (typically 2 mg over 3–5 minutes) is effective in 85–94% of cases and are the basis for the off-label use of this drug in patients with ACPO [66]. Neostigmine usually results in clinical decompression within about 10–30 minutes and has a half-life of about 60 minutes. Redosing neostigmine in patients who did not respond adequately to a first dose is successful in 40–100% of cases [67]. Risk factors associated with failure of neostigmine include male gender, younger age, postoperative status, and electrolyte imbalances [62]. After successful decompression, daily polyethylene glycol has been demonstrated to decrease the risk of recurrent ACPO [67].

Given the potential side effects of bradycardia and respiratory distress, neostigmine should be administered in a continuously monitored setting with access to the variety of supportive medications (e.g., atropine) and devices in the event cardiac or respiratory support or resuscitation is needed. Administering glycopyrrolate may prevent side effects like bronchospasm and hypersalivation. Neostigmine is contraindicated in patients with intestinal or urinary tract obstruction or known hypersensitivity and should be used with caution in patients with bradycardia, asthma, renal insufficiency, peptic ulcer disease, or recent myocardial infarction.

It is generally believed that rates of endoscopic and operative interventions for the treatment of patients with ACPO have decreased in recent decades because of the wider recognition of the syndrome as well as the efficacy of medical therapy and of appropriate pharmacotherapy [62]. While neostigmine has traditionally been administered via intravenous bolus delivery, subcutaneous and continuous infusion protocols are also effective and may be associated with fewer side effects. Other agents may be tried in cases of refractory ACPO including oral pyridostigmine, a long-acting acetylcholinesterase inhibitor; methylnaltrexone, a peripherally acting μ-opioid receptor antagonist; and prokinetics like metoclopramide and erythromycin.

Colonic Decompression

Patients who do not respond adequately to supportive measures and fail neostigmine therapy may be treated by colonoscopic decompression with a success rate as high as 95% [61]. While colonoscopy in this setting carries the usual risks of the procedure including perforation, typical patients hospitalized with ACPO have comorbidities and have not had a bowel preparation; they may be at higher than usual risk when undergoing colonoscopy in this setting. As with other etiologies for bowel obstruction, these patients require careful attention to protect their airway while undergoing a procedure under sedation. While there is some evidence supporting endoscopic decompression as superior to pharmacotherapy, given the low cost, overall safety, and efficacy of neostigmine and the cost and risks related to endoscopic decompression, colonoscopy is generally reserved as a second-line treatment [68].

In cases of ACPO, colonoscopy is generally performed using water immersion or minimal CO_2 insufflation rather than ambient air with the goal of evacuating as much colonic gas as possible. The sedation for these cases usually relies on benzodiazepines and other non-narcotics, as narcotics can interfere with colonic motility. The goal of insertion, in general, is to reach the ascending colon rather than the cecum, upon which a long intestinal tube can be deployed to effectively stent the colon allowing for continued postprocedure decompression. Repeated colonoscopy may be required in as many as 40% of patients, especially if a long decompression tube is not utilized. Often symptoms of ACPO resolve within about 48 hours after successful colonoscopic decompression [60]. Case reports detail treating patients with endoscopic or CT-guided percutaneous cecostomy to vent and decompress patients with ACPO, but the utility of these approaches is not well documented [65].

Surgical Therapy

While patients with perforation or concern for ischemia require exploration, patients who do not resolve their ACPO should be considered for exploration in order to decompress the colon prior to developing an emergency indication for operation. The timing and circumstances of proceeding with surgery under these circumstances are variable and should be individualized especially in light of the mortality rate associated with surgery in the setting of ACPO, which is variably reported as about 30% and as high as 60% [65]. In a retrospective review of the National Inpatient Sample, ACPO patients treated with medical therapy, colonoscopic decompression, or surgery experienced higher mortality rates with each escalation in therapy documented as 7.3%, 9.0%, and 12.3%, respectively [62]. In practice, patients without a firm indication for operation may undergo continued medical therapy with repeated attempts of pharmacotherapy and/or endoscopic decompression before ultimately moving to a surgical intervention.

In terms of operative options in the setting of medically refractory ACPO, patients with viable colon without perforation most commonly undergo exploration to confirm there is

no compromised colon and are then decompressed and vented through a colostomy. The role of colectomy under these circumstances is questionable. Meanwhile, patients with ischemic colon and/or perforation require resection of the diseased segment and are commonly left with an end stoma. The extent of the resection under these circumstances depends on the operative findings and clinical course.

Rare Causes of LBO

Intussusception

Intussusception accounts for only 1–3% of mechanical bowel obstructions in the adult population; a demonstrable lesion can be found in 80% of cases [11]. The classic triad of symptoms seen in pediatric intussusceptions (abdominal pain, vomiting, and red currant stools) is rare in adults who tend to present in a non-specific manner [69]. While the most common cause of large bowel intussusception is malignancy (65–87% of cases), benign processes can be implicated and include adenomatous polyps, GISTs, diverticular disease, and villous adenoma of the appendix [11, 70]. CT scan, the most accurate modality to diagnose an intussusception, has a reporting accuracy of 58–100% and can show a characteristic target or sausage-shaped lesion [71]. While colonoscopy can be a useful adjunct to identify a benign lead point such as an adenomatous polyp, concern has been raised that endoscopic reduction of an intussusception could theoretically result in the dissemination of malignant cells if a cancer is present [72]. Given the high incidence of malignancy as the lead point, there should be a low threshold for surgical exploration and an oncological resection of the affected segment.

Hernia

Abdominal wall hernias are a very rare cause of LBO due to the colon's larger caliber and relatively fixed nature. Femoral, inguinal, umbilical, incisional, Spigelian, lumbar, and diaphragmatic hernias can contain large bowel and cause LBO [11]. The management in these cases should follow principles of bowel rest and fluid resuscitation and typically requires surgical exploration.

Infection

While a rare cause of LBO, infectious causes such as actinomycosis can occur where the infection leads to a desmoplastic reaction with multiple abscesses causing extrinsic compression of the colon and LBO. Treatment in these cases can include defunctioning ostomy, directed antimicrobial therapy, and/or surgical resection [3]. LBO can occasionally be seen with abdominal *Mycobacterium tuberculosis* which is typically treated with antibiotic therapy [73]. LBO can also occur secondary to worms arising from schistosomiasis or helminthic infections.

Endometriosis

While endometriosis is a relatively common condition (affecting 8–15% of women), it accounts for less than 1% of cases of bowel obstruction [74]. Intestinal endometriosis can cause luminal stenosis secondary to serosal infiltration, with the rectosigmoid being the most common site of intestinal endometriosis. Most of the literature pertaining to LBO secondary to endometriosis is comprised of case reports that utilize fecal diversion; stent placement and resection have been reported [3, 75].

Other Malignancies

While colorectal cancer accounts for 50–60% of cases of LBO, other malignancies including ovarian, gastric, pancreatic, and bladder can be responsible. With these pathologies, LBO occurs due to intraluminal obstruction, intramural blockage, or extrinsic compression. Management options should be based on clinical presentation and disease extent. A defunctioning ostomy can help relieve the obstruction and may allow for appropriate staging and cancer therapy. Lymphoma accounts for less than 0.5% of colorectal malignancies but can cause LBO. Perforations of large bowel lymphomas are treated by resection with or without anastomosis. Colonic obstruction secondary to lymphoma may be treated with resection, defunctioning ostomy, stenting, or possibly chemoradiation [76].

References

1. Cappell MS, Batke M. Mechanical obstruction of the small bowel and colon. Med Clin North Am. 2008;92:575–97. viii
2. Jaffe T, Thompson WM. Large-bowel obstruction in the adult: classic radiographic and CT findings, etiology, and mimics. Radiology. 2015;275:651–63.
3. Farkas NG, Welman TJP, Ross T, Brown S, Smith JJ, Pawa N. Unusual causes of large bowel obstruction. Curr Probl Surg. 2019;56:49–90.
4. Mastoraki A, Mastoraki S, Tziava E, Touloumi S, Krinos N, Danias N, Lazaris A, Arkadopoulos N. Mesenteric ischemia: pathogenesis and challenging diagnostic and therapeutic modalities. World J Gastrointest Pathophysiol. 2016;7:125–30.
5. Saegesser F, Chapuis G, Rausis C, Tabrizian M, Sandblom P. Intestinal distension and colonic ischemia: occlusive complications and perforations of colo-rectal cancers. A clinical application

of Laplace's law. Chirurgie; memoires de l'Academie de chirurgie. 1974;100:502–16.
6. Davis L, Lowman RM. An evaluation of cecal size in impending perforation of the cecum. Surg Gynecol Obstet. 1956;103:711–8.
7. Markogiannakis H, Messaris E, Dardamanis D, Pararas N, Tzertzemelis D, Giannopoulos P, Larentzakis A, Lagoudianakis E, Manouras A, Bramis I. Acute mechanical bowel obstruction: clinical presentation, etiology, management and outcome. World J Gastroenterol. 2007;13:432–7.
8. Sawai RS. Management of colonic obstruction: a review. Clin Colon Rectal Surg. 2012;25:200–3.
9. Koruth NM, Koruth A, Matheson NA. The place of contrast enema in the management of large bowel obstruction. J R Coll Surg Edinb. 1985;30:258–60.
10. Taourel P, Kessler N, Lesnik A, Pujol J, Morcos L, Bruel JM. Helical CT of large bowel obstruction. Abdom Imaging. 2003;28:267–75.
11. Gore RM, Silvers RI, Thakrar KH, Wenzke DR, Mehta UK, Newmark GM, Berlin JW. Bowel obstruction. Radiol Clin N Am. 2015;53:1225–40.
12. Pisano M, Zorcolo L, Merli C, Cimbanassi S, Poiasina E, Ceresoli M, Agresta F, Allievi N, Bellanova G, Coccolini F, Coy C, Fugazzola P, Martinez CA, Montori G, Paolillo C, Penachim TJ, Pereira B, Reis T, Restivo A, Rezende-Neto J, Sartelli M, Valentino M, Abu-Zidan FM, Ashkenazi I, Bala M, Chiara O, De' Angelis N, Deidda S, De Simone B, Di Saverio S, Finotti E, Kenji I, Moore E, Wexner S, Biffl W, Coimbra R, Guttadauro A, Leppaniemi A, Maier R, Magnone S, Mefire AC, Peitzmann A, Sakakushev B, Sugrue M, Viale P, Weber D, Kashuk J, Fraga GP, Kluger I, Catena F, Ansaloni L. 2017 WSES guidelines on colon and rectal cancer emergencies: obstruction and perforation. World J Emerg Surg. 2018;13:36.
13. Imuta M, Awai K, Nakayama Y, Murata Y, Asao C, Matsukawa T, Yamashita Y. Multidetector CT findings suggesting a perforation site in the gastrointestinal tract: analysis in surgically confirmed 155 patients. Radiat Med. 2007;25:113–8.
14. Garcia-Valdecasas JC, Llovera JM, deLacy AM, Reverter JC, Grande L, Fuster J, Cugat E, Visa J, Pera C. Obstructing colorectal carcinomas. Prospective study. Dis Colon Rectum. 1991;34:759–62.
15. Desai MG, Rodko EA. Perforation of the colon in malignant tumors. J Can Assoc Radiol. 1973;24:344–9.
16. Chen SC, Yen ZS, Wang HP, Lin FY, Hsu CY, Chen WJ. Ultrasonography is superior to plain radiography in the diagnosis of pneumoperitoneum. Br J Surg. 2002;89:351–4.
17. Murphy KP, Twomey M, McLaughlin PD, O'Connor OJ, Maher MM. Imaging of ischemia, obstruction and infection in the abdomen. Radiol Clin N Am. 2015;53:847–69. ix-x
18. Chapman AH, McNamara M, Porter G. The acute contrast enema in suspected large bowel obstruction: value and technique. Clin Radiol. 1992;46:273–8.
19. Aquina CT, Becerra AZ, Xu Z, Boscoe FP, Schymura MJ, Noyes K, Monson JRT, Fleming FJ. Nonelective colon cancer resection: a continued public health concern. Surgery. 2017;161:1609–18.
20. Tekkis PP, Kinsman R, Thompson MR, Stamatakis JD. The Association of Coloproctology of Great Britain and Ireland study of large bowel obstruction caused by colorectal cancer. Ann Surg. 2004;240:76–81.
21. Baer C, Menon R, Bastawrous S, Bastawrous A. Emergency presentations of colorectal cancer. Surg Clin North Am. 2017;97:529–45.
22. Bass G, Fleming C, Conneely J, Martin Z, Mealy K. Emergency first presentation of colorectal cancer predicts significantly poorer outcomes: a review of 356 consecutive Irish patients. Dis Colon Rectum. 2009;52:678–84.
23. Mege D, Manceau G, Beyer-Berjot L, Bridoux V, Lakkis Z, Venara A, Voron T, Brunetti F, Sielezneff I, Karoui M. Surgical management of obstructive right-sided colon cancer at a national level results of a multicenter study of the French Surgical Association in 776 patients. Eur J Surg Oncol: J Eur Soc Surg Oncol Br Assoc Surg Oncol. 2018;44:1522–31.
24. Kronborg O. Acute obstruction from tumour in the left colon without spread. A randomized trial of emergency colostomy versus resection. Int J Color Dis. 1995;10:1–5.
25. De Salvo GL, Gava C, Pucciarelli S, Lise M. Curative surgery for obstruction from primary left colorectal carcinoma: primary or staged resection? Cochrane Database Syst Rev. 2004;(2):Cd002101.
26. Lim JF, Tang CL, Seow-Choen F, Heah SM. Prospective, randomized trial comparing intraoperative colonic irrigation with manual decompression only for obstructed left-sided colorectal cancer. Dis Colon Rectum. 2005;48:205–9.
27. Klatt GR, Martin WH, Gillespie JT. Subtotal colectomy with primary anastomosis without diversion in the treatment of obstructing carcinoma of the left colon. Am J Surg. 1981;141:577–8.
28. Finan PJ, Campbell S, Verma R, MacFie J, Gatt M, Parker MC, Bhardwaj R, Hall NR. The management of malignant large bowel obstruction: ACPGBI position statement. Colorectal Dis: Off J Assoc Coloproctol Great Br Ireland. 2007;9(Suppl 4):1–17.
29. Single-stage treatment for malignant left-sided colonic obstruction: a prospective randomized clinical trial comparing subtotal colectomy with segmental resection following intraoperative irrigation. The SCOTIA Study Group. Subtotal Colectomy versus On-table Irrigation and Anastomosis. Br J Surg. 1995;82:1622–7.
30. Deen KI, Madoff RD, Goldberg SM, Rothenberger DA. Surgical management of left colon obstruction: the University of Minnesota experience. J Am Coll Surg. 1998;187:573–6.
31. Poon RT, Law WL, Chu KW, Wong J. Emergency resection and primary anastomosis for left-sided obstructing colorectal carcinoma in the elderly. Br J Surg. 1998;85:1539–42.
32. Ansaloni L, Andersson RE, Bazzoli F, Catena F, Cennamo V, Di Saverio S, Fuccio L, Jeekel H, Leppaniemi A, Moore E, Pinna AD, Pisano M, Repici A, Sugarbaker PH, Tuech JJ. Guidelines in the management of obstructing cancer of the left colon: consensus conference of the world society of emergency surgery (WSES) and peritoneum and surgery (PnS) society. World J Emerg Surg. 2010;5:29.
33. Bellows CF, Webber LS, Albo D, Awad S, Berger DH. Early predictors of anastomotic leaks after colectomy. Tech Coloproctol. 2009;13:41–7.
34. Guenaga KF, Matos D, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev. 2011:CD001544.
35. Kube R, Granowski D, Stubs P, Mroczkowski P, Ptok H, Schmidt U, Gastinger I, Lippert H. Surgical practices for malignant left colonic obstruction in Germany. Eur J Surg Oncol: J Eur Soc Surg Oncol Br Assoc Surg Oncol. 2010;36:65–71.
36. Atukorale YN, Church JL, Hoggan BL, Lambert RS, Gurgacz SL, Goodall S, Maddern GJ. Self-expanding metallic stents for the management of emergency malignant large bowel obstruction: a systematic review. J Gastroint Surg: Off J Soc Surg Alimentary Tract. 2016;20:455–62.
37. Maruthachalam K, Lash GE, Shenton BK, Horgan AF. Tumour cell dissemination following endoscopic stent insertion. Br J Surg. 2007;94:1151–4.
38. van Hooft JE, Bemelman WA, Oldenburg B, Marinelli AW, Lutke Holzik MF, Grubben MJ, Sprangers MA, Dijkgraaf MG, Fockens P. Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction: a multicentre randomised trial. Lancet Oncol. 2011;12:344–52.
39. Pirlet IA, Slim K, Kwiatkowski F, Michot F, Millat BL. Emergency preoperative stenting versus surgery for acute left-sided malignant colonic obstruction: a multicenter randomized controlled trial. Surg Endosc. 2011;25:1814–21.
40. Alcantara M, Serra-Aracil X, Falco J, Mora L, Bombardo J, Navarro S. Prospective, controlled, randomized study of intraoperative

colonic lavage versus stent placement in obstructive left-sided colonic cancer. World J Surg. 2011;35:1904–10.
41. Arezzo A, Passera R, Lo Secco G, Verra M, Bonino MA, Targarona E, Morino M. Stent as bridge to surgery for left-sided malignant colonic obstruction reduces adverse events and stoma rate compared with emergency surgery: results of a systematic review and meta-analysis of randomized controlled trials. Gastrointest Endosc. 2017;86:416–26.
42. Hill J, Kay C, Morton D, Magill L, Handley K, Gray RG, Group CTC. CREST: randomised phase III study of stenting as a bridge to surgery in obstructing colorectal cancer—results of the UK ColoRectal Endoscopic Stenting Trial (CREST). J Clin Oncol. 2016;34:3507–3507.
43. Mashar M, Mashar R, Hajibandeh S. Uncovered versus covered stent in management of large bowel obstruction due to colorectal malignancy: a systematic review and meta-analysis. Int J Color Dis. 2019;34:773–85.
44. Shimura T, Joh T. Evidence-based clinical management of acute malignant colorectal obstruction. J Clin Gastroenterol. 2016;50:273–85.
45. Halabi WJ, Jafari MD, Kang CY, Nguyen VQ, Carmichael JC, Mills S, Pigazzi A, Stamos MJ. Colonic volvulus in the United States: trends, outcomes, and predictors of mortality. Ann Surg. 2014;259:293–301.
46. Kasten KR, Marcello PW, Roberts PL, Read TE, Schoetz DJ, Hall JF, Francone TD, Ricciardi R. What are the results of colonic volvulus surgery? Dis Colon Rectum. 2015;58:502–7.
47. Perrot L, Fohlen A, Alves A, Lubrano J. Management of the colonic volvulus in 2016. J Visc Surg. 2016;153:183–92.
48. Lung BE, Yelika SB, Murthy AS, Gachabayov M, Denoya P. Cecal bascule: a systematic review of the literature. Tech Coloproctol. 2018;22:75–80.
49. Gomes CA, Soares C Jr, Catena F, Di Saverio S, Sartelli M, Gomes CC, Gomes FC. Laparoscopic Management of Mobile Cecum. JSLS: J Soc Laparoendoscop Surg. 2016;20:e2016.00076.
50. Sugimoto S, Hosoe N, Mizukami T, Tsunoda Y, Ito T, Imamura S, Tamura T, Nagakubo S, Morohoshi Y, Koike Y, Fujita Y, Komatsu H, Ogata H, Kanai T. Effectiveness and clinical results of endoscopic management of sigmoid volvulus using unsedated water-immersion colonoscopy. Digest Endosc: Off J Japan Gastroenterol Endosc Soc. 2014;26:564–8.
51. Naveed M, Jamil LH, Fujii-Lau LL, Al-Haddad M, Buxbaum JL, Fishman DS, Jue TL, Law JK, Lee JK, Qumseya BJ, Sawhney MS, Thosani N, Storm AC, Calderwood AH, Wani SB. American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in the management of acute colonic pseudo-obstruction and colonic volvulus. Gastrointest Endosc. 2020;91:228–35.
52. Vogel JD, Feingold DL, Stewart DB, Turner JS, Boutros M, Chun J, Steele SR. Clinical practice guidelines for colon volvulus and acute colonic pseudo-obstruction. Dis Colon Rectum. 2016;59:589–600.
53. Ifversen AK, Kjaer DW. More patients should undergo surgery after sigmoid volvulus. World J Gastroenterol. 2014;20:18384–9.
54. Swenson BR, Kwaan MR, Burkart NE, Wang Y, Madoff RD, Rothenberger DA, Melton GB. Colonic volvulus: presentation and management in metropolitan Minnesota, United States. Dis Colon Rectum. 2012;55:444–9.
55. Gingold D, Murrell Z. Management of colonic volvulus. Clin Colon Rectal Surg. 2012;25:236–44.
56. Mullen R, Church NI, Yalamarthi S. Volvulus of the sigmoid colon treated by percutaneous endoscopic colostomy. Surg Laparosc Endosc Percutan Tech. 2009;19:e64–6.
57. Gordon-Weeks AN, Lorenzi B, Lim J, Cristaldi M. Laparoscopic-assisted endoscopic sigmoidopexy: a new surgical option for sigmoid volvulus. Dis Colon Rectum. 2011;54:645–7.
58. Selcuk AS. Treatment for ileosigmoid knotting: a single-center experience of 74 patients. Tech Coloproctol. 2014;18:233–7.
59. Wells CI, O'Grady G, Bissett IP. Acute colonic pseudo-obstruction: a systematic review of aetiology and mechanisms. World J Gastroenterol. 2017;23:5634–44.
60. Mankaney GN, Sarvepalli S, Arora Z, Kamal A, Lopez R, Vargo JJ, Burke CA. Colonic decompression reduces proximal acute colonic pseudo-obstruction and related symptoms. Dis Colon Rectum. 2020;63:60–7.
61. Saunders MD. Acute colonic pseudo-obstruction. Gastrointest Endosc Clin N Am. 2007;17:341–60. vi-vii
62. Ross SW, Oommen B, Wormer BA, Walters AL, Augenstein VA, Heniford BT, Sing RF, Christmas AB. Acute colonic pseudo-obstruction: defining the epidemiology, treatment, and adverse outcomes of Ogilvie's syndrome. Am Surg. 2016;82:102–11.
63. Harnsberger C. Acute colonic pseudo-obstruction (Ogilvie's syndrome). Semin Colon Rectal Surg. 2019;30:1–4.
64. Yeo HL, Lee SW. Colorectal emergencies: review and controversies in the management of large bowel obstruction. J Gastrointest Surg: Off J Soc Surg Alimentary Tract. 2013;17:2007–12.
65. De Giorgio R, Knowles CH. Acute colonic pseudo-obstruction. Br J Surg. 2009;96:229–39.
66. Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. N Engl J Med. 1999;341:137–41.
67. Sgouros SN, Vlachogiannakos J, Vassiliadis K, Bergele C, Stefanidis G, Nastos H, Avgerinos A, Mantides A. Effect of polyethylene glycol electrolyte balanced solution on patients with acute colonic pseudo obstruction after resolution of colonic dilation: a prospective, randomised, placebo controlled trial. Gut. 2006;55:638–42.
68. Tsirline VB, Zemlyak AY, Avery MJ, Colavita PD, Christmas AB, Heniford BT, Sing RF. Colonoscopy is superior to neostigmine in the treatment of Ogilvie's syndrome. Am J Surg. 2012;204:849–55; discussion 855.
69. Marinis A, Yiallourou A, Samanides L, Dafnios N, Anastasopoulos G, Vassiliou I, Theodosopoulos T. Intussusception of the bowel in adults: a review. World J Gastroenterol. 2009;15:407–11.
70. Syed H, Syed L, Parampalli U and Uheba M. Adult intussusception secondary to diverticular disease. BMJ Case Rep. 2018;2018.
71. Lindor RA, Bellolio MF, Sadosty AT, Earnest F, Cabrera D. Adult intussusception: presentation, management, and outcomes of 148 patients. J Emerg Med. 2012;43:1–6.
72. Yalamarthi S, Smith RC. Adult intussusception: case reports and review of literature. Postgrad Med J. 2005;81:174–7.
73. Anand BS, Nanda R, Sachdev GK. Response of tuberculous stricture to antituberculous treatment. Gut. 1988;29:62–9.
74. Katsikogiannis N, Tsaroucha A, Dimakis K, Sivridis E, Simopoulos C. Rectal endometriosis causing colonic obstruction and concurrent endometriosis of the appendix: a case report. J Med Case Rep. 2011;5:320.
75. Prystowsky JB, Stryker SJ, Ujiki GT, Poticha SM. Gastrointestinal endometriosis. Incidence and indications for resection. Arch Surg (Chicago, Ill : 1960). 1988;123:855–8.
76. Abbott S, Nikolousis E, Badger I. Intestinal lymphoma--a review of the management of emergency presentations to the general surgeon. Int J Color Dis. 2015;30:151–7.
77. Gore RM. Textbook of gastrointestinal radiology. 3rd ed: Saunders/Elsevier; 2008.

Lower GI Hemorrhage

40

Mehraneh D. Jafari and Joshua I. S. Bleier

Key Concepts

- LGIB comprises 30–40% of all GI bleeds and is the most common cause of hospitalization due to GI disease in the United States.
- The incidence of LGIB is increasing, especially in octogenarians.
- The most common cause of LGIB is diverticular disease followed by anorectal disease and ischemia.
- A focused H&P (history and physical examination) is most effective in determining the cause of bleeding, and initial resuscitation should be focused on restoring hemodynamic stability with volume and/or blood.
- Characteristics of timing, type of bleeding, volume, and anoscopy can help to rapidly identify appropriate treatment based on potential source and rate of bleeding.
- Appropriate risk stratification can help better predict morbidity and mortality as well as guide appropriate management schemes.
- Upper and lower endoscopy is the preferred initial mode of diagnosis for LGIB. This method best allows for not only potential source identification but offers the potential for therapeutic intervention.
- Radiologic studies can be effective early diagnostic modalities in identifying the source of bleeding. CT angiography has a high sensitivity and specificity and is widely available. Catheter-based angiography can both diagnose and potentially treat bleeding sources if bleeding is brisk enough via transcatheter embolization.
- Nuclear scintigraphy, either via ^{99m}Tc-sulfur colloid or ^{99m}Tc-labeled RBC, can be used to identify bleeding sources that are intermittent or too slow to be identified by CTA or direct angiography.
- Recurrent LGIB is a common problem, and repeated evaluation has additive success rates.
- All attempts at localization should be made in the stable patient prior to consideration of surgical intervention.
- Obscure GI bleeding is defined as bleeding from a source that has not been identified after appropriate endoscopic and radiologic evaluation.
- Most sources of obscure GI bleeding tend to come from the small bowel, and capsule endoscopy is indicated to try and diagnose.
- Double balloon enteroscopy is an advanced modality which may be employed to diagnose and treat bleeding sources in the proximal small bowel.
- Surgery is indicated in patients in whom conservative measures have failed and/or bleeding is causing hemodynamic instability or who have reached significant transfusion thresholds.
- For refractory LGIB that are colonic in origin, but remain unlocalized, a total colectomy with ileostomy should be performed.
- For bleeding from an ongoing or refractory source that is localized, a segmental colectomy may be performed.
- Combining clinical pathways incorporating risk stratification may be helpful in providing a more systematic approach to management of LGIB and improving patient outcomes.

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Introduction

Lower gastrointestinal bleeding (LGIB) is defined as a bleeding from a source distal to the ligament of Treitz. Severity and quantification are often difficult to assess, and patient history can vary. In addition to prompt resuscitation, risk stratification should be considered at initial presentation to guide the clinician in appropriate management. The large anatomical range of the "lower GI" distribution can pose as a challenge for clinicians, as it is difficult at times to pinpoint the source of the bleeding, and this is critical for optimal management. The recommended initial localization methods are generally endoscopy and CT angiography. Ultimately, endoscopy and catheter-based angiography can localize and control the bleeding for the majority of patients. In instances of failure, these modalities can help inform appropriate surgical intervention.

Epidemiology

Good-quality epidemiologic studies of lower gastrointestinal bleeding (LGIB) are lacking. LGIB comprises 30–40% of all gastrointestinal bleeds with an estimated incidence of 33–87/100,000 [1, 2]. Gastrointestinal bleeding is the most common cause of hospitalization related to gastrointestinal disease in the United States [3]. The number of LGIB reported is likely underestimated as minor episodes may never present to a hospital or emergency department [4]. Acute LGIB, defined as sudden onset of hematochezia, accounts for 20% of all gastrointestinal bleeding leading to diagnostic evaluation and hospitalization. This consumes a significant amount of medical resources [5, 6]. In the United States, GI hemorrhage leads to 800,000 annual admissions at a cost of $5 billion [3]. Acute colonic bleeding (defined as that occurring from the colon, rectum, and/or anus) has an annual incidence of 36/100,000 [7]. The overall mortality from LGIB is reported as ranging from 1.3 to 3.9% [3, 7, 8]. Importantly, approximately 15% of patients with symptoms of LGIB actually have an upper GI source [9]; early recognition is critical. Fortunately, mortality from uncontrolled LGIB is rare, and most incidence of mortality is related to patient comorbidities [10].

The incidence of LGIB is increasing [3]. There was a 22% increase in the number of LGIB between 2000 and 2009, most likely as a consequence of an aging population and increasing usage of anticoagulants [11]. A recent national audit of the United Kingdom found that the majority of patients are elderly with a median age of 74 and multiple comorbidities [10]. The consensus of the European and American studies is that the incidence of upper GI bleed is decreasing, while the incidence of LGIB is increasing [1–3]. The elderly are at an increased risk of both frequency and mortality from LGIB [1, 3, 5]. In fact, the incidence of LGIB is increased more than 200-fold in patients >80 years old compared to those of 20 years old [12]. This increase can be attributed to a higher incidence of diverticulosis and angiodysplasia with age.

In an era of increasing usage of anticoagulation, this increase in the incidence of bleeding in the elderly with multiple comorbidities is of great concern. In fact, in a large French study, 75% of patients were found to have a predisposing medication contributing to LGIB [13]. Despite this, there has been a decline in morbidity and mortality over the years most likely due to improved access and experience with minimally invasive interventions and improved critical care practices [11].

Etiology

The cause of LGIB can be divided into vascular, anatomical, inflammatory, neoplastic, and small bowel causes (Table 40.1). The most common cause of LGIB is diverticulosis, followed by anorectal disease and ischemia. Less common causes of LGIB include angioectasias, inflammatory bowel disease, and neoplastic processes. Rare causes of LGIB are post-polypectomy bleeding, radiation proctitis, NSAID-induced ulcerations, and Dieulafoy's lesions (Table 40.1) [14–16].

Table 40.1 Etiology of LGIB with associated incidence [14–16]

Etiology	Incidence
Anatomic	
Diverticulosis	30–65%
Anorectal	5–20%
Vascular	
Ischemic colitis	5–20%
Angioectasias	5–10%
Inflammatory	
Inflammatory bowel disease	3–5%
Infectious colitis	2–5%
Neoplastic	3–11%
Others	
Post-polypectomy	2–7%
Radiation proctitis	0–2%
NSAID-induced ulceration	0–2%
Dieulafoy's lesion	0–2%
Small bowel	3–13%
Meckel's diverticulum	
Inflammatory bowel disease	
Angioectasias	
Neoplasms	
NSAID-induced ulcers	
Dieulafoy's lesion	

Diverticulosis is the most common cause of LGIB, accounting for 30–65% of cases, and constitutes the most likely etiology for severe acute hemorrhage [10, 17–21]. Diverticula develop at weak points in the colonic wall caused by penetration of the vasa recta, creating a thin-walled sac where the mucosa is closely apposed to the vessel. It is thus not surprising that this represents a point of vulnerability for vascular erosion. Sigmoid and descending colon diverticulosis is prevalent in 50% of the population with a cumulative incidence of bleeding of 2% at 5 years and 10% at 10 years [22]. The second most common cause of LGIB is anorectal disease (5–20%) [8, 16, 18, 21], of which the most common sources are hemorrhoids and anal fissures [21].

Presentation

Lower GI bleed can have a variety of presentations due to the diversity of its causes. Bleeding may present acutely or in a more chronic manner. LGIB that is acute presents as sudden onset of hematochezia and/or melena and may be associated with hemodynamic instability. Chronic LGIB is associated with longer duration with slow loss of blood resulting in iron deficiency anemia and/or positive fecal occult blood testing. Approximately 15% of patients with hematochezia are ultimately found to have an upper GI bleed. Slower upper GI bleeding sources result in dark, tarry stools, or melena, due to oxidation of heme as it traverses the lower GI tract; thus with a presentation of melena, an upper GI source must be investigated first. However, brisk upper GI bleeds may transit the GI tract much more quickly, too fast to be converted into melena. Therefore, hematochezia associated with hemodynamic instability can be indicative of an upper GI source and typically warrants evaluation with nasogastric lavage and/or endoscopic evaluation [6, 9, 23, 24].

Evaluation

A focused history and physical examination should be performed on any patient who presents acutely in combination with laboratory studies. Assessment of hemodynamic stability is of paramount importance at the time of presentation for both acute and chronic LGIB. Initial presentation can identify patients at higher risk of adverse events and severe bleeding and allow the clinician to triage appropriately [6].

The goal of the history and physical exam is to elicit the source of bleeding. Therefore, history should be focused on color, amount, frequency, and duration of bleeding. Associated abdominal symptoms such as constipation, obstipation, change in bowel habits, or weight loss should be solicited. It is important to have a high suspicion for colorectal malignancy in patients with unintentional weight loss and change in bowel habits. Associated symptoms such as diarrhea and abdominal pain can point to an ischemic, inflammatory, or infectious etiology. Patients should also be asked specifically about upper GI symptoms, vascular surgery, recent endoscopic procedures, history of radiation, and/or inflammatory bowel disease. Family history is especially important to rule out patients at high risk for malignancy. History of liver disease, alcohol consumption, and bleeding disorders (both personal and familial) should be included.

Medication history especially the use of anticoagulants that increase bleeding risk such as nonsteroidal anti-inflammatory drugs (NSAIDs) and antiplatelet therapy should be obtained. Upper GI sources of bleed should be highly suspected in patients with history of portal hypertension and those on anticoagulants [6, 9, 23, 24]. It is important to note the patient's coexisting cardiopulmonary, renal, and hepatic conditions, as these comorbid conditions can uniquely increase the risk of morbidity and mortality and affect management [6, 16, 25].

Initial assessment guides utilization of the potential diagnostic and therapeutic modalities. The initial assessment of a LGIB patient should include vital signs (including postural changes), abdominal exam, and a digital rectal exam. Nasogastric lavage can quickly rule out a gastric source. Anoscopy or anorectal exam is mandatory to rule out a hemorrhoidal source which occurs in <20% of cases [16]. If anoscopy does not reveal obvious stigmata of recent bleeding, further evaluation is needed. Also, it should be mentioned that hemorrhoidal bleeding causing hemodynamic instability is rare, and other sources need to be ruled out in the unstable patient.

Risk Stratification

It is important to risk stratify LGIB patients to improve morbidity and mortality [26]. The shock index (SI), which is determined by dividing the heart rate by systolic blood pressure, can be used to stratify stability. SI >1 is classified as unstable and is predictive of active bleeding. An increasing SI has been associated with mortality and can predict patients with active extraversion on imaging [27, 28]. Once a patient's stability is determined, other risk stratification scores can be used to determine the outcomes of the patient and potential outpatient management of the stable patient.

Risk stratification models for LGIB using predictors are not as well developed as those for upper GI bleeds. These models are not well designed to predict outcomes for outpatient management and are limited in predicting poor outcomes [16, 25, 26, 29–34]. Although the definition of severity can be controversial, clinicians agree that severity is dependent on hemodynamic stability, laboratory findings, and comorbid conditions. Risk factors that are associated with

severe bleeding and poor outcomes are hemodynamic instability, ongoing bleeding, comorbid conditions, age > 60, history of diverticulosis and angioectasia, elevated creatinine, and anemia. In general, risk of bleed and morbidity increases with the increase in number of risk factors [16, 25, 26, 29–34].

Velayos demonstrated that 79% of patients with the presence of the following three risk factors will have recurrent and/or ongoing bleeding: hemodynamic stability longer than 1 hour, hematocrit <35%, and active gross rectal bleeding [31, 32]. The Oakland score is the only risk stratification score specifically designed and externally validated for LGIB. It is comprised of seven variables: age, gender, previous hospital admission with LGIB, digital rectal examination findings, heart rate, systolic blood pressure, and hemoglobin. The score is a summation of risk factors, and any patient with score ≤ 8 can be managed as an outpatient (Table 40.2). However, this scoring system has only been validated in the United Kingdom and may underreport patients who can be safely discharged [27, 35].

Das created an artificial neural network to predict the risk of death, rebleed, and intervention. Essentially, they created a computer-based clinical decision support system which was externally validated with a negative predictive value of 98%. However, clinical use of this non-logistic modeling is difficult to implement due to its requirements for advanced software and data entry [29]. Currently, risk stratification is highly dependent on clinical judgment, and the abovementioned patient risk factors may be used to guide the clinician as to the appropriate treatment and care setting. Table 40.3 discusses the current risk calculators available to guide clinical management [26, 32, 35, 36].

Table 40.2 Oakland scoring system

Predictor	Score value
Age	
40–69	1
>70	2
Male gender	1
Previous LGIB	1
Blood on DRE	1
Heart rate	
70–89	1
90–109	2
≥110	3
Systolic blood pressure	
130–159	2
120–129	3
90–119	4
<90	5
Hemoglobin (g/L)	
130–159	4
110–129	8
90–109	13
70–89	17
<70	22

A score of 8 or less predicts a 95% probability of safe discharge [35]

Management

Due to the diversity of presentation, management of LGIB can be especially challenging. In fact, 80% of LGIB resolve spontaneously [4, 11, 37]. The best way to stratify these patients is to initially assess the severity of the situation. As described above, risk stratification tools using vital signs, patient factors, and laboratory data in combination with clinical judgment can determine whether patient can be evaluated in an outpatient setting. For example, patients with chronic LGIB, anemia, and hemodynamic stability can be assessed in an outpatient setting. Shock index is also a good predictor of active extravasation and can be used to guide management.

Data driving the initial parenteral resuscitative management of hemodynamic unstable patient is mainly derived from management of severe upper GI bleed. These randomized clinical trials do not include LGIB; however, practice may logically follow these guidelines. Based on this data, transfusion of packed red blood cells is used to maintain a hemoglobin of 9 g per deciliter in patients with clinically significant coexisting illness (such as cardiovascular disease) and 7 g per deciliter for everyone else [6, 16, 38, 39]. Essentially, the goal of resuscitation is to normalize the patient's hemodynamics. This includes both blood products and intravenous fluids. The data does not show a difference with regard to colloid versus crystalloid resuscitation. In the upper GI bleed literature, intravenous fluid resuscitation is associated with decreased morbidity and mortality [6, 40, 41].

In our aging population, it is important to assess the patient's anticoagulation status and reverse any coagulopathy which can exacerbate ongoing bleeding. In a stable patient, it is important to communicate with the specialist managing the anticoagulation; the risk and benefit of both reversal and stopping of anticoagulation must be balanced [42, 43]. The American College of Gastroenterology guidelines, based on very low-quality evidence [44–46], dictates that reversal agents be used for an international normalized ratio (INR) >2.5 [6]. INR >1.5 has been a predictor of mortality but not rebleeding [44, 45]. This observed increase in mortality is an effect of INR's association with underlying comorbid disease. Platelet transfusion is generally recommended in patients with platelets <50 x10^9/l [43, 47]. In the setting of massive transfusion, principles of trauma massive transfusion protocols should be observed [47]; but there is no specific literature in GI bleeds to support this recommendation [6].

Table 40.3 Current risk calculators available to guide clinical management

Risk score	Outcome measured	Variables	Score cutoff
Oakland [35]	95% probability of safe discharge	Age	≤8[a]
		Gender	
		History of LGIB	
		Rectal exam	
		Heart rate	
		Systolic blood pressure	
		Hemoglobin	
BLEED [30]	Inpatient morbidity	Continuing hemorrhage	Low risk does not have any of the variables
		Systolic blood pressure < 100	
		Prothrombin time > 1.2	
		Altered mental status	
		Unstable comorbid disease	
NOBLADS[b] [26]	Risk of bleeding	NSAIDS	0 = 0% 1 = 20% 2 = 25% 3 = 40% 4 = 50% 5 = 92.9%
		Diarrhea	
		Abdominal tenderness	
		SBP ≤ 100	
		Antiplatelet therapy	
		Albumin <3.0 g/dl	
		Charlson comorbidity score > 2	
		Syncope	
Sengupta[c] [36]	30-day mortality	Age, anticoagulant use	Quartile 1: 2.6–4.45 Quartile 2: 4.9–7.3% Quartile 3: 9.1–9.9% Quartile 4: 24–26%
		Dementia	
		Metastatic cancer	
		Chronic kidney disease	
		Chronic pulmonary disease	
		Hematocrit	
		Albumin	
Strate et. al [32]	Bleeding severity	Heart rate	0 = low risk 1–3 variables present is intermediate risk >3 high risk
		Systolic blood pressure	
		Syncope	
		Nontender exam	
		Hematochezia within 4 hours	
		Aspirin use	
		Charlson comorbidity score	

[a]Refer to Table 3 for calculation
[b]Each predictor is given a weight of 1. Rate of severe bleeding based on score 0–5
[c]Calculated score based on variables. Scores placed in quartiles with associated risk factors. Has not been externally validated

The management of target-specific anticoagulants such as rivaroxaban, dabigatran, and apixaban can be very challenging. In a meta-analysis of 43 randomized clinical trials, an odds ratio of 1.45 (95% CI 1.07–1.97) was observed for bleeding risk with these agents [48]. Management is especially challenging as the degree of anticoagulation is not reflected in clotting panels. These agents have half-lives ranging from 5 to 19 hours. Nonspecific agents such as activated prothrombin complex concentrate (aPCC), which is an anti-inhibitor coagulant complex, can be used. No high-level evidence exists in literature with regard to the current available reversal agents [43, 49, 50]. In cases of severe life-threatening bleeding, hematology should be consulted to help manage these oral anticoagulants.

Endoscopic Evaluation

Endoscopy is often the preferred initial mode of diagnosis for LGIB. The major advantage of endoscopic evaluation is its ability to provide source identification and provide for therapeutic intervention [6, 51]. In patients with hemodynamic instability and hematochezia, an upper endoscopy should also be performed in addition to a colonoscopy [6, 16, 51]. The diagnostic yield of colonoscopy ranges from 42 to 90% [9, 23, 27, 52–54] (Table 40.4).

Colonoscopy may be performed on all patients with LGIB with careful evaluation of the mucosa upon insertion and withdrawal. Attempts at irrigation of residual blood and stool should be made, and the terminal ileum should be intubated

Table 40.4 Initial treatment modality

Colonoscopy	
Timing	Within 24 hours
Bowel preparation	Recommended – NGT can be placed to help facilitate
Rule out small bowel source	By intubating terminal ileum
Localization	Place tattoo in case of rebleed
Visualize entire mucosa	Use water-jet irrigation and a large working channel
CT angiography	
High predictive value	0.3 cc–0.5 cc/min of bleedings
	Shock index (SI) >1
	5 U PRBC within 24 h
Obtain 3 phases	Non-contrast, arterial, portal venous phase
Critical finding	Active extravasation
Subtle finding	Site of clot can be visualized on maximum intensity projection images

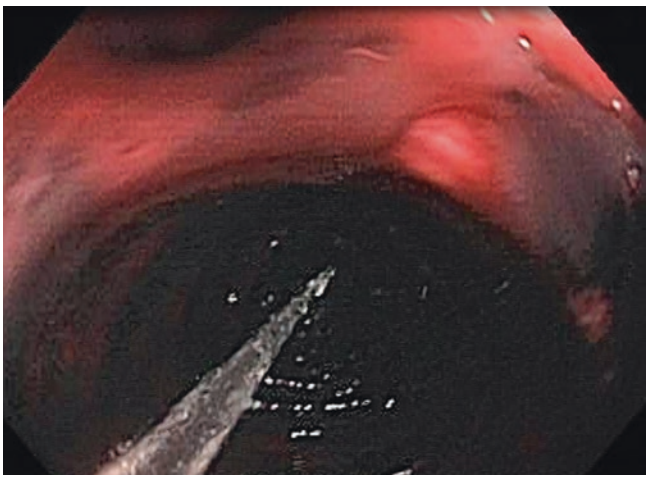

Fig. 40.1 Water-jet irrigation during colonoscopic evaluation of LGIB. (Courtesy of Gregory Ginsberg, MD)

to rule out a small bowel source. Therefore, colonoscopy with water-jet irrigation and a large working channel should be used to facilitate clearing of food and clot (Figs. 40.1 and 40.2) [6]. Bowel preparation is recommended when feasible, to allow for adequate visualization [6, 16, 23, 24].

The appropriate timing of colonoscopy in LGIB is not well defined [6, 27]. A randomized trial of urgent colonoscopy (<8 hours from presentation) compared to standard of care (next available) demonstrated a significantly improved rate of definitive diagnoses with early colonoscopy (42% vs. 22%, OR 2.6, 95% CI 1.1–6.2). There was no difference in rebleeding, surgery, and/or length of stay [23]. In contrast, Lain randomized 72 patients to colonoscopy within 12 hours or delayed colonoscopy (30–60 hours) and demonstrated no difference in rebleeding, diagnosis, and/or need for therapy [9]. A recent meta-analysis reported improved therapeutic and diagnostic yield and length of stay with early colonoscopy [55]. The American College of Gastroenterology, based on the findings of improved length of stay and diagnostic/therapeutic yields, recommends colonoscopy within 24 hours in high-risk patients. However, it should be stated that this recommendation is not associated with improved clinical outcomes and/or a decrease in the possibility of surgical intervention [6, 16, 27, 53].

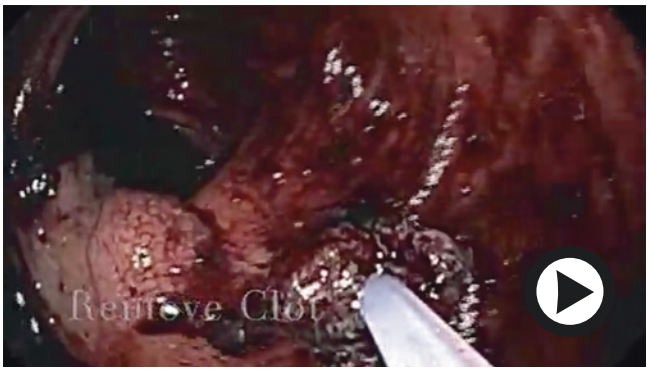

Fig. 40.2 Use of jet irrigation and endoloop removal of clot followed by endoclipping of bleeding polypectomy site. Courtesy of Gregory Ginsberg, MD, editing by Mehraneh D. Jafari. https://doi.org/10.1007/000-33s

Endoscopic Intervention

After localization, the primary strength of endoscopy is the ability to potentially stop bleeding sources. Techniques of endoscopic hemostasis are safe, with reported adverse event rates as low as 0.3–1.3% [15, 37]. If high-risk stigmata of bleeding are visualized during colonoscopy, there are multiple endoscopic interventions that can stop the bleeding. These high-risk stigmata include active bleeding/non-bleeding visible vessel and/or adherent clot [54, 56]. These findings suggest a high rate of bleeding recurrence if no intervention is performed [56, 57]. Interventions include injection, contact and non-contact thermal coagulation, topical sprays/powders, and mechanical therapies such as clips (Figs. 40.3 and 40.4). These therapies can be used as combination therapy and have been deemed safe [58, 59]. It is advised that CO_2 insufflation be used to avoid perforations during long procedure times [27]. Endoscopic intervention is effective; however, data is lacking with regard to optimal technique. Technique is dependent on the clinician's experience and location and type of bleeding.

Endoscopic hemostatic intervention has the highest benefit when treating diverticulosis, angioectasias, and post-polypectomy bleeds [6, 16, 51]. LGIB caused by ischemic colitis, inflammatory bowel disease, and/or colorectal neoplasms are generally not amenable to durable endoscopic hemostasis, but the diagnosis is highly effective in guiding focused surgical and multimodal therapy [16].

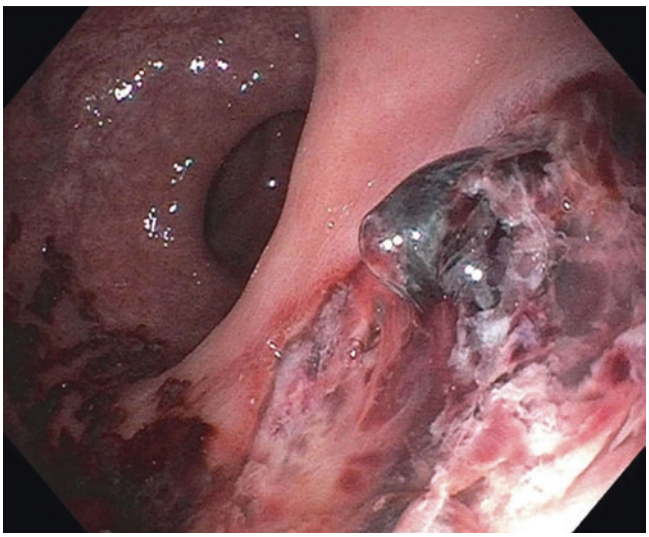

Fig. 40.3 Bleeding polypectomy site. (Courtesy of Gregory Ginsberg, MD)

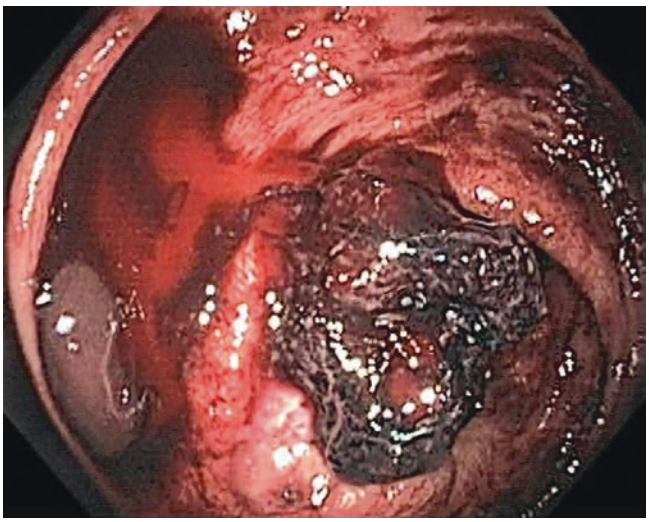

Fig. 40.5 Adherent clot over bleeding diverticulum. (Courtesy of Gregory Ginsberg, MD)

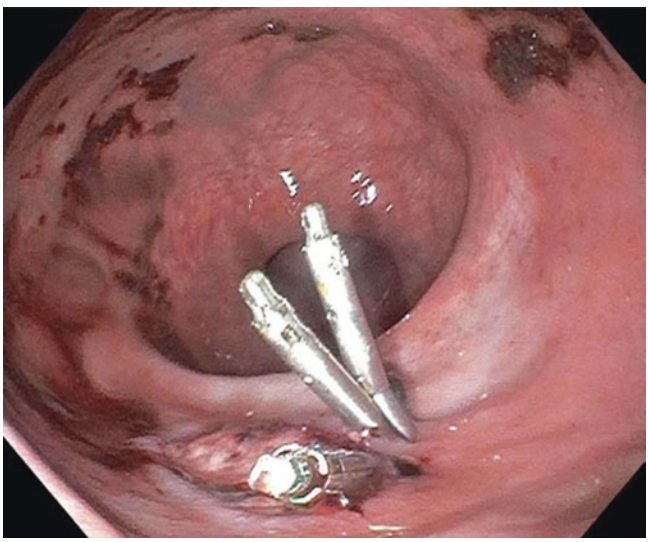

Fig. 40.4 Bleeding polypectomy site after clips applied. (Courtesy of Gregory Ginsberg, MD)

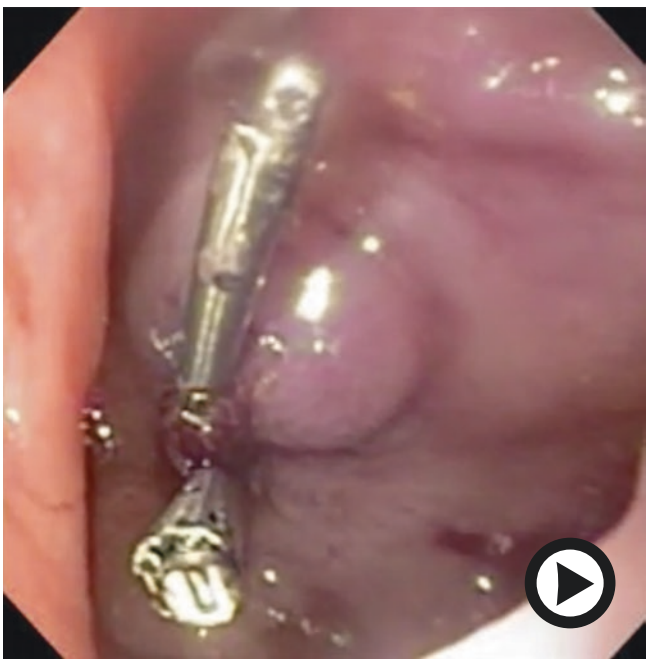

Fig. 40.6 Bleeding diverticulum treated with epinephrine injection and endoclipping. Courtesy of Gregory Ginsberg, MD, editing by Mehraneh D. Jafari. https://doi.org/10.1007/000-33r

Endoscopic intervention for diverticular bleeding is indicated when active bleeding is seen or when a non-bleeding visible vessel and/or adherent clot is visualized (Figs. 40.5 and 40.6) [54]. In a pooled analysis of 847 patients, Strate reported 80% successful hemostasis in diverticular bleeds with a reported 8% early rebleeding and 12% late rebleeding rate. No advantage was reported in terms of monotherapy versus combination therapy (e.g., epinephrine injection and clips) [15]. Clips are preferred to cautery in diverticular bleeds, as the inherently thin wall of diverticula may be prone to delayed perforation after thermal treatment. In instances of active bleeding, epinephrine injection should be performed to cause local vasoconstriction and slow down the bleeding, followed by clipping [60]. The clip can be applied to the bleeding vessel and/or applied to close the diverticulum creating tamponade [61–65]. A translucent cap and/or injections can also be used to evert the diverticulum for more precise localization and treatment of diverticular bleed [66]. Left-sided endoscopic banding, similar to that of variceal banding, has also been described as successful [67–69]. India ink tattoo should be placed at the site of intervention to assist localization in cases of rebleeding [6].

Endoscopic treatment in patients with angioectasia (also referred to as angiodysplasia or arteriovenous malformations) is safe and feasible. Angioectasias are more common in the elderly (age > 70) and tend to occur in the right colon. Angioectasias account for 3–15% of patients with LGIB. Risk factors associated with bleeding from angioectasias include multiple comorbidities, the presence of multiple lesions, and use of anticoagulation and/or antiplatelet therapy. Endoscopic evaluation and treatment via thermal therapy is indicated in patients with active bleeding. Argon plasma coagulation (APC) is considered the treatment of choice due to its ease of use, safety profile, and reduction of blood of transfusions [70, 71]. In patients with Heyde syndrome (bleeding angioectasias and aortic stenosis), aortic valve replacement should also be considered [72, 73].

Endoscopic treatment of post-polypectomy bleeding is associated with a 95–100% success rate [74]. Risk factors for post-polypectomy bleeding include polyp size (>2 cm), thick stalk, resection site located in the right colon, and anticoagulation therapy. It occurs in 0.6–9.7% of polypectomy patients [56]. All the abovementioned endoscopic treatment modalities can be used for control of bleeding; however, the best practice is to avoid further tissue damage with energy-based therapies. Therefore, when possible, use of endoscopic clips is preferred [74].

Radiologic Evaluation

CT Angiography

Computed tomography angiography (CTA) can be used as a highly effective early diagnostic modality to localize LGIB (Table 40.4) [75]. A shock index ≥1 can predict extravasation on CTA, and its use may be beneficial to select for those who would most benefit from CTA [28]. A three-phase CTA including non-contrast, arterial, and venous phase imaging should be used for evaluation of LGIB [76–78]. CTA has a reported 85.2% sensitivity and 92.1% specificity of detecting acute GI bleeding [79]. The critical image finding is active extravasation of intravenous contrast into bowel lumen. Fluid distention of the bowel may dilute contrast extravasation and cause false-negative results [80]. Rates of bleeding above 0.25–3 ml/min can be detected with a 79–100% sensitivity and 50–100% specificity when using a portal and arterial phase CTA [78, 79, 81–84]. A negative CTA in a hemodynamic stable patient has been shown to be a good prognostic indicator that no further treatment will be needed [85]. Chen in a review of 62 patients demonstrated that 77.4% did not rebleed with a negative CTA [86].

With the ubiquity of CT scans, CTA can be used as an initial localizing modality to help facilitate localization of GI bleed (Fig. 40.7). A randomized controlled trial compared early colonoscopy to a more conservative algorithm of scintigraphy and angiography followed by colonoscopy only when the other tests were negative. This study showed no difference in outcomes including rebleeding and hospital stay. However, this study was underpowered and did show that colonoscopy definitively diagnosed source of bleeding in 42% of patients compared to 22% in the standard arm [23]. The primary advantage of CTA is its ability to rapidly diagnose and localize bleeding without the need for bowel preparation. Rapid and noninvasive definition of the anatomical source of bleeding informs treatment options and can help target therapeutic interventions. However, contrast nephropathy needs to be considered in patients with renal insufficiency.

Catheter-Based Angiography

Mesenteric angiography is the sole radiographic modality that allows for both localization and therapeutic treatment of the bleeding source (Fig. 40.8). In order for this testing

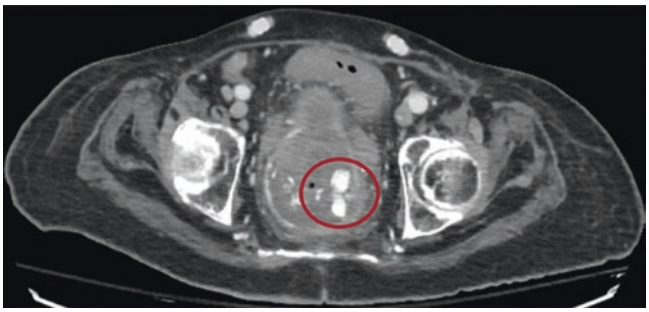

Fig. 40.7 CTA showing contrast extravasation in the upper rectum

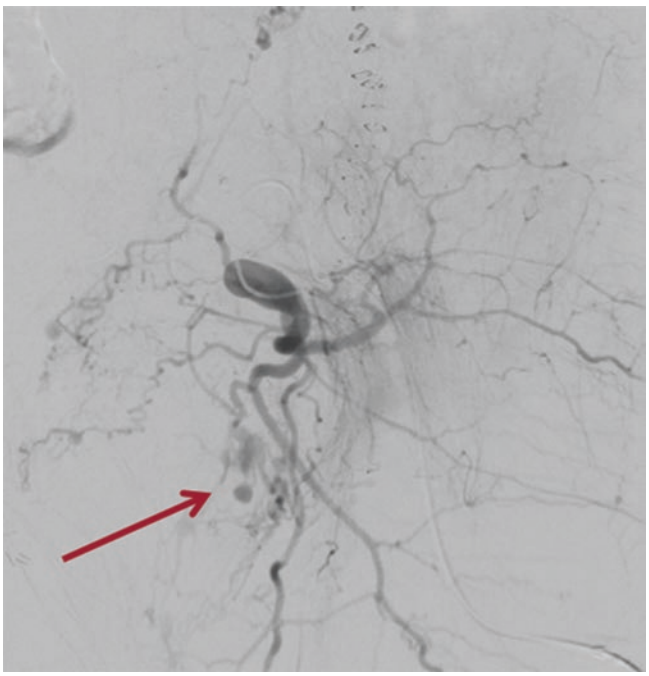

Fig. 40.8 Mesenteric angiography showing contrast extravasation

modality to be successful, the rate of bleeding must be >0.5 ml/minute and continuous [16]. Angiography has a higher success rate at localization in hemodynamically unstable patients who have required >5 units of blood in 24 hours and have a systolic blood pressure of <90 mm Hg [79, 87]. A negative angiogram after a positive CTA is common. Provocative angiography with the use of heparin, nitroglycerin, urokinase, or tissue plasminogen activator can be utilized to increase the likelihood of localization. However, this may lead to uncontrolled bleeding and should only be considered at experienced centers [88, 89]. Super-selective embolization can be achieved in arteries <1 mm in diameter with the use of microcoils, absorbable gelatin sponges, cyanoacrylate glue, or ethylene vinyl or polyvinyl [16]. Angiography has an associated rate of technical success of 73–100% and clinical success of 63–96% and rebleeding rate of 11–50% [16, 90–102]. In the event of unsuccessful control of bleeding, angiography can assist in directing surgical resection of the bleeding source. Self-limited ischemic bowel injury following angiography (abdominal pain, asymptomatic rise in lactic acid) is common. Major ischemic complications are reported in <3% of cases [16, 90–102].

Nuclear Medicine

Nuclear scintigraphy has been a historic gold standard for localization of LGIB, largely due to its extreme sensitivity. ^{99m}Tc-sulfur colloid and ^{99m}Tc-labeled RBC are the two techniques utilized. Technetium-99m-labeled red blood cell scintigraphy has been shown to be superior to that of ^{99m}Tc-sulfur colloid and can detect bleeding rates as slow as 0.04–0.05 ml/minute [103–105]. Despite this, its role in localization is debated due to its major limitations such as its ability to yield a precise anatomical localization and lack of therapeutic capability. In addition, relative patient stability is required, as time is needed to radiolabel the patient's red cells and reinject them. Radiolabeled RBC scintigraphy can detect bleeding for up to 24 hours, at which point most of the label has been lost.

This modality has the advantage of being able to re-scan the patient if the initial scan is negative. Sulfur colloid scanning is an alternative approach in which pre-labeled sulfur colloid is injected. This has the advantage of immediate use, since no autologous radiolabeling is required; however the half-life of the radiolabeled colloid is shorter, and delayed imaging is not possible [105, 106]. Radionuclide scans provide incorrect localization in 10–25% of cases, which can lead to inaccurate surgical treatment [107, 108]. Despite the high sensitivity of radionuclide scans, there is a 55% false-negatives rate using this modality [108]. In a retrospective study, Gunderman suggested that performing scintigraphy before angiography is associated with more selective contrast injection [109]. However, other studies have shown that CTA is the preferred modality for localization of bleed prior to intervention [110] and may obviate the need for the two other studies.

Recurrent LGIB

Early rebleeding, defined as rebleeding before hospital discharge, is reported in 22% of cases and late rebleeding, defined as after hospital discharge, in 16% [9, 23]. Recurrent readmission rates for recurrent LGIB are reported to be as high as 13.7% at 14 days and 19% at 1 year [36, 111]. Patient risk factors include anticoagulation, multiple comorbid conditions, malignancy, non-aspirin antiplatelet agents, dual antiplatelet therapy, age > 65, source of index bleeding (diverticulosis), and initial hemostasis modality [36, 111, 112]. Prevention of recurrent bleeding includes avoidance of NSAIDs and of regular aspirin for primary prevention of cardiovascular events. Repeat endoscopic evaluation and treatment is indicated in patients with recurrent lower GI bleed and has an associated diagnostic yield of 3–60% [16, 113, 114]. If bleeding is unable to be controlled with colonoscopy, and the location is known, angiography and embolization should be considered. In patients with early rebleeds and previous localization, surgical resection can be considered.

Recurrent LGIB without previous localization poses a clinical challenge. Repeat upper and lower endoscopy has diagnostic yields between 40% and 65% [114]. Continued bleeding, without endoscopic localization, should prompt evaluation of small bowel source. Surgical intervention in the absence of a known location, discussed below, is to be avoided.

Small Bowel GIB

Obscure GI bleeding is defined as an unlocalized source of bleeding after endoscopic and imaging evaluations. Most obscure GI bleeding sources tend to be from the small bowel, and therefore it is commonly referred to as "suspected small bowel bleeding." The most common etiologies of small bowel bleeding are inflammatory bowel disease, angioectasia, neoplasms, NSAID-induced ulcers, and Dieulafoy's lesions (mucosal erosion over visible vessel) [113]. Small bowel bleeding should only be considered after second-look endoscopy rules out both upper and lower GI bleeds. During second-look endoscopy, colonoscopy should attempt to evaluate the ileum, and upper endoscopy should attempt to evaluate the distal portion of duodenum and jejunum via push enteroscopy. Small bowel bleeding usually presents as stable occult bleeding. If no source of bleeding is found, other modalities such as video capsule endoscopy or enteroscopy (double or single balloon) should be considered.

Capsule endoscopy (CE) is a modality in which a video-recording capsule is swallowed. It transmits video of its tran-

sit throughout the small bowel wirelessly, allowing diagnostic evaluation of the mucosa. It is associated with a diagnostic yield of 38–83% and allows for noninvasive evaluation of the entire small bowel in 70–90% of patients [115]. CE can lead to a change in management in 37–87% of patients [116, 117]; it is associated with high positive (94–97%) and negative predictive (83–100%) values [117, 118]. CE is associated with positive findings in patients with hemoglobin <10 g/dl, >6 months' duration of bleeding, more than one episode of bleeding, overt bleeding, and CE performed within 2 weeks of bleeding episode [119–122]. The major drawbacks of CE are the inability to render therapeutic intervention and difficulty in precise localization of the lesion. Viazis demonstrated that a repeat CE can be diagnostic in occult bleeding with hemoglobin drop of >4 g/dl [123]. Multiple retrospective and prospective studies have shown CE to be superior in evaluation of small bowel bleed when compared to enteroscopy [114, 124].

Enteroscopy

Double balloon enteroscopy (DBE) can be used to evaluate a distance of approximately 240–360 cm of the bowel distal to the pylorus. It is advantageous in comparison to CE due to its diagnostic and therapeutic capabilities [121, 125, 126]. It is associated with a diagnostic yield of 60–80% and therapeutic intervention yields of 40–73% [121, 127–129]. DBE is limited by its invasive nature, prolonged intubation times, and need for properly trained and multiple personnel. Overall complication rates including perforation and pancreatitis are reported at 1.2% [130]. Single balloon enteroscopy (SBE) is similar to that of DBE except this device has no balloon at the end of the enteroscope. SBE is equivalent to DBE for the evaluation of a small bowel bleeding source [131, 132]. Use of CE prior to DBE is encouraged to minimize the performance of an invasive procedure in patients with low probability of small bowel findings [133–135]. However, in patients with high suspicion for small bowel bleed, CE may be falsely negative, and therefore enteroscopy may need to be performed to rule out a small bowel etiology [136].

Surgery

In instances where radiological and endoscopic attempts fail at localization and/or treatment of LGIB, surgical consultation should be obtained. Surgical consultation should also be considered in patients who are hemodynamically unstable so that the surgeons can be part of the decision-making process. Surgical resection is required in only 7–25% of patients to stop LGIB [21, 137]. Localization and diagnosis is critical in the evaluation for surgical intervention. Bleeding associated with inflammatory bowel disease and malignancy may markedly change the operative strategy and approach. For cases of colonic and/or small bowel malignancy in which patients have ongoing hemorrhage, oncological resection when possible should be attempted. In cases of rectal cancer, consideration for imminent start of radiation therapy to stop bleeding should be considered as part of the treatment paradigm.

Non-localized LGIB

In the case of a LGIB where a small bowel source has been ruled out (e.g., only colonic blood is seen, anoscopy is negative, and terminal ileal intubation is negative, for blood), subtotal colectomy should be considered. The planned approach for totally non-localized LGIB when surgery cannot be avoided should be diagnostic laparoscopy and/or exploratory laparotomy in which the bowel is run in its entirety to rule out any palpable lesions. Intraoperative colonoscopy and enteroscopy are options if no lesion is found.

Intraoperative enteroscopy involves the evaluation of the small bowel during laparotomy or laparoscopy. It can be performed transorally, transrectally, and/or through an enterotomy. It has a reported diagnostic yield of 50–88% with rebleeding rates of 60% [138–142]. If no source is identified despite colonoscopy and/or enteroscopy and colonic origin is suspected, a blind subtotal colectomy can be considered. Consideration can be given, in the relatively stable patient, to performance of a temporary loop ileostomy. This may afford the opportunity to better distinguish between a small and large bowel source. Rebleeding rates after blind subtotal colectomy are approximately 4% [143–148].

Segmental resection is the most appropriate option when the source has been confidently identified, due to improved bowel function when compared to subtotal colectomy [145, 149]. Segmental colectomy has been associated with bleeding rates of up to 4–14% [143–145, 150]. Subtotal colectomy should be performed in patients when the source of colonic bleeding is uncertain. The role of stoma in subtotal colectomy will be dependent on the hemodynamics of the patients.

Conclusion

Lower GI bleeding is common and potentially morbid; however, it is rarely a surgical disease. Current endoscopic and radiologic modalities and techniques have allowed for diagnosis and management of the majority of these bleeds. Risk stratification strategies may help guide therapy. While surgeons should commonly be involved in the management of these patients as part of the multidisciplinary team, surgical resection is only occasionally warranted. Surgery for non-localized bleeding should be avoided whenever possible.

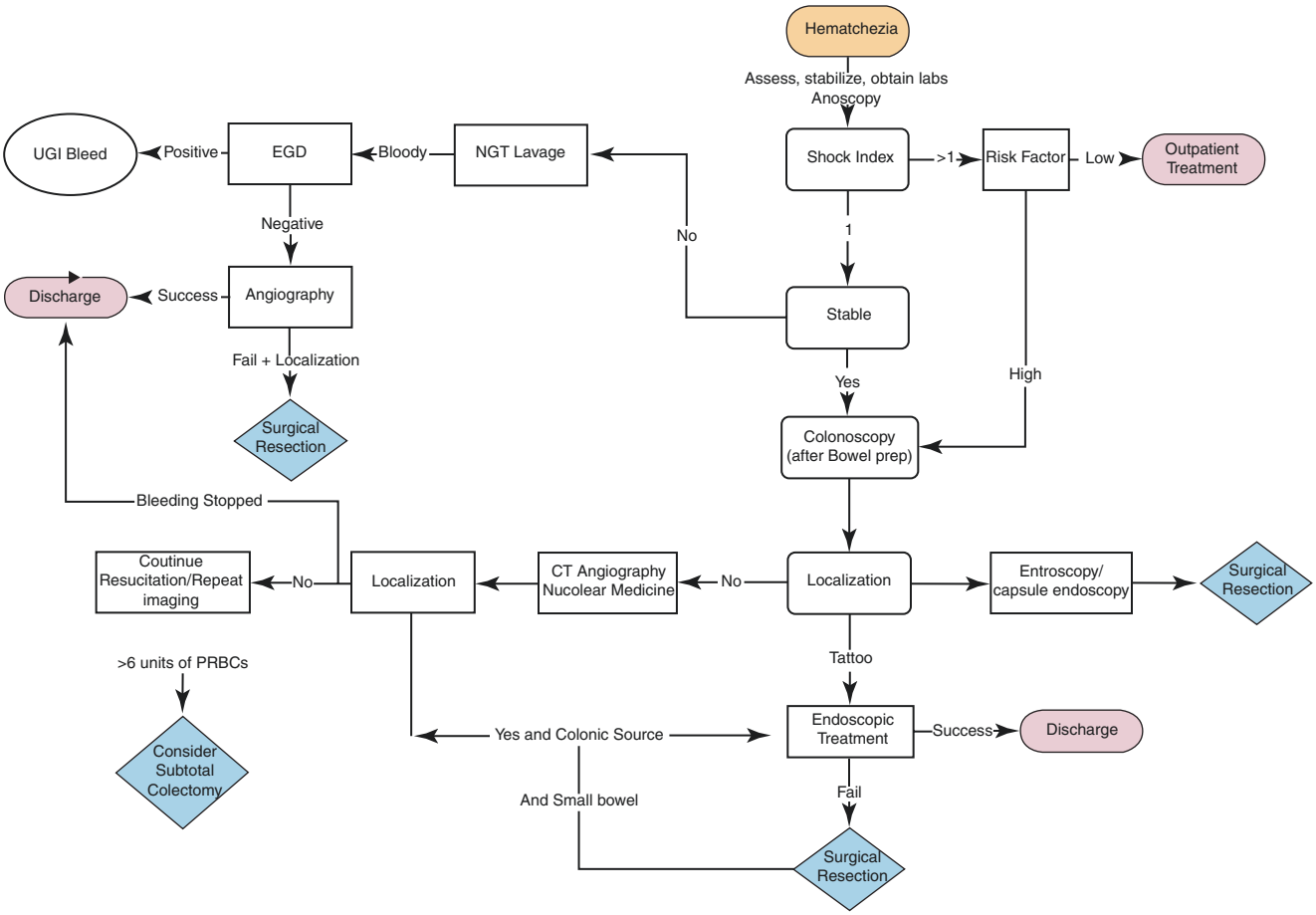

Fig. 40.9 Algorithm for the treatment of lower GI bleeding

The algorithm in Fig. 40.9 shows the treatment schema for lower GI bleeding.

References

1. Hreinsson JP, Gumundsson S, Kalaitzakis E, Bjornsson ES. Lower gastrointestinal bleeding: incidence, etiology, and outcomes in a population-based setting. Eur J Gastroenterol Hepatol. 2013;25:37–43.
2. Lanas A, Garcia-Rodriguez LA, Polo-Tomas M, et al. Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice. Am J Gastroenterol. 2009;104:1633–41.
3. Peery AF, Crockett SD, Barritt AS, et al. Burden of gastrointestinal, liver, and pancreatic diseases in the United States. Gastroenterology. 2015;149:1731–1741 e1733.
4. Qayed E, Dagar G, Nanchal RS. Lower gastrointestinal hemorrhage. Crit Care Clin. 2016;32:241–54.
5. Chait MM. Lower gastrointestinal bleeding in the elderly. World J Gastrointest Endosc. 2010;2:147–54.
6. Strate LL, Gralnek IM. ACG clinical guideline: management of patients with acute lower gastrointestinal bleeding. Am J Gastroenterol. 2016;111:459–74.
7. Laine L, Yang H, Chang SC, Datto C. Trends for incidence of hospitalization and death due to GI complications in the United States from 2001 to 2009. Am J Gastroenterol. 2012;107:1190–5; quiz 1196.
8. Ghassemi KA, Jensen DM. Lower GI bleeding: epidemiology and management. Curr Gastroenterol Rep. 2013;15:333.
9. Laine L, Shah A. Randomized trial of urgent vs. elective colonoscopy in patients hospitalized with lower GI bleeding. Am J Gastroenterol. 2010;105:2636–41; quiz 2642.
10. Oakland K, Guy R, Uberoi R, et al. Acute lower GI bleeding in the UK: patient characteristics, interventions and outcomes in the first nationwide audit. Gut. 2018;67:654–62.
11. Whitehurst BD. Lower gastrointestinal bleeding. Surg Clin North Am. 2018;98:1059–72.
12. Longstreth GF. Epidemiology and outcome of patients hospitalized with acute lower gastrointestinal hemorrhage: a population-based study. Am J Gastroenterol. 1997;92:419–24.
13. Marion Y, Lebreton G, Le Pennec V, et al. The management of lower gastrointestinal bleeding. J Visc Surg. 2014;151:191–201.
14. Strate LL. Lower GI bleeding: epidemiology and diagnosis. Gastroenterol Clin N Am. 2005;34:643–64.
15. Strate LL, Naumann CR. The role of colonoscopy and radiological procedures in the management of acute lower intestinal bleeding. Clin Gastroenterol Hepatol. 2010;8:333–43; quiz e344.
16. Gralnek IM, Neeman Z, Strate LL. Acute lower gastrointestinal bleeding. N Engl J Med. 2017;376:e50.
17. Cheskin LJ, Bohlman M, Schuster MM. Diverticular disease in the elderly. Gastroenterol Clin N Am. 1990;19:391–403.

18. Gayer C, Chino A, Lucas C, et al. Acute lower gastrointestinal bleeding in 1,112 patients admitted to an urban emergency medical center. Surgery. 2009;146:600–6; discussion 606–607.
19. McGuire HH Jr, Haynes BW Jr. Massive hemorrhage for diverticulosis of the colon: guidelines for therapy based on bleeding patterns observed in fifty cases. Ann Surg. 1972;175:847–55.
20. Parks TG. Natural history of diverticular disease of the colon. Clin Gastroenterol. 1975;4:53–69.
21. Feinman M, Haut ER. Lower gastrointestinal bleeding. Surg Clin North Am. 2014;94:55–63.
22. Niikura R, Nagata N, Shimbo T, et al. Natural history of bleeding risk in colonic diverticulosis patients: a long-term colonoscopy-based cohort study. Aliment Pharmacol Ther. 2015;41:888–94.
23. Green BT, Rockey DC, Portwood G, et al. Urgent colonoscopy for evaluation and management of acute lower gastrointestinal hemorrhage: a randomized controlled trial. Am J Gastroenterol. 2005;100:2395–402.
24. Jensen DM, Machicado GA. Diagnosis and treatment of severe hematochezia. The role of urgent colonoscopy after purge. Gastroenterology. 1988;95:1569–74.
25. Newman J, Fitzgerald JE, Gupta S, et al. Outcome predictors in acute surgical admissions for lower gastrointestinal bleeding. Color Dis. 2012;14:1020–6.
26. Aoki T, Nagata N, Shimbo T, et al. Development and validation of a risk scoring system for severe acute lower gastrointestinal bleeding. Clin Gastroenterol Hepatol. 2016;14:1562–1570 e1562.
27. Oakland K, Chadwick G, East JE, et al. Diagnosis and management of acute lower gastrointestinal bleeding: guidelines from the British Society of Gastroenterology. Gut. 2019;68:776–89.
28. Rassameehiran S, Teerakanok J, Suchartlikitwong S, Nugent K. Utility of the shock index for risk stratification in patients with acute upper gastrointestinal bleeding. South Med J. 2017;110:738–43.
29. Das A, Ben-Menachem T, Cooper GS, et al. Prediction of outcome in acute lower-gastrointestinal haemorrhage based on an artificial neural network: internal and external validation of a predictive model. Lancet. 2003;362:1261–6.
30. Kollef MH, O'Brien JD, Zuckerman GR, Shannon W. BLEED: a classification tool to predict outcomes in patients with acute upper and lower gastrointestinal hemorrhage. Crit Care Med. 1997;25:1125–32.
31. Strate LL, Orav EJ, Syngal S. Early predictors of severity in acute lower intestinal tract bleeding. Arch Intern Med. 2003;163:838–43.
32. Strate LL, Saltzman JR, Ookubo R, et al. Validation of a clinical prediction rule for severe acute lower intestinal bleeding. Am J Gastroenterol. 2005;100:1821–7.
33. Velayos FS, Williamson A, Sousa KH, et al. Early predictors of severe lower gastrointestinal bleeding and adverse outcomes: a prospective study. Clin Gastroenterol Hepatol. 2004;2:485–90.
34. Patel R, Clancy R, Crowther E, et al. A rectal bleeding algorithm can successfully reduce emergency admissions. Color Dis. 2014;16:377–81.
35. Oakland K, Jairath V, Uberoi R, et al. Derivation and validation of a novel risk score for safe discharge after acute lower gastrointestinal bleeding: a modelling study. Lancet Gastroenterol Hepatol. 2017;2:635–43.
36. Sengupta N, Tapper EB, Patwardhan VR, et al. Risk factors for adverse outcomes in patients hospitalized with lower gastrointestinal bleeding. Mayo Clin Proc. 2015;90:1021–9.
37. Zuckerman GR, Prakash C. Acute lower intestinal bleeding: part I: clinical presentation and diagnosis. Gastrointest Endosc. 1998;48:606–17.
38. Villanueva C, Colomo A, Bosch A. Transfusion for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368:1362–3.
39. Wang J, Bao YX, Bai M, et al. Restrictive vs liberal transfusion for upper gastrointestinal bleeding: a meta-analysis of randomized controlled trials. World J Gastroenterol. 2013;19:6919–27.
40. Baradarian R, Ramdhaney S, Chapalamadugu R, et al. Early intensive resuscitation of patients with upper gastrointestinal bleeding decreases mortality. Am J Gastroenterol. 2004;99:619–22.
41. Lim CH. Early intensive resuscitation of patients with upper gastrointestinal bleeding decreases mortality. Am J Gastroenterol. 2004;99:2502; author reply 2502–2503.
42. Baron TH, Kamath PS, McBane RD. New anticoagulant and antiplatelet agents: a primer for the gastroenterologist. Clin Gastroenterol Hepatol. 2014;12:187–95.
43. Siegal DM. Managing target-specific oral anticoagulant associated bleeding including an update on pharmacological reversal agents. J Thromb Thrombolysis. 2015;39:395–402.
44. Jairath V, Kahan BC, Stanworth SJ, et al. Prevalence, management, and outcomes of patients with coagulopathy after acute non-variceal upper gastrointestinal bleeding in the United Kingdom. Transfusion. 2013;53:1069–76.
45. Shingina A, Barkun AN, Razzaghi A, et al. Systematic review: the presenting international normalised ratio (INR) as a predictor of outcome in patients with upper nonvariceal gastrointestinal bleeding. Aliment Pharmacol Ther. 2011;33:1010–8.
46. Wolf AT, Wasan SK, Saltzman JR. Impact of anticoagulation on rebleeding following endoscopic therapy for nonvariceal upper gastrointestinal hemorrhage. Am J Gastroenterol. 2007;102:290–6.
47. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA. 2015;313:471–82.
48. Holster IL, Valkhoff VE, Kuipers EJ, Tjwa E. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. Gastroenterology. 2013;145:105–112 e115.
49. Kaatz S, Kouides PA, Garcia DA, et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. Am J Hematol. 2012;87(Suppl 1):S141–5.
50. Siegal DM, Garcia DA, Crowther MA. How I treat target-specific oral anticoagulant-associated bleeding. Blood. 2014;123:1152–8.
51. Committee ASoP, Pasha SF, Shergill A, et al. The role of endoscopy in the patient with lower GI bleeding. Gastrointest Endosc. 2014;79:875–85.
52. Davila RE, Rajan E, Adler DG, et al. ASGE guideline: the role of endoscopy in the patient with lower-GI bleeding. Gastrointest Endosc. 2005;62:656–60.
53. Strate LL, Syngal S. Timing of colonoscopy: impact on length of hospital stay in patients with acute lower intestinal bleeding. Am J Gastroenterol. 2003;98:317–22.
54. Jensen DM, Machicado GA, Jutabha R, Kovacs TO. Urgent colonoscopy for the diagnosis and treatment of severe diverticular hemorrhage. N Engl J Med. 2000;342:78–82.
55. Oakland K, Isherwood J, Lahiff C, et al. Diagnostic and therapeutic treatment modalities for acute lower gastrointestinal bleeding: a systematic review. Endosc Int Open. 2017;5:E959–73.
56. Gupta S, Greenwald DA. Prevention of recurrent lower gastrointestinal hemorrhage. Gastrointest Endosc Clin N Am. 2018;28:409–24.
57. Jensen DM, Ohning GV, Kovacs TO, et al. Natural history of definitive diverticular hemorrhage based on stigmata of recent hemorrhage and colonoscopic Doppler blood flow monitoring for risk stratification and definitive hemostasis. Gastrointest Endosc. 2016;83:416–23.
58. Barkun AN, Moosavi S, Martel M. Topical hemostatic agents: a systematic review with particular emphasis on endoscopic application in GI bleeding. Gastrointest Endosc. 2013;77:692–700.

59. Leung Ki EL, Lau JY. New endoscopic hemostasis methods. Clin Endosc. 2012;45:224–9.
60. Kaltenbach T, Watson R, Shah J, et al. Colonoscopy with clipping is useful in the diagnosis and treatment of diverticular bleeding. Clin Gastroenterol Hepatol. 2012;10:131–7.
61. Binmoeller KF, Thonke F, Soehendra N. Endoscopic hemoclip treatment for gastrointestinal bleeding. Endoscopy. 1993;25:167–70.
62. Hokama A, Uehara T, Nakayoshi T, et al. Utility of endoscopic hemoclipping for colonic diverticular bleeding. Am J Gastroenterol. 1997;92:543–6.
63. Kumar A, Artifon E, Chu A, Halwan B. Effectiveness of endoclips for the treatment of stigmata of recent hemorrhage in the colon of patients with acute lower gastrointestinal tract bleeding. Dig Dis Sci. 2011;56:2978–86.
64. Simpson PW, Nguyen MH, Lim JK, Soetikno RM. Use of endoclips in the treatment of massive colonic diverticular bleeding. Gastrointest Endosc. 2004;59:433–7.
65. Yen EF, Ladabaum U, Muthusamy VR, et al. Colonoscopic treatment of acute diverticular hemorrhage using endoclips. Dig Dis Sci. 2008;53:2480–5.
66. Wong Kee Song LM, Baron TH. Endoscopic management of acute lower gastrointestinal bleeding. Am J Gastroenterol. 2008;103:1881–7.
67. Farrell JJ, Graeme-Cook F, Kelsey PB. Treatment of bleeding colonic diverticula by endoscopic band ligation: an in-vivo and ex-vivo pilot study. Endoscopy. 2003;35:823–9.
68. Ishii N, Setoyama T, Deshpande GA, et al. Endoscopic band ligation for colonic diverticular hemorrhage. Gastrointest Endosc. 2012;75:382–7.
69. Setoyama T, Ishii N, Fujita Y. Endoscopic band ligation (EBL) is superior to endoscopic clipping for the treatment of colonic diverticular hemorrhage. Surg Endosc. 2011;25:3574–8.
70. Kwan V, Bourke MJ, Williams SJ, et al. Argon plasma coagulation in the management of symptomatic gastrointestinal vascular lesions: experience in 100 consecutive patients with long-term follow-up. Am J Gastroenterol. 2006;101:58–63.
71. Olmos JA, Marcolongo M, Pogorelsky V, et al. Long-term outcome of argon plasma ablation therapy for bleeding in 100 consecutive patients with colonic angiodysplasia. Dis Colon Rectum. 2006;49:1507–16.
72. Pate GE, Mulligan A. An epidemiological study of Heyde's syndrome: an association between aortic stenosis and gastrointestinal bleeding. J Heart Valve Dis. 2004;13:713–6.
73. Pate GE, Chandavimol M, Naiman SC, Webb JG. Heyde's syndrome: a review. J Heart Valve Dis. 2004;13:701–12.
74. Parra-Blanco A, Kaminaga N, Kojima T, et al. Colonoscopic polypectomy with cutting current: is it safe? Gastrointest Endosc. 2000;51:676–81.
75. Wortman JR, Landman W, Fulwadhva UP, et al. CT angiography for acute gastrointestinal bleeding: what the radiologist needs to know. Br J Radiol. 2017;90:20170076.
76. Artigas JM, Marti M, Soto JA, et al. Multidetector CT angiography for acute gastrointestinal bleeding: technique and findings. Radiographics. 2013;33:1453–70.
77. Frattaroli FM, Casciani E, Spoletini D, et al. Prospective study comparing multi-detector row CT and endoscopy in acute gastrointestinal bleeding. World J Surg. 2009;33:2209–17.
78. Kennedy DW, Laing CJ, Tseng LH, et al. Detection of active gastrointestinal hemorrhage with CT angiography: a 4(1/2)-year retrospective review. J Vasc Interv Radiol. 2010;21:848–55.
79. Garcia-Blazquez V, Vicente-Bartulos A, Olavarria-Delgado A, et al. Accuracy of CT angiography in the diagnosis of acute gastrointestinal bleeding: systematic review and meta-analysis. Eur Radiol. 2013;23:1181–90.
80. Stuber T, Hoffmann MH, Stuber G, et al. Pitfalls in detection of acute gastrointestinal bleeding with multi-detector row helical CT. Abdom Imaging. 2009;34:476–82.
81. Shih SL, Liu YP, Tsai YS, et al. Evaluation of arterial phase MDCT for the characterization of lower gastrointestinal bleeding in infants and children: preliminary results. AJR Am J Roentgenol. 2010;194:496–9.
82. Yoon W, Jeong YY, Shin SS, et al. Acute massive gastrointestinal bleeding: detection and localization with arterial phase multidetector row helical CT. Radiology. 2006;239:160–7.
83. Marti M, Artigas JM, Garzon G, et al. Acute lower intestinal bleeding: feasibility and diagnostic performance of CT angiography. Radiology. 2012;262:109–16.
84. Sun H, Jin Z, Li X, et al. Detection and localization of active gastrointestinal bleeding with multidetector row computed tomography angiography: a 5-year prospective study in one medical center. J Clin Gastroenterol. 2012;46:31–41.
85. Foley PT, Ganeshan A, Anthony S, Uberoi R. Multi-detector CT angiography for lower gastrointestinal bleeding: can it select patients for endovascular intervention? J Med Imaging Radiat Oncol. 2010;54:9–16.
86. Chen Q, Tulloh R, Caputo M, et al. Does the persistence of pulsatile antegrade pulmonary blood flow following bidirectional Glenn procedure affect long term outcome? Eur J Cardiothorac Surg. 2015;47:154–8; discussion 158.
87. Abbas SM, Bissett IP, Holden A, et al. Clinical variables associated with positive angiographic localization of lower gastrointestinal bleeding. ANZ J Surg. 2005;75:953–7.
88. Kim CY, Suhocki PV, Miller MJ Jr, et al. Provocative mesenteric angiography for lower gastrointestinal hemorrhage: results from a single-institution study. J Vasc Interv Radiol. 2010;21:477–83.
89. Widlus DM, Salis AI. Reteplase provocative visceral arteriography. J Clin Gastroenterol. 2007;41:830–3.
90. Bandi R, Shetty PC, Sharma RP, et al. Superselective arterial embolization for the treatment of lower gastrointestinal hemorrhage. J Vasc Interv Radiol. 2001;12:1399–405.
91. d'Othee BJ, Surapaneni P, Rabkin D, et al. Microcoil embolization for acute lower gastrointestinal bleeding. Cardiovasc Intervent Radiol. 2006;29:49–58.
92. Funaki B, Kostelic JK, Lorenz J, et al. Superselective microcoil embolization of colonic hemorrhage. AJR Am J Roentgenol. 2001;177:829–36.
93. Khanna A, Ognibene SJ, Koniaris LG. Embolization as first-line therapy for diverticulosis-related massive lower gastrointestinal bleeding: evidence from a meta-analysis. J Gastrointest Surg. 2005;9:343–52.
94. Kickuth R, Rattunde H, Gschossmann J, et al. Acute lower gastrointestinal hemorrhage: minimally invasive management with microcatheter embolization. J Vasc Interv Radiol. 2008;19:1289–1296 e1282.
95. Kuo WT, Lee DE, Saad WE, et al. Superselective microcoil embolization for the treatment of lower gastrointestinal hemorrhage. J Vasc Interv Radiol. 2003;14:1503–9.
96. Lipof T, Sardella WV, Bartus CM, et al. The efficacy and durability of super-selective embolization in the treatment of lower gastrointestinal bleeding. Dis Colon Rectum. 2008;51:301–5.
97. Neuman HB, Zarzaur BL, Meyer AA, et al. Superselective catheterization and embolization as first-line therapy for lower gastrointestinal bleeding. Am Surg. 2005;71:539–44. discussion 544–535.
98. Tan KK, Wong D, Sim R. Superselective embolization for lower gastrointestinal hemorrhage: an institutional review over 7 years. World J Surg. 2008;32:2707–15.
99. Gillespie CJ, Sutherland AD, Mossop PJ, et al. Mesenteric embolization for lower gastrointestinal bleeding. Dis Colon Rectum. 2010;53:1258–64.

100. Huang CC, Lee CW, Hsiao JK, et al. N-butyl cyanoacrylate embolization as the primary treatment of acute hemodynamically unstable lower gastrointestinal hemorrhage. J Vasc Interv Radiol. 2011;22:1594–9.
101. Hur S, Jae HJ, Lee M, et al. Safety and efficacy of transcatheter arterial embolization for lower gastrointestinal bleeding: a single-center experience with 112 patients. J Vasc Interv Radiol. 2014;25:10–9.
102. Tan KK, Strong DH, Shore T, et al. The safety and efficacy of mesenteric embolization in the management of acute lower gastrointestinal hemorrhage. Ann Coloproctol. 2013;29:205–8.
103. Thorne DA, Datz FL, Remley K, Christian PE. Bleeding rates necessary for detecting acute gastrointestinal bleeding with technetium-99m-labeled red blood cells in an experimental model. J Nucl Med. 1987;28:514–20.
104. Currie GM, Towers PA, Wheat JM. Improved detection and localization of lower gastrointestinal tract hemorrhage by subtraction scintigraphy: phantom analysis. J Nucl Med Technol. 2006;34:160–8.
105. Grady E. Gastrointestinal bleeding scintigraphy in the early 21st century. J Nucl Med. 2016;57:252–9.
106. Padia SA, Bybel B, Newman JS. Radiologic diagnosis and management of acute lower gastrointestinal bleeding. Cleve Clin J Med. 2007;74:417–20.
107. Dolezal J, Vizda J, Kopacova M. Single-photon emission computed tomography enhanced Tc-99m-pertechnetate disodium-labelled red blood cell scintigraphy in the localization of small intestine bleeding: a single-centre twelve-year study. Digestion. 2011;84:207–11.
108. Tabibian JH, Wong Kee Song LM, Enders FB, et al. Technetium-labeled erythrocyte scintigraphy in acute gastrointestinal bleeding. Int J Color Dis. 2013;28:1099–105.
109. Gunderman R, Leef J, Ong K, et al. Scintigraphic screening prior to visceral arteriography in acute lower gastrointestinal bleeding. J Nucl Med. 1998;39:1081–3.
110. Zink SI, Ohki SK, Stein B, et al. Noninvasive evaluation of active lower gastrointestinal bleeding: comparison between contrast-enhanced MDCT and 99mTc-labeled RBC scintigraphy. AJR Am J Roentgenol. 2008;191:1107–14.
111. Aoki T, Nagata N, Niikura R, et al. Recurrence and mortality among patients hospitalized for acute lower gastrointestinal bleeding. Clin Gastroenterol Hepatol. 2015;13:488–494 e481.
112. Anthony T, Penta P, Todd RD, et al. Rebleeding and survival after acute lower gastrointestinal bleeding. Am J Surg. 2004;188:485–90.
113. Gerson LB, Fidler JL, Cave DR, Leighton JA. ACG clinical guideline: diagnosis and management of small bowel bleeding. Am J Gastroenterol. 2015;110:1265–87; quiz 1288.
114. Gerson LB. Small bowel bleeding: updated algorithm and outcomes. Gastrointest Endosc Clin N Am. 2017;27:171–80.
115. Rondonotti E, Villa F, Mulder CJ, et al. Small bowel capsule endoscopy in 2007: indications, risks and limitations. World J Gastroenterol. 2007;13:6140–9.
116. Ben Soussan E, Antonietti M, Herve S, et al. Diagnostic yield and therapeutic implications of capsule endoscopy in obscure gastrointestinal bleeding. Gastroenterol Clin Biol. 2004;28:1068–73.
117. Pennazio M, Santucci R, Rondonotti E, et al. Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: report of 100 consecutive cases. Gastroenterology. 2004;126:643–53.
118. Delvaux M, Fassler I, Gay G. Clinical usefulness of the endoscopic video capsule as the initial intestinal investigation in patients with obscure digestive bleeding: validation of a diagnostic strategy based on the patient outcome after 12 months. Endoscopy. 2004;36:1067–73.
119. Bresci G, Parisi G, Bertoni M, et al. The role of video capsule endoscopy for evaluating obscure gastrointestinal bleeding: usefulness of early use. J Gastroenterol. 2005;40:256–9.
120. Carey EJ, Leighton JA, Heigh RI, et al. A single-center experience of 260 consecutive patients undergoing capsule endoscopy for obscure gastrointestinal bleeding. Am J Gastroenterol. 2007;102:89–95.
121. May A, Nachbar L, Ell C. Double-balloon enteroscopy (push-and-pull enteroscopy) of the small bowel: feasibility and diagnostic and therapeutic yield in patients with suspected small bowel disease. Gastrointest Endosc. 2005;62:62–70.
122. Mishkin DS, Chuttani R, Croffie J, et al. ASGE technology status evaluation report: wireless capsule endoscopy. Gastrointest Endosc. 2006;63:539–45.
123. Viazis N, Papaxoinis K, Vlachogiannakos J, et al. Is there a role for second-look capsule endoscopy in patients with obscure GI bleeding after a nondiagnostic first test? Gastrointest Endosc. 2009;69:850–6.
124. Triester SL, Leighton JA, Leontiadis GI, et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with obscure gastrointestinal bleeding. Am J Gastroenterol. 2005;100:2407–18.
125. Heine GD, Hadithi M, Groenen MJ, et al. Double-balloon enteroscopy: indications, diagnostic yield, and complications in a series of 275 patients with suspected small-bowel disease. Endoscopy. 2006;38:42–8.
126. Nakamura M, Niwa Y, Ohmiya N, et al. Preliminary comparison of capsule endoscopy and double-balloon enteroscopy in patients with suspected small-bowel bleeding. Endoscopy. 2006;38:59–66.
127. Gross SA, Stark ME. Initial experience with double-balloon enteroscopy at a U.S. center. Gastrointest Endosc. 2008;67:890–7.
128. Yamamoto H, Kita H, Sunada K, et al. Clinical outcomes of double-balloon endoscopy for the diagnosis and treatment of small-intestinal diseases. Clin Gastroenterol Hepatol. 2004;2:1010–6.
129. Zhang Q, He Q, Liu J, et al. Combined use of capsule endoscopy and double-balloon enteroscopy in the diagnosis of obscure gastrointestinal bleeding: meta-analysis and pooled analysis. HepatoGastroenterology. 2013;60:1885–91.
130. Moschler O, May A, Muller MK, et al. Complications in and performance of double-balloon enteroscopy (DBE): results from a large prospective DBE database in Germany. Endoscopy. 2011;43:484–9.
131. Domagk D, Mensink P, Aktas H, et al. Single- vs double-balloon enteroscopy in small-bowel diagnostics: a randomized multicenter trial. Endoscopy. 2011;43:472–6.
132. Takano N, Yamada A, Watabe H, et al. Single-balloon versus double-balloon endoscopy for achieving total enteroscopy: a randomized, controlled trial. Gastrointest Endosc. 2011;73:734–9.
133. Gay G, Delvaux M, Fassler I. Outcome of capsule endoscopy in determining indication and route for push-and-pull enteroscopy. Endoscopy. 2006;38:49–58.
134. Hendel JW, Vilmann P, Jensen T. Double-balloon endoscopy: who needs it? Scand J Gastroenterol. 2008;43:363–7.
135. Kaffes AJ, Siah C, Koo JH. Clinical outcomes after double-balloon enteroscopy in patients with obscure GI bleeding and a positive capsule endoscopy. Gastrointest Endosc. 2007;66:304–9.
136. Pasha SF, Leighton JA, Das A, et al. Double-balloon enteroscopy and capsule endoscopy have comparable diagnostic yield in small-bowel disease: a meta-analysis. Clin Gastroenterol Hepatol. 2008;6:671–6.
137. Yi WS, Vegeler R, Hoang K, et al. Watch and wait: conservative management of lower gastrointestinal bleeding. J Surg Res. 2012;177:315–9.
138. Cave DR, Cooley JS. Intraoperative enteroscopy. Indications and techniques. Gastrointest Endosc Clin N Am. 1996;6:793–802.

139. Douard R, Wind P, Panis Y, et al. Intraoperative enteroscopy for diagnosis and management of unexplained gastrointestinal bleeding. Am J Surg. 2000;180:181–4.
140. Lopez MJ, Cooley JS, Petros JG, et al. Complete intraoperative small-bowel endoscopy in the evaluation of occult gastrointestinal bleeding using the sonde enteroscope. Arch Surg. 1996;131:272–7.
141. Ress AM, Benacci JC, Sarr MG. Efficacy of intraoperative enteroscopy in diagnosis and prevention of recurrent, occult gastrointestinal bleeding. Am J Surg. 1992;163:94–8; discussion 98–99.
142. Zaman A, Sheppard B, Katon RM. Total peroral intraoperative enteroscopy for obscure GI bleeding using a dedicated push enteroscope: diagnostic yield and patient outcome. Gastrointest Endosc. 1999;50:506–10.
143. Leitman IM, Paull DE, Shires GT 3rd. Evaluation and management of massive lower gastrointestinal hemorrhage. Ann Surg. 1989;209:175–80.
144. Britt LG, Warren L, Moore OF, 3rd. Selective management of lower gastrointestinal bleeding. Am Surg. 1983;49:121–5.
145. Colacchio TA, Forde KA, Patsos TJ, Nunez D. Impact of modern diagnostic methods on the management of active rectal bleeding. Ten year experience. Am J Surg. 1982;143:607–10.
146. Gianfrancisco JA, Abcarian H. Pitfalls in the treatment of massive lower gastrointestinal bleeding with "blind" subtotal colectomy. Dis Colon Rectum. 1982;25:441–5.
147. Baker R, Senagore A. Abdominal colectomy offers safe management for massive lower GI bleed. Am Surg. 1994;60:578–81; discussion 582.
148. Farner R, Lichliter W, Kuhn J, Fisher T. Total colectomy versus limited colonic resection for acute lower gastrointestinal bleeding. Am J Surg. 1999;178:587–91.
149. Browder W, Cerise EJ, Litwin MS. Impact of emergency angiography in massive lower gastrointestinal bleeding. Ann Surg. 1986;204:530–6.
150. Parkes BM, Obeid FN, Sorensen VJ, et al. The management of massive lower gastrointestinal bleeding. Am Surg. 1993;59:676–8.

Endometriosis

41

Heidi Chua and Michael J. Snyder

Key Concepts

- Endometriosis is a common cause of young women undergoing pelvic surgery.
- Endometriosis causes pelvic pain, infertility, and dyschezia.
- Laparoscopy and pathologic identification of endometriosis are the gold standard for diagnosis.
- Symptomatic Stage 4 endometriosis requires surgery.
- A multidisciplinary approach with gynecologists and urologists for advanced endometriosis is optimal.

Introduction

Endometriosis is simply a disease characterized by the presence of viable endometrial-like glands and stroma outside the uterine cavity. For the millions of women afflicted with endometriosis, however, there is nothing simple about the evaluation and management of this painful, chronic, and inflammatory disease. While it is one of the most common conditions requiring surgery for women during their reproductive years, diagnostic delays remain a significant barrier to patients seeking appropriate and timely care with a delay in diagnosis from the onset of symptoms of 7–12 years [1, 2]. Endometriosis is often associated with disabling pelvic pain, intractable infertility, and gastrointestinal instability around the time of menses. The degree of symptomatology is variable and may not be indicative of the extent of pathology encountered at surgery. Small lesions may cause severe pain and infertility, while larger lesions may be asymptomatic and be found only incidentally during surgery for other diagnoses. Laparoscopy is the gold standard for diagnosis, but many patients are found during laparotomy for other conditions, such as appendicitis or ruptured ovarian cysts (endometrioma of the ovary). Colon and rectal surgeons often become involved in the management of patients with intestinal endometriosis. This involvement often occurs as a result of a combined procedure with a gynecologist or in management of an endometrioma masquerading as a neoplastic or inflammatory lesion. Treatment for endometriosis is usually multimodal and may require surgery in those patients with infertility, pelvic pain, obstruction, or a poor response to hormonal suppression. While advances in diagnostic tests and therapy have been made, endometriosis remains a frustrating and incompletely understood disease for both the patient and her physicians.

Epidemiology

The true prevalence of endometriosis is unknown. There is no noninvasive screening test for endometriosis, and its diagnosis depends on the visual or pathologic identification of implants during laparoscopy or laparotomy. Various authors have estimated that up to 15% of all women of reproductive age representing an estimated 200 million women worldwide are afflicted with the disease [3–5]. Endometriosis is more common in women suffering from infertility (25–50%) and chronic pelvic pain (71–87%) [4–6]. A study by Houston et al. is the only population-based study of endometriosis [7]. After reviewing the medical records for Caucasian women in Rochester, Minnesota, during the 1970s, they estimated that 6.2% of premenopausal women have endometriosis. The cost of endometriosis to the individual and society is significant with an estimated $69.4 billion per year in health expenditures [4]. The health costs are similar to diseases such as diabetes, rheumatoid arthritis, and inflammatory bowel disease with direct costs over $12,000 per year [8]. For women

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in the prime working years, 50% of women with endometriosis lost nearly 18 days a year in productivity [9].

While endometriosis is primarily a disease of the reproductive years, the widespread use of exogenous estrogens and increasing obesity in our society have made it more prevalent in postmenopausal women. Conversely, there is a decrease in the incidence of the disease when women use oral contraceptives or experience multiple pregnancies [10]. These observations, coupled with the fact that the incidence of endometriosis increases over time after a woman's last childbirth, suggest that uninterrupted menstrual cycles predispose susceptible individuals to the development of endometrial implants [11]. Spontaneous regression can occur, but in primate studies, with females who suffer from a similar disease, endometriosis is a progressive disorder [12]. There is no racial predilection for endometriosis other than in Japanese women who have doubled the incidence of the disease than do Caucasian women [13].

Diagnostic delays are a critical barrier to women with endometriosis. The inability to receive timely and appropriate care frequently causes physical and emotional damage, severely impacts quality of life, may lead to addiction, and is often accompanied by a diminished relationship with physicians. As previously mentioned, the delay in definitive diagnosis is on average 7–12 years. The reason for this is multifactorial. Laparoscopy is invasive and costly and has its own risks. Despite recommendations for medical treatment before definitive diagnosis is confirmed, few practitioners have changed their practice [14]. Gynecologists believe that the absence of a valid noninvasive diagnostic test contributes to the significant delay in diagnosis in many patients [15].

Stigma around menstrual issues and pelvic pain also play a role in the delay. One study revealed that women do not make an appointment for a little over 2 years from the onset of symptoms before seeking help [2]. In addition, chronic pain is not specific to endometriosis, and the process of ruling out the myriad of other disorders contributes to the delay in diagnosis and treatment. Women with endometriosis make approximately seven appointments with their primary care physician before being referred to a specialist, and three quarters experience a misdiagnosis. Despite the prevalence of endometriosis, one survey of primary care physicians found that half could not name three of the main symptoms of endometriosis and two-thirds did not feel competent in the diagnostic evaluation and follow-up [16].

Etiology

The precise etiology that completely explains the cause and pathogenesis of endometriosis is unknown. The two most popular theories as to its etiology are coelomic metaplasia and the implantation of viable endometrial cells from retrograde menstruation through the fallopian tubes. Coelomic metaplasia, postulated by Meyers, suggests that under the correct hormonal milieu, the coelomic epithelium will undergo metaplastic changes and transform into endometrial tissue [17]. He bases his theory on studies demonstrating that the peritoneum and uterine endometrium both originate from embryonic coelomic epithelium. While this theory offers a good explanation for endometriosis in men and nonmenstruating women, it does not adequately address the anatomical distribution and clinical pattern of endometriosis. The vast majority of endometriosis occurs in the pelvis, but the peritoneum at risk with this theory is evenly distributed throughout the abdominal cavity. In addition, metaplasia should worsen with age and endometriosis clearly does not.

Retrograde menstruation, first proposed by Sampson in 1921, remains the most plausible explanation for the distribution of endometrial implants [18]. This theory postulates that endometriosis arises from retrograde menstruation through the fallopian tubes and into the peritoneal cavity. Viable endometrial tissue has been demonstrated in menstrual effluent, and endometriosis has been induced both in primates, with artificially produced retrograde menstruation, [19] and in women volunteers who permitted injection of menstrual tissue into their peritoneum [20]. This theory, however, is probably only part of the answer.

While retrograde menstruation is very common, occurring in virtually all women, endometriosis affects only a small minority. Clearly other factors must be involved to permit the implantation and growth of endometrial tissue. Several studies indicate a possible genetic aspect to endometriosis. Simpson et al. demonstrated that the disease appears to occur more commonly within families. He found a 7% relative risk for blood relatives of affected individuals as opposed to a 1% relative risk for non-blood controls [21]. Additionally, the clinical manifestations of the disease were more severe among the related group. It appears that the inheritance pattern is polygenic or a combination of genetic and environmental factors. This conclusion is consistent with the clinical associations with delayed childbearing and uninterrupted cyclic menstruation.

Dmowski et al. have theorized that the genetic factor may involve the immune system [22]. They demonstrated depressed cellular immunity in monkeys with spontaneous endometriosis. Other investigators have confirmed alterations in both cellular and humoral immunity in humans [23, 24]. The most striking change observed in cellular immunity is the high concentration of activated macrophages and decreased functional capacity of natural killer cells. The most significant abnormality in humoral immunity is the presence of autoantibodies against different cellular components. These changes have been observed in both the perito-

neal cavity and the systemic circulation, suggesting that endometriosis may be a systemic disease. It is still unclear whether these changes represent manifestations of the disease or a subsequent reaction to it. This research, however, suggests that mild subclinical immunosuppression may subsequently lead to endometriosis many years later.

Endometriosis has such a diversity of symptoms, severity, and lesion appearance which many believe that endometriosis represents a group of disorders. Superficial peritoneal disease, ovarian endometriomas, deeply infiltrating lesions into the rectum and rectovaginal septum, and extra pelvic endometriosis all behave clinically different and respond differently to medical management [25]. Except for the dyspareunia found in infiltrative lesions in the rectovaginal septum, lesion size and number correlates poorly with severity of symptoms and degree of patient disability (Figs. 41.1, 41.2, and 41.3) [26].

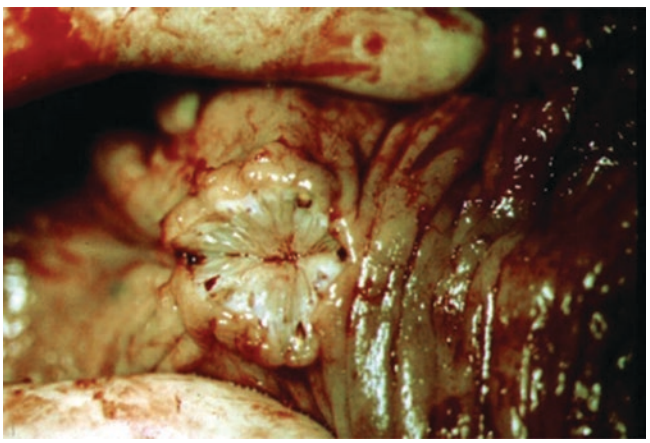

Fig. 41.1 Polypoid endometrial implant of the colon causing mucosal abnormalities

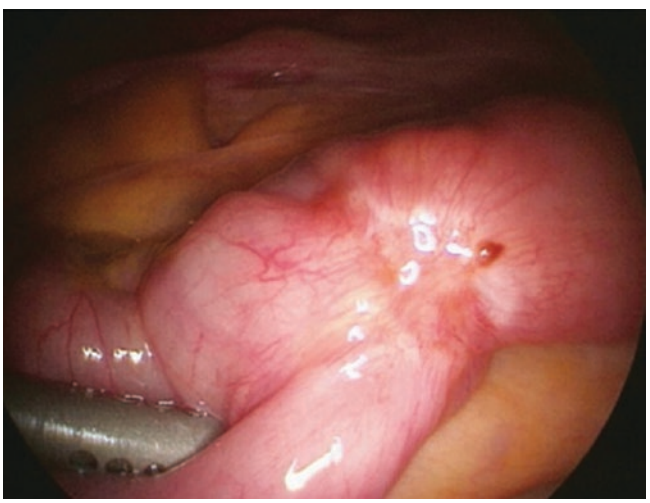

Fig. 41.2 Laparoscopic view of an endometrial implant on the small intestine

Clinical Manifestations

Clinical manifestations of endometriosis are based on the organs involved, but most patients complain of pelvic pain, pelvic mass, and infertility. Patients may describe the pelvic pain as pain with defecation or dyspareunia (especially with deep penetration). Women with abnormal menstrual cycles, family history of endometriosis, or congenital or traumatic defects in the reproductive tracts presenting with pain should be evaluated for endometriosis. Because endometriotic cysts can occur in wounds after cesarean sections or episiotomies, these lesions can cause pain and swelling during the perimenstrual cycle. Other unusual locations of involvement include the bladder, lungs, or brain [27].

Traditionally thought to affect women in their mid-reproductive years, endometriosis can affect adolescents and those postmenopausal. Teens who present with pelvic pain, worsening dysmenorrhea, rectal pain, and dyspareunia should be evaluated for endometriosis. And with the increasing use of hormone replacement in the postmenopausal women, symptoms for endometriosis may recur in those who had disease earlier in life. In other cases, the diagnosis of endometriosis is made during surgery either for gynecology-related or other concerns.

Pelvic pain in patients with endometriosis maybe described as deep, constant, or a dull ache in the pelvis. It usually occurs during the menstrual cycle but may occur before or close to the onset of the menstrual cycle. Some will not have pain, while others will have significant pain with minimal lesions. The pain may occur during sexual activity, with bowel movements, in cases of GI involvement, or during pelvic examinations. With colonic involvement of endometriosis, patients may complain of pain with defecation or with rectal filling. With larger and deeper lesions involving the GI tract, symptoms of obstruction, perforation, and bleeding can occur.

With bladder involvement, pain during micturition and cyclic hematuria have been described, and cystoscopy will aid in its evaluation. If suspected, cystoscopy should be performed during the menstrual cycle. With ureteral involvement, ureteral obstruction can lead to renal dysfunction if left undiagnosed and rarely is bilateral.

Another unusual location for endometriosis is in the lungs (thoracic endometriosis syndrome) or diaphragm where pneumothoraxes have been described. With erosions into the lung parenchyma, perimenstrual hemoptysis, dyspnea, and chest pain can occur. Brain lesions can cause perimenstrual headaches and seizures and will need a high index of suspicion for diagnosis and treatment.

Pain during pelvic examination with a pelvic mass may be indicative of endometriosis, particularly if pain is elicited upon palpation of the uterosacral ligaments during rectovaginal exam. The mass may be an endometrioma or secondary

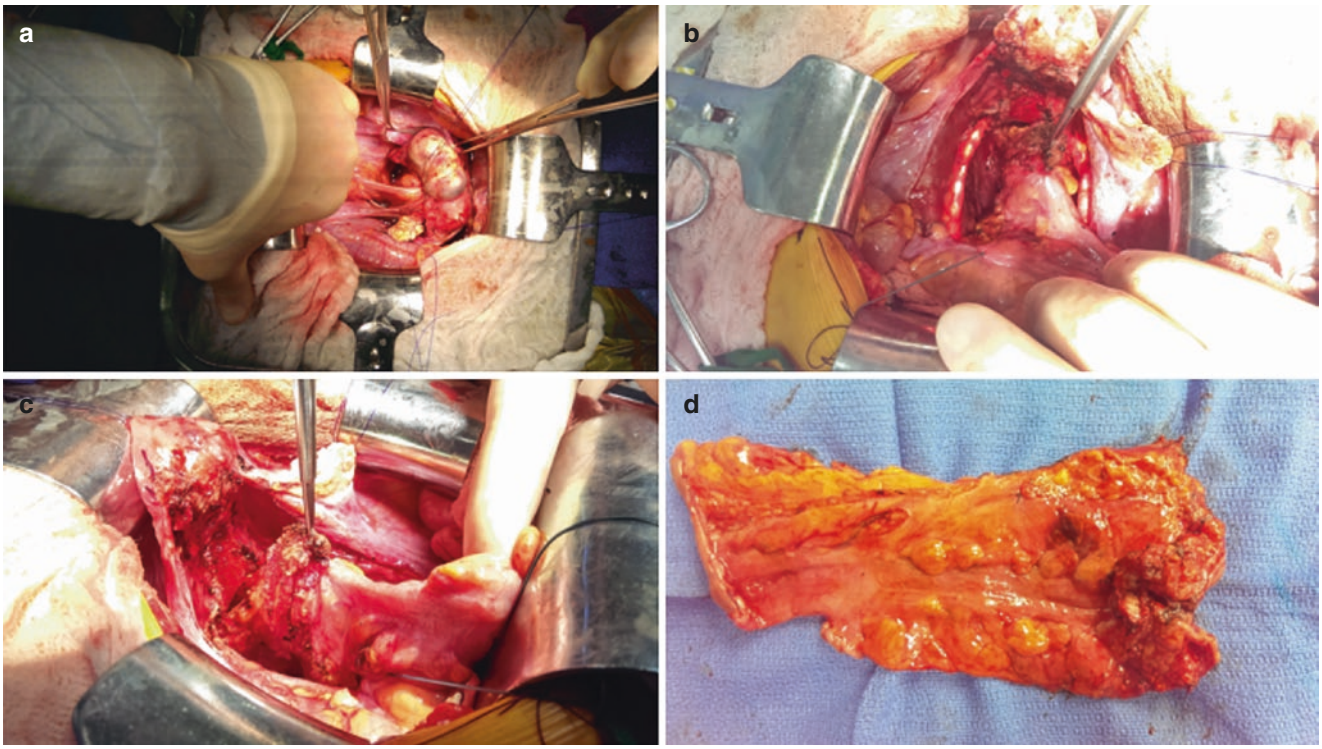

Fig. 41.3 (**a**) Demonstrates the view of the endometrial implants obliterating the pouch of Douglas and an associated large endometrioma on the left ovary at the start of the procedure; (**b**) the large nodule of endometriosis has been dissected from the ureters and posterior vagina (note the lighted ureteral catheters that facilitate the dissection); (**c**) demonstrates visualization of the normal fat within the rectovaginal plane after fully dissecting cul-de-sac of Douglas and mobilizing the lesion rostrally out of the pelvis to allow resection; (**d**) demonstrates sectioning of the specimen to show the typical appearance of an endometrioma after hormonal therapy which induces diminished vascularity of the lesion

to adhesions from the endometriotic tissue. The endometrioma is a fluid-filled endometriotic cyst which is most commonly found in the ovaries. The endometrioma may be single and can grow to a large size without symptoms. In other cases, the mass is secondary to adhesions between pelvic structures binding them together. Radiologically, bilateral endometriomas may fuse the ovaries at the midline; this sign is called "kissing ovaries" and is pathognomonic for endometriosis.

Infertility is the most common presenting complaint in patients who suffer from endometriosis. The exact prevalence is unknown, but reports as high as 30% of women with endometriosis are infertile. The mechanism of infertility in patients with endometriosis is quite variable. Referral to the appropriate fertility specialist will aid in the evaluation and management of patients with infertility – whether the cause is related to endometriosis or others.

Possible mechanisms of infertility in endometriosis [27]:

"Extensive" endometriosis

1. Tuboovarian adhesions preventing ovum pickup
2. Adhesions surrounding ovary of blocked fallopian tube
3. Destruction of ovarian tissue

"Mild" endometriosis

1. Abnormal menstrual cycle
   (a) Anovulation
   (b) Abnormal LH surge
   (c) LUFS – luteinized unruptured follicle syndrome
   (d) Luteal phase inadequacy
2. Hyperprolactinemia
3. Immune dysfunction
4. Altered peritoneal fluid
   (a) Prostaglandins
   (b) Macrophages
5. Spontaneous abortion

In 2013, the Endometriosis: History, Diagnosis and Outcomes (ENDO) group reported on risk factors associated with endometriosis. In their prospective matched, exposure cohort design, 495 women aged 18–44 years were compared to age-matched population cohort of 131 women. The diagnosis of endometriosis was done at laparoscopy or by pelvic magnetic resonance imaging. They found an incidence of endometriosis at 40% of the operative cohort (per criteria from the American Society for Reproductive Medicine)

compared to 11% in the population cohort. History of infertility increased the odds of endometriosis in both groups – operative (adjusted odds ratio (AOR) 2.43; 95% CI, 1.57–3.76) and population (AOR 7.91; 95% CI 1.69–37.2). Dysmenorrhea (AOR 2.46; 95% CI, 1.28–4.72) and pelvic pain (AOR 3.67; 95% 2.44–5.50) increased the diagnosis in the operative group only. Gravidity (AOR 0.49, 95% CI 0.32–0.75), parity (AOR 0.42; 95% CI 0.28–0.64), and body mass index (BMI) (AOR 0.95; 95% CI 0.93–0.98) decreased the odds of the diagnosis in the operative group [28].

A study by Hemmings indicated a higher rate of endometriosis in educated women. A total of 2777 subjects who underwent diagnostic laparoscopy, tubal ligation, or hysterectomy were included; 890 subjects were classified with endometriosis, whereas 1881 served as controls. Their study showed a higher rate of endometriosis in women with higher education. They reported no significant association between BMI, smoking, and alcohol use with endometriosis. They did find an inverse relation with gravidity and endometriosis [29].

Diagnosis

Since endometriosis can affect the entire pelvis and the signs and symptoms sometimes nonspecific, diagnosis can present as a challenge to the clinician. A high index of suspicion is key to helping these patients. No serum markers are currently available for the diagnosis, but CA −125 has been used. Recent interest in biomarkers have yielded a few options for early "screening" for endometriosis, but further research is needed for validation (Table 41.1) [30].

Table 41.1 Biomarkers for early "screening" for endometriosis

Biomarker		Test characteristic for prediction
CA-125 + prolactin		Sensitivity 77%, specificity 88%
Glycoproteins	Follistatin	Sensitivity 92%, specificity 96%
	Zn-alpha-2-glycoprotein	Sensitivity 69.4%, specificity 100%
	Glycodelin	Sensitivity 78.4%, specificity 82.1%
Cytokines	Serum IL −6	Sensitivity 100%, specificity 100%
	Serum IL-8	Sensitivity 90%, specificity 92%
	TNF-alpha	Sensitivity 95%, specificity 86.2%
	Serum CRP	Sensitivity 85%, specificity 93.7%
miRNA		Sensitivity 93.22%, specificity 96%
ICAM-1 (intercellular cell adhesion molecule)		Sensitivity 58.3%, specificity 60.0%
Circulating cell free DNA		Sensitivity 70%, specificity 87%
Autoantibodies		Sensitivity 83%, specificity 79%

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Several imaging modalities are available for the evaluation of endometriosis. These include physical exam, transvaginal ultrasound (TVUS), MRI, rectal ultrasound, and endoscopy. On pelvic exam, the finding of an irregular and/or painful nodule will lead one to suspect endometriosis. Thickening and/or the presence of an irregular hypoechoic cystic or non-cystic mass within the rectovaginal septum or anterior-lateral to the rectum on TVUS would also be concerning for endometriosis. With MRI, irregular thickness or spiculated nodules in the rectovaginal septum with hypointense signal on T1- and T2-weighted images would be concerning for endometriosis. The use of rectal ultrasound and endoscopy for diagnosis for endometriosis would be of benefit in deep infiltrating endometriosis with direct involvement of the rectal wall. Deep infiltrating endometriosis is a form of endometriosis where ectopic endometrial tissue invades >5 mm deep to the peritoneum. It is often found in the posterior cul-de-sac of Douglas, uterosacral ligaments, and rectosigmoid colon [31]. The sensitivity, specificity, and accuracy of transvaginal ultrasound for identification of the direct rectal involvement were 26.7%, 85.7%, and 52.7% and with MRI 73.3%, 92.9%, and 82% respectively. With endorectal ultrasound, the sensitivity, specificity, and accuracy are 86.7%, 85.7%, and 86.2% [32]. Lastly, laparoscopy with direct visualization of the pelvis is currently the gold standard for diagnosis of endometriosis. Laparoscopy is described later in the chapter.

Rectal involvement, with partial or complete obliteration of the pouch of Douglas, brings another concern to the management of patients with endometriosis. Not only can it cause significant pain, it also adds to the operative management. Appropriate assessment preoperatively allows for the multidisciplinary approach to surgery. When the posterior aspect of the cervix or uterus does not "slide" freely again into the rectum or sigmoid, it is called the "negative sliding sign" and is concerning for obliteration of the pouch of Douglas. Reid and Condous reported a sensitivity of 83.3% and specificity of 97.1% in predicting the pouch of Douglas obliteration when using the sliding sign [33].

The use of US for evaluation of cul-de-sac obliteration was also confirmed by Arion and her group who compared point-of-care TVUS with manual pelvic exam. They compared TVUS to manual pelvic exam (specifically the finding of a palpable mass) for the prediction of the pouch of Douglas obliteration. They reported a preoperative negative sliding sign had a sensitivity of 73.2% (95% confidence interval, 57.1–85.8%) and specificity of 93.9% (95% confidence interval, 89.9–

96.6%) in predicting the pouch of Douglas obliteration versus a sensitivity of 24.4% (95% confidence interval, 12.4–40.3%) and specificity of 93.4% (95% confidence interval, 89.4–96.3%) on palpation of a nodule on pelvic exam. They also reported on longer operating times and more difficult surgery in the setting of the pouch of Douglas obliteration [34].

Leonardi et al. argue that deep infiltrating endometriosis warrants more in-depth evaluation as management may require a multidisciplinary approach. They proposed the use of the advanced, expert-guided transvaginal sonography or ETVS. Transvaginal sonography allows for assessment of the uterus and ovaries, while he argues that ETVS assess for deep infiltrating endometriosis, cul-de-sac obliteration, ovarian mobility, and site-specific tenderness [35].

The role of colonoscopy in the diagnostic workup of endometriosis is to rule out other causes of abdominal discomfort. In a prospective observational study performed by Milone et al., endoscopic findings suggestive of endometriosis were detected in only 4% of their study population. Endoscopy failed to diagnose endometriosis in over 92% of the patients. It did, however, diagnose endometriosis if there was mucosal involvement [36]. Therefore, the role of colonoscopy in the diagnostic workup of endometriosis is to identify other causes of abdominal pain. In cases where there is mucosal involvement of endometriosis, the clinical features can mimic other diseases, namely, inflammatory bowel disease, solitary rectal ulcer, or cancer to name a few. Even with biopsies, the diagnosis for endometriosis can be difficult. A high index of suspicion with appropriate histologic testing in pathology would be helpful. Wei et al. presented a series of 15 patients with gastrointestinal endometriosis. The most common presenting complaints were pelvic pain, rectal bleeding, rectal urgency, abdominal mass, and bowel obstruction. The most common endoscopic finding is a polypoid mass with the most common preoperative diagnosis as colorectal carcinoma. Since endometriosis affects the serosa or muscularis propria more commonly, the mucosa may exhibit nonspecific inflammatory changes or ulcerations on biopsy specimens which could mimic inflammatory bowel disease. Fibromuscular hyperplasia within the lamina propria as seen in solitary rectal ulcers can also be seen with mucosal involvement of endometriosis. Immunohistochemical stains are important to differentiate these disease entities and direct management. The panel of CK7, ER, CK20, and CDX 2 are commonly used. Ectopic endometrial glands express CK7 and ER, while the stroma expresses CD 10 and ER. Rectal glands express CK20 and CDX 2 [37]. In limited tissue samples, CD7 and ER are adequate.

Endometrial glands can also exhibit metaplasia. In the 15 cases presented by Jiang et al., the most common metaplastic change was the ciliated (tubal) hyperplasia, which is a helpful clinical differentiator since intestinal glands do not have cilia. Other metaplastic changes are squamous, eosinophilic, hobnail, and mucinous metaplasia [38]. This raises the concern for malignancy which will be discussed later in the chapter.

While physical exam and imaging are important in the initial evaluation of pelvic pain, laparoscopy continues to be the gold standard for diagnosis of endometriosis. Surgical resection of all lesions is essential to provide maximal clinical benefit to patients who suffer from endometriosis. Therefore, identification of all lesions during laparoscopy is important. Early-stage disease and atypical lesions are difficult to identify during laparoscopy. The study by Ma et al. was designed to identify whether narrowband imaging will improve laparoscopic identification of superficial and early-stage endometriosis. Fifty-three patients underwent standard white laparoscopy followed by narrowband imaging to assess for additional areas of concern. They found only three additional areas of concern with narrow band imaging (NBI) if the white light survey was negative, but none of the lesions were positive for endometriosis. They concluded that the additional predictive value of NBI was 86% if the white light survey was positive but 0% if the white light survey was negative [39]. This is in contrast to the pilot study by Barrueto et al. who described the technique in 2008, where 14 of the 20 patients had lesions identified by NBI that were not identified by the standard white light laparoscopy [40].

While laparoscopy continues to be the gold standard for identification of endometriosis, the addition of NBI may improve identification of additional lesions in the early stages.

On laparoscopy, the lesions can be superficial patches ranging in colors from red, brown, black, white, clear, yellow, or blue. Classically, blue-tinted implants are called powder burn lesions and are highly suspicious for endometriosis. Alternatively, endometriosis implants can be subtle and appear as fibrotic areas of peritoneum or convalescence of small vessels on the pelvic side wall. Fibrosis can accompany the lesions or, if large enough, can form nodules. Ovarian endometriomas are filled with a brown fluid and are called "chocolate cysts." The lesions can involve the ovaries, the anterior and posterior cul-de-sac, broad ligaments, fallopian tubes, uterosacral ligaments, uterus, round ligament, sigmoid colon, and appendix. Other less common areas of involvement are the vagina, cervix, rectovaginal septum, cecum, ileum, inguinal canal, perineal wounds, bladder, and ureter. It is therefore crucial during surgery to evaluate all these areas to assess the full extent of involvement and tailor surgery based on the findings and symptoms.

Classification of Endometriosis

The most widely used classification for endometriosis is the revised American Society for Reproductive Medicine (r-ASRM) classification (Fig. 41.4) [41]. It is a scoring

Patient's Name _____ Date _____

Stage I (Minimal) - 1–5
Stage II (Mild) - 6–15
Stage III (Moderate) - 16–40
Stage IV (Severe) - > 40
Total _____

Laparoscopy _____ Laparotomy _____ Photography _____
Recommended Treatment _____
_____
Prognosis _____

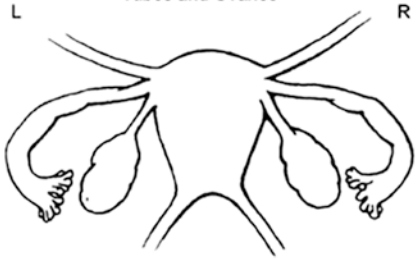
PERITONEUM	ENDOMETRIOSIS	< 1cm	1–3cm	> 3cm
	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	6	16	20
	L Superficial	1	2	4
	Deep	4	16	20
	POSTERIOR CUL-DE-SAC OBLITERATION	Partial		Complete
		4		40
OVARY	**ADHESIONS**	< 1/3 Enclosure	1/3–2/3 Enclosure	<2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4•	8•	16
	L Filmy	1	2	4
	Dense	4•	8•	16

•If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.
Denote appearance of superficial implant types as red [(R), red, red-pink, flamelike, vesicular blobs, clear vesicles], white [(W), opacifications, peritoneal defects, yellow-brown], or black [(B) black, hemosiderin deposits, blue]. Denote percent of total described as R___ %,W___ % and B___%. Total should equal 100%.

Additional Endometriosis: _____

Associated Pathology: _____

To Be Used with Normal Tubes and Ovaries



To Be Used with Abnormal Tubes and/or Ovaries

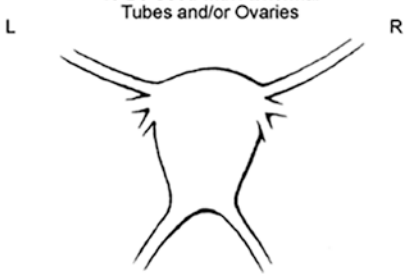


Fig. 41.4 r-ASRM classification. (Reused with permission from Ref. [41]. Copyright © Springer Nature)

system for lesions in the peritoneum, ovaries, fallopian tubes, and cul-de-sac. The size and depth of lesions, adhesions on the ovaries and fallopian tubes, and severity of cul-de-sac obliterations are assigned points. The summation of all the points allows classification of endometriosis to four grades of severity: Stage I (minimal endometriosis, 1–5 points), Stage II (mild endometriosis, 6–15 points), Stage III (moderate endometriosis, 16–39 points), and Stage IV (severe endometriosis, 40 points). This has led to the use of the ENZIAN classification for deep infiltrating endometriosis (DIE). With the ENZIAN classification for DIE, the pelvis is divided into three compartments, namely, A, B, and C, with a second group designated as F ("far") for lesions in the bladder, ureter, or bowel. A, B, and C groups are subjected to a metric level system for depth of infiltration (Fig. 41.5).

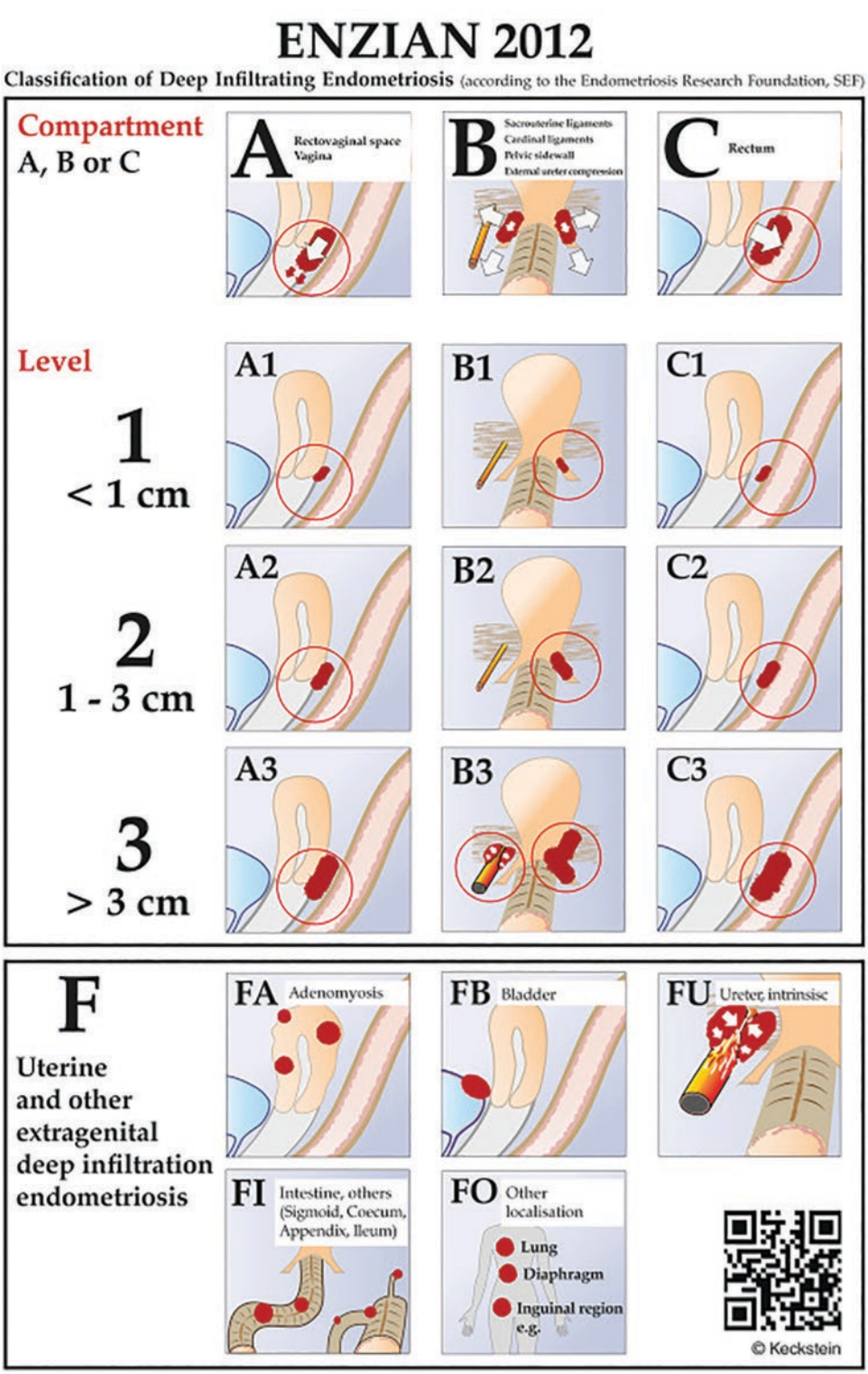


Fig. 41.5 ENZIAN classification (Reused with permission from Ref. [25]. Copyright © Oxford University Press)

In April 2014, a consensus meeting [42] was held to discuss the development of a classification system that included the r-ASRM and the ENZIAN system – both of which are based on lesion appearance and locations but not ovarian function or fertility outcome. They proposed the addition of the endometriosis fertility index staging system which predicts fertility outcomes in patients following surgical staging of endometriosis when appropriate

ENDOMETRIOSIS FERTILITY INDEX (EFI) SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score		Description
4	=	Normal
3	=	Mild Dysfunction
2	=	Moderate Dysfunction
1	=	Severe Dysfunction
0	=	Absent or Nonfunctional

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

	Left		Right		
Fallopian Tube					
Fimbria					
Ovary					
Lowest Score		+		=	
	Left		Right		LF Score

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors		
Factor	Description	Points	Factor	Description	Points
Age			LF Score		
	If age is ≤ 35 years	2		If LF Score = 7 to 8 (high score)	3
	If age is 36 to 39 years	1		If LF Score = 4 to 6 (moderate score)	2
	If age is ≥ 40 years	0		If LF Score = 1 to 3 (low score)	0
Years Infertile			AFS Endometriosis Score		
	If years infertile is ≤ 3	2		If AFS Endometriosis Lesion Score is < 16	1
	If years infertile is > 3	0		If AFS Endometriosis Lesion Score is ≥ 16	0
Prior Pregnancy			AFS Total Score		
	If there is a history of a prior pregnancy	1		If AFS total score is < 71	1
	If there is no history of prior pregnancy	0		If AFS total score is ≥ 71	0
Total Historical Factors					

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS: Historical + Surgical = EFI Score

ESTIMATED PERCENT PREGNANT BY EFI SCORE

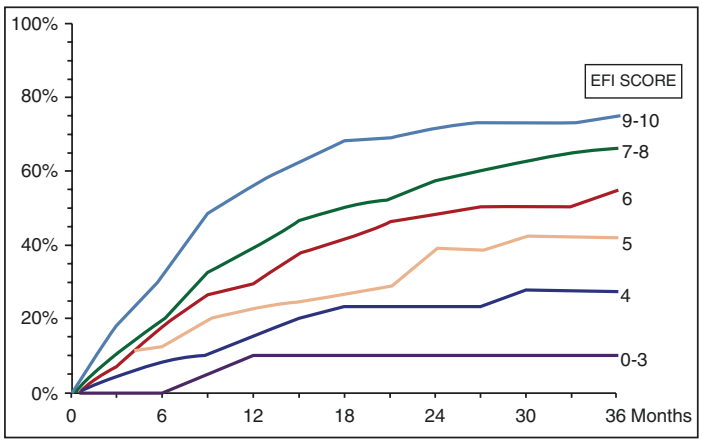


Fig. 41.6 Endometriosis fertility index (EFI). (Reused with permission from Ref. [25]. Copyright © Oxford University Press)

(Fig. 41.6). The group acknowledges that the classification systems do not predict pelvic pain, response to medications, disease recurrence, and quality of life measures. Further research into a more comprehensive classification system is needed.

Endometriosis and Cancer

Endometriosis is a benign disease but has been shown to increase the risk of certain types of ovarian cancer, namely, clear-cell ovarian cancer (CCOC) and endometrioid ovarian cancer (EOC). The World Health Organization has classified ovarian cancer into two major groups. Type I tumors are the clear-cell, endometrioid, low-grade serous, and mucinous carcinomas and seromucinous and malignant Brenner tumors. Type II tumors are the high-grade serous carcinoma, carcinosarcoma, and undifferentiated carcinoma. Both CCOC and EOC are considered Type I tumors. Barreta et al. reviewed 50 women with CCOC and EOC treated in their institution and found histologic confirmation of endometriosis in 80% of their study population. Forty-two percent were nulliparous and 42% were premenopausal. The tumor marker CA 125 was elevated in both International Federation of Gynecology and Obstetrics Stages 1–2 disease (mean 614.7 Ui/ml) and Stages 3–4 disease (mean 2361.2 Ui/ml). Patients with endometriosis-associated CCOC presented at an earlier stage. Endometrioid ovarian carcinoma and early-stage CCOC were shown to have good prognosis, while late-stage CCOC had sooner recurrences and shorter overall survival (OS) [43].

Saavalainen et al. reported on the relative risk of ovarian cancer based on the type of endometriosis in their population-based study in 2018. The subtypes of endometriosis were divided into ovarian, peritoneal, and deep infiltrating. Gynecological cancers were obtained from the Finnish Cancer Registry. They reported a standardized incidence ratio of 1.76 (95% CI 1.47–2.08) for ovarian cancer in patients with endometriosis, specifically, the risk of ovarian cancer with endometrioid (3.12 [95% CI 2.15–4.38]), clear cell (5.17 [95% CI 3.20–7.89]), and serous (1.37 [95% CI1.02–1.80]) histology. Of the various subtypes, the ovarian endometriosis subtype was shown to have an increased standardized incidence ratio of ovarian cancer: EOC (4.72 [95% CI 2.75–7.56]) and CCOC (10.1 [95% CI 5.50–16.9]). The peritoneal endometriosis subtype was associated with an increased risk for the endometrioid ovarian cancer (2.03 [1.05–3.54]). They did not see any association with the deep infiltrating endometriosis and ovarian cancer. There was no increase in the risk for endometrial, vaginal, or vulvar cancer in the study group, while a decreased standardized incidence ratio was noted in squamous cell cervical cancer and noninvasive neoplasms of the cervix [44].

Treatment

Medical Management

Medical management of endometriosis includes both pain control and cessation of growth of the endometriotic lesions. Understanding the pathophysiology of endometriosis is important in deciding the appropriate medical management for the disease (Table 41.2) [45].

Nonsteroidal anti-inflammatory, oral contraceptive pills, gonadotropin-releasing hormone agonist, and aromatase inhibitors are commonly used (Table 41.3).

Medical management is usually the first line of treatment for endometriosis and can be delivered either orally, by injection, or using an implantable device. For example, in advanced endometriosis cases, preoperative GNRH agonist injections can decrease the disease burden and allow for more localized resection. It does have limitations as they suppress ovulation and have limited use for patients who desire fertility. Oral contraceptive medications also have venous thromboembo-

Table 41.2 Pathophysiology of endometriosis

Increased production of estradiol
Increased intrinsic aromatase activity
Increased production of inflammatory marker
Progesterone resistance

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Table 41.3 Medications for endometriosis management

Medication	
NSAIDS	Decrease production of inflammatory markers
Oral contraceptive pills	Hormone suppression
Gonadotropin-releasing hormone agonist/antagonist	Hormone suppression by blocking ovarian estrogen production
Progestins	Inhibits growth of the endometriotic implants by inhibiting angiogenesis, inhibiting estrogen-induced mitosis, altering estrogen receptors
Aromatase inhibitors	Decrease conversion of steroid precursor into estrogen, particularly peripheral conversion in adipose tissue

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lism concerns and carry increased risk in older women, women with migraine with aura, and other chronic medical conditions (lupus, hypertension, liver disease).

Surgical Management

Surgery in most cases is for diagnosis and treatment of endometriosis. Currently, the laparoscopic approach is the preferred method. A thorough evaluation of the abdomen and pelvis to document areas of involvement and biopsy for histology would be necessary both to treat the disease and for future management. Biopsy showing endometrial glands and stroma with inflammation and fibrosis provide definitive diagnosis.

Endometriosis can present in a variety of scenarios: peritoneal endometriosis (superficial endometriosis), endometriomas (endometriotic cysts), and deep infiltrative endometriosis (invasion of anatomical structures and organs created 5 mm beyond the peritoneum). The endometrial tissue could involve the uterosacral ligaments, the rectosigmoid colon, the vagina, and the bladder; therefore, surgical management depends on the location and size the endometrial tissue. Superficial lesions can be excised or ablated/fulgurated with different energy devices such as cautery, the harmonic scalpel, or laser as deemed appropriate. Smaller but deeper lesions can be managed by shaving or disc excision with larger lesions requiring segmental resections. Location-specific considerations will be discussed here.

Ovarian endometriomas occur in 17–44% of endometriosis cases [46]. Oophorectomy is performed in the older patient and if the cyst is potentially malignant. Cystectomy is preferred in the younger patient to preserve ovarian function, but disease recurrence should be discussed with the patient. In the appropriate setting, cystectomy can still be performed in large, multiloculated cysts. Unilateral oophorectomy can be considered in unilateral involvement, but recurrence in the contralateral ovary can be as high as 24.75% in the first 5 years as reported by Hidari [47].

Involvement of a hollow viscus such as the colon and rectum presents other dilemmas. Shaving is described as nodule excision without opening the colon or rectum, while disc excision requires excision of the bowel wall. Lesions <3 cm, unifocal, and involve <60% of the circumference of the bowel wall are amendable to disc excision [48]. More extensive involvement of the bowel wall may require a segmental resection (i.e., low anterior resection with diverting stoma). In cases where rectosigmoid mucosa or submucosal involvement is identified, more than 40% of the bowel circumferences will be involved with endometriosis [48, 49].

As with any surgery, postoperative complications such as rectovaginal fistulas, pelvic abscess, anastomotic leaks, and strictures are a concern. But incomplete excision of the lesions could lead to decrease success in treating symptoms and lack of improvement in fertility. Major complications (those requiring immediate intervention such as surgery) are reported in the range of 2.9–8.4% for deep infiltrating endometriosis without bowel resection and 7.4–25% in patients with DIE and bowel resection [50–53].

In addition to increased complications with bowel resection, there is also a difference in sexual function in patients with bowel resection as reported by Lermann [54]. They compared 89 patients without bowel resection, 87 patients with bowel resection, and 100 control (no history of endometriosis) patients. Preoperatively, the study groups had poorer scores in the German version of the Massachusetts General Hospital Sexual Functioning Questionnaire (KFSP). The KFSP is based on five questions on a six-point scale (1, more than before; 2, normal;3, minimally less than before; 4, less than before; 5, considerably less than before; 6, nonexistent), with questions documenting the level of sexual interest and their ability to reach sexual arousal, experience orgasm, lubrication, and sexual satisfaction. Lermann and colleagues reported poorer KFSP scores in the study groups when compared to the control group. After surgery, the group without bowel resection had improved scores in all categories and was comparable to the control group. The bowel resection group, on the other hand, did not show any improvements in their scores; in fact, they had poorer scores when compared to the control group. Possible explanation for the lower scores could be worse disease, which required more extensive resections (Fig. 41.7).

Colorectal anastomotic stenosis is a known complication after bowel resection. The study by Bertocchi showed endoscopic dilation is a valid option for management of anastomotic stenosis after resection for endometriosis and should be considered. The use of a protective ileostomy is a modifiable factor related to anastomotic stenosis. Patients with deep infiltrating endometriosis may benefit from a combined multidisciplinary approach with colorectal and gynecologic surgeons [55–58].

Recurrence After Surgery

Disease recurrence can happen despite aggressive surgical management. Both patient- and surgery-associated factors have been described. The recurrence rate has been reported

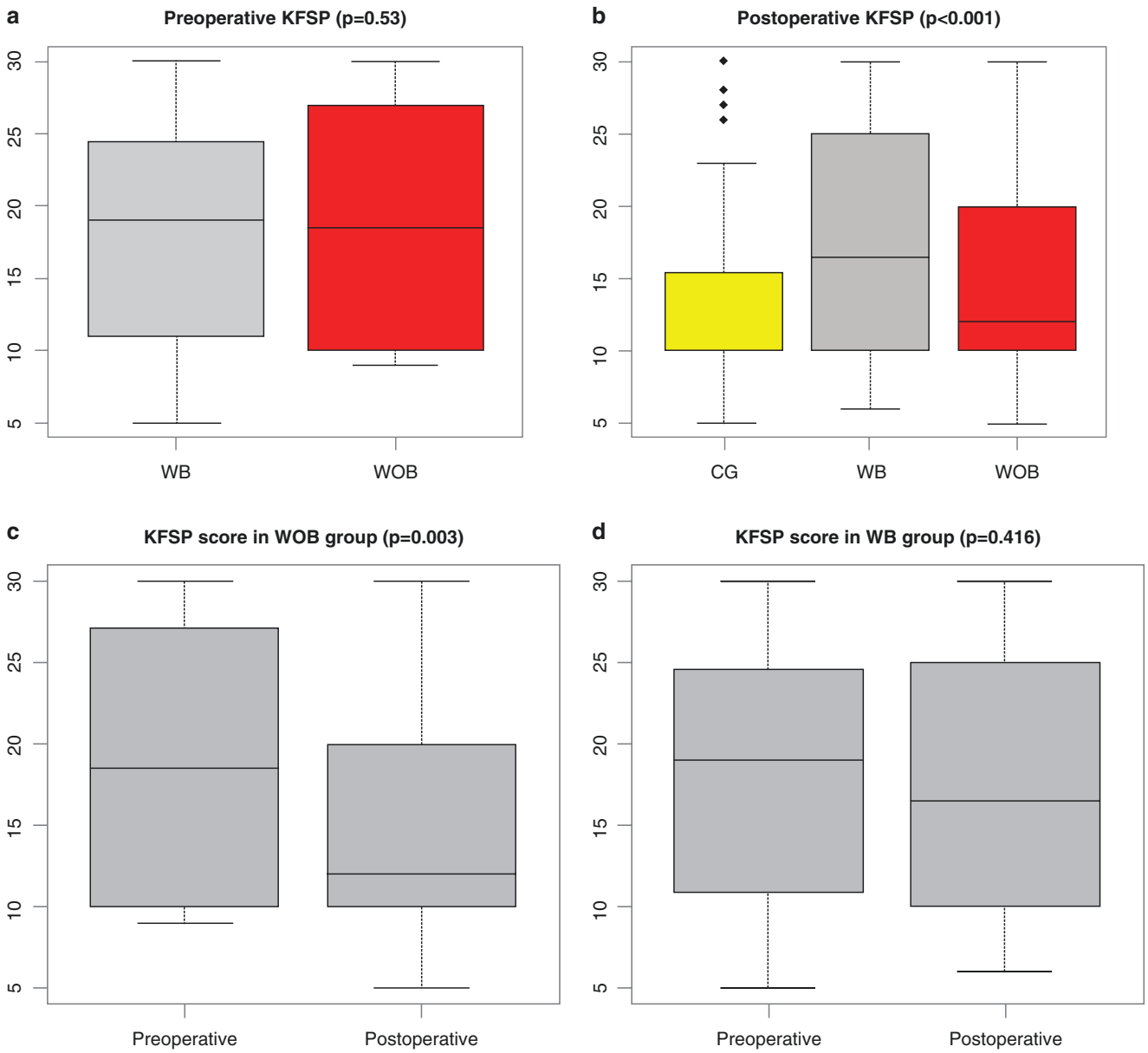

Fig. 41.7 Preoperative and postoperative KFSP scores. (Reused with permission from Ref. [54]. Copyright © Elsevier)

to be between 6% and 67% depending on the criteria used. Current definition of recurrence includes relapse of pain, absence of improvement in infertility, or revisualization of the lesions on US or surgery. Vignali reported recurrence rates at 3 and 5 years of 20.5 and 43.5% for pain and 9% and 28% for clinical recurrence. The success of the initial surgery is a prognostic factor for recurrence in patients undergoing resection for endometriosis [59]. Other risk factors are shown in Table 41.4 [60]. Most agree that disease recurrence after surgery should be managed medically first.

Table 41.4 Risk factors for the recurrence of endometriosis according to the available data

Study (year)	Risk factors
Fedele (2004)	Younger age
Vignali (2005	
Vercellini (2006)	
Liu (2007)	
Moini A (2014)	
Ghezzi (2001)	Laterality of lesions
Jones and Sutton (2002)	
Waller and Shaw (1993)	rAFS stage rAFS >70 rAVS score
Busacca (1999)	
Parazzini (2005)	
Abbott (2003)	
Li (2005)	
Kikuchi (2006)	
Liu (2007)	
Moini A (2014)	
Saleh and Tulandi (1999)	Size of cyst
Koga (2006)	
Moini A (2014)	
Renner (2010)	High preoperative pain
Bulletti (2001)	Absence of pregnancy
Fedele (2004)	
Li (2005)	
Koga (2006)	Previous medical treatment
Liu (2007)	
Vignali (2005)	Completeness of the first surgery Extent of surgical excision
Fedele (2000)	
Li (2005)	Painful module

rAFS Revised American Fertility Society
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Conclusion

The diagnosis and management of intestinal endometriosis have evolved tremendously over the last 40 years with the widespread availability of laparoscopy and a clear understanding of the necessity to remove all endometrial implants in symptomatic patients. With the advent of stapling devices that facilitate low pelvic anastomoses, the intestinal surgeon should be able to resect the endometrial implants and restore bowel continuity in virtually all patients with minimal morbidity and preserved fertility, when desired. Further improvements in outcomes will probably not occur until a better understanding of the precise etiology and growth of the endometrial implant is elucidated.

References

1. Nnoaham KE, Hummelshoj L, Webster P, et al. Impact of endometriosis on quality of life and work productivity: a multi center study across ten countries. Fertil Steril. 2011;96:366–73.
2. Hudelist G, Fritzer N, Thomas A, et al. Diagnostic delay for endometriosis in Austria and Germany: causes and possible consequences. Hum Reprod. 2012;27:3412–6.
3. Adamson GD, Kennedy S, Hummelshoj L. Creating solutions in endometriosis: global collaboration through the world Endometriosis Research Foundation. J Endometriosis. 2010;2:3–6.
4. Soliman AM, Surrey E, Bonafede M, et al. Real world evaluation of direct and indirect economic burden among endometriosis patients in the United States. Adv Ther. 2018;35:408–23.
5. Shafrir A, Farland L, Shah D, et al. Risk for and consequence of endometriosis: a critical epidemiologic review. Best Pract Res Clin Obste Gynaecol. 2018;51:1–15.
6. American Colleg of Obstetricians and Gynecology. Management of endometriosis. ACOG Practice bulletin no. 114. Obste Gynecol. 2010;116:225–36.
7. Houston DE, Noller KL, Melton J III, Selwyn BJ. The epidemiology of pelvic endometriosis. Clin Obstet Gynecol. 1988;31(4):787–800.
8. Soliman AM, Yang H, Du EX, et al. The direct and indirect costs associated with endometriosis: a systematic literature review. Hum Reprod. 2016;31:712–22.
9. Kjerulff KH, Erickson BA, Langenberg PW. Chronic gynecological conditions reported by US women: findings from the National Health Information Survey, 1984 to 1992. Am J Public Health. 1996;86:195.
10. Halme J, Stovall D. Endometriosis and its medical management. In: Walch EE, Zacur HA, editors. Reproductive medicine and surgery. St. Louis: Mosby; 1995. p. 695–710.
11. Moen MH. Is a long period without childbirth a risk factor for endometriosis? Hum Reprod. 1991;6:1404–7.
12. D'Hooghe TM, Bambra CS, Raeymaekers BM, et al. Serial laparoscopies over 30 months show that endometriosis in captive baboons (Papio Anubis, Papio cyancephalus) is a progressive disease. Feril Steril. 1996;65:645–9.
13. Miyazawa K. Incidence of endometriosis among Japanese women. Obstet Gynecol. 1976;48:407–9.
14. Taylor HS, Adamson GD, Diamond MP, et al. An evidence –based approach to assessing surgical versus clinical diagnosis of symptomatic endometriosis. Int J Gynaecol Obstet. 2018;142:131–42.
15. Weitraub A, Soriano D, Seidman D, et al. Think endometriosis: delay in diagnosis or delay in referral to adequate treatment. J Fertil In Vitro IVF Worldw Reprod Med Genet Stem cell Biol. 2014;2:127.
16. Quibel A, Puscasiu L, Marpeau L, et al. General practitioners and the challenge of endometriosis screening and care: results of a survey. Gynecol Obstet Fertil. 2013;41:372–80.
17. Ridley JH. The histogenesis of endometriosis. A review of facts and fancies. Obstet Gynecol Surv. 1968;20:1–35.
18. Sampson JA. Perforating hemorrhagic (chocolate) cysts of the ovary, their importance and especially their relation to pelvic adenomas of endometrial type. Arch Surg. 1921;3:245–323.
19. Telinde RW, Scott RB. Experimental endometriosis. Am J Obstet Gynecol. 1950;60:1147–73.
20. Ridley JH, Edwards KI. Experimental endometriosis in the human. Am J Obstet Gynecol. 1958;76:783–90.
21. Simpson JL, Elias S, Malinak LR, Buttram VC. Heritable aspects of endometriosis. 1. Genetic studies. Am J Obstet Gynecol. 1980;137:327–31.
22. Dmowski WP, Steele RW, Baker GF. Deficient cellular immunity in endometriosis. Am J Obstet Gynecol. 1981;141:377–83.
23. Vigano P, Vercellini P, DiBlasio AM, et al. Deficient anti-endometrium lymphocyte mediated cytotoxicity in patients with endometriosis. Fertil Steril. 1991;56:894–9.
24. Oosterlynck DJ, Cornillie FJ, Waer M, et al. Women with endometriosis show a defect in natural killer activity resulting in a decreased cytotoxicity to autologous endometrium. Fertil Steril. 1991;56:45–51.

25. Johnson NP, Hummelshoj L. Consensus on current management of endometriosis. Hum Reprod. 2013;28:1552–68.
26. Fauconnier A, Chapron C, Dubuisson JB, et al. Relation between pain symptoms and the anatomic location of deep infiltrating endometriosis. Fertil Steril. 2002;78:719–26.
27. Muse K. MD. Clinical manifestations and classification of endometriosis. Clin Obstet Gynecol. 1988;31(4):813–22.
28. Peterson, et al. Risk factors associated with endometriosis: importance of study population for characterizing disease in the ENDO Study. Am J Obstet Gynecol. 2013;208(6):451.e1–11.
29. Hemmings, et al. Evaluation of risk factors associated with endometriosis. Fertil Steril. 2004;81(6):1513–21.
30. Wahid B, et al. Biomarkers of diagnosis of pre-eclampsia and endometriosis. Biomark Med. 2018;12(10):1161–73.
31. Koninkx PR, Martin D. Treatment of deeply infiltrating endometriosis. Curr Opin Obstet Gynecol. 1994;6:231–41.
32. Chen, et al. Accuracy of physical examination, transvaginal sonography, magnetic resonance imaging, and rectal disc optic sonography for preoperative evaluation of rectovaginal endometriosis. Ultrasound Quart. 2019;35(1):54–60.
33. Reid S, Condous G. Transvaginal sonographic sliding sign: accurate prediction of pouch of Douglas obliteration. Ultrasound Obstet Gynecol. 2013;41:605–7.
34. Arion, et al. Prediction of pouch of douglas obliteration: point of care ultrasound versus pelvic examination. J Minim Invasive Gynecol. 2019;26(5):928–34.
35. Leonardi M, et al. Deep endometriosis: a diagnostic dilemma with significant surgical consequences. J Obstet Gynecol Can. 2018;40(9):1198–203.
36. Milone V, et al. Role of colonoscopy in the diagnostic workup endometriosis. World J Gastroenterol. 2015;21(16):4997–5001.
37. Chen H, et al. Case Report: Rectal Mucosa endometriosis primarily misinterpreted as adenocarcinoma: a case report and review of the literature. Int Journal Exp Pathol. 2015;8(5):5902–7.
38. Jiang W, et al. Endometriosis involving the mucosa of the intestinal tract: a clinicopathologic study of 15 cases. Mod Pathol. 2013;26:1270–8.
39. Ma, et al. Can narrowband imaging improve the laparoscopic identification of superficial endometriosis? A prospective cohort trial. J Minim Invasive Gynecol. 2019;26(3):427–33.
40. Barrueto F, Audlin K. The use of narrow band imaging for identification of endometriosis. J Minim Invasive Gynecol. 2008;15(5):36–639.
41. Tinneberg HR, et al. Classification of Endometriosis Chapter 21. In: Harada T, editor. Endometriosis: Pathogenesis and Treatment: Springer; 2014. p. 341–62.
42. Johnson NP, et al. World Endometriosis Society consensus on the classification of endometriosis. Hum Reprod. 2017;32(2):315–24.
43. Barreta A, et al. Endometriosis -Associated Ovarian Cancer. Population characteristic and prognosis. Int J Gynecol Cancer. 2018;28(7):1251–7.
44. Saavalainen L, et al. Risk of Gynecological Cancer According to the type of endometriosis. Obstet Gynecol. 2018;131(6):1095–102.
45. Rafique S, Decherney AH. Medical management of endometriosis. Clinical obstetrics and gynecology, September. 2017;60(3):485–96.
46. Chapron, et al. Management of Ovarian Endometriomas. Hum Reprod Update. 2002;8(6):91–7.
47. Hidari T, et al. Contralateral ovarian endometrioma recurrence after unilateral salpingo-oophorectomy. BMC Womens Health. 2019;19:59.
48. Almeida A, et al. Disc resection is the first option in the management of rectal endometriosis for unifocal lesions with less than 3 centimeters of longitudinal diameter. Surg Technol Int. 24:243–8.
49. Abrao MS, et al. Endometriosis lesions that compromise the rectum deeper than the inner muscular layer have more than 40% of the circumference of the rectum affected by the disease. J Minim Invasive Gynecol. 2008;15(3):280–5.
50. Angioli, et al. Surgical treatment of rectovaginal endometriosis with extensive vaginal infiltration: results of a systemic three-step vagino-laparoscopic approach. Euro J Obstet Gynecol Reprod Biol. 2014;173:83–7.
51. Minelli, et al. Laparoscopic conservative surgery for stage IV symptomatic endometriosis: short-term surgical complications. Fertil Steril. 2010;94:1218–22.
52. Keckstein, et al. Deep endometriosis, including intestinal involvement – the interdisciplinary approach. Minn Invasive Ther Allied Technol. 2005;14:160–6.
53. Ruffo, et al. Laparoscopic colorectal resection for deep infiltrating endometriosis: analysis of 436 cases. Surg Endosc. 2010;24:63–7.
54. Lermann, et al. Comparison of preoperative and postoperative sexual function in patients with deeply infiltrating endometriosis with and without bowel resection. Europ J Obstet Gynecol Reprod Biol. 2019;239:21–9.
55. Meuleman, et al. Clinical outcomes after radical excision of moderate to severe endometriosis with without bowel resection and reanastomosis; a prospective cohort study. Ann Surg. 2014;259(3):522–31.
56. Abo, et al. Postoperative complications after bowel endometriosis surgery by shaving, disc excision or segmental resection: A three arm comparative analysis of 364 consecutive cases. Fertil Steril. 2018;109(1):172–8.
57. Bertocchi V, et al. Colorectal anastomotic stenosis: lessons learned after 1643 colorectal resections for deep infiltrating endometriosis. J Minim Invasive Gynecol. 2019;26:100–4.
58. Donnez O, Roma H. Choosing the right surgical technique for deep endometriosis: shaving, disc excision or bowel resection? Fertil Steril. 2017;108(6):931–42.
59. Vignali M, et al. Surgical treatment of deep endometriosis and risk of recurrence. J Minim Invasive Gynecol. 2005;12(6):508–13.
60. Bozdag G. Recurrence of endometriosis: risk factors, mechanisms and biomarkers. Special report. Women Health. 2015;11(5):693–9.

Benign Colorectal Disease Trauma of the Colon and Rectum

42

Reza Askari, Ali Salim, and Matthew Martin

Key Concepts

- Most colonic injuries are associated with penetrating trauma.
- Colonic injuries can often be treated by primary repair or resection with anastomosis.
- Extraperitoneal rectal injuries are usually treated with colostomy; washout and presacral drainage are not generally indicated.

Introduction and Historical Perspective

Over the past several decades, the management of colon trauma has changed dramatically. These changes have led to a significant improvement in colon-related mortality. Mortality rates have fallen from approximately 60% during World War I to <10% in the more recent conflicts in Iraq and Afghanistan. A recent multicenter study of modern civilian colon trauma found a colon-related mortality of only 1.3% [1]. Similarly, low morbidity and mortality rates have been reported from several combat operations in Iraq and Afghanistan [2, 3]. Many factors have led to the overall decline in mortality rates. These include quicker transport times, as well as improvements in resuscitation strategies, antibiotic use, and surgical techniques. However, morbidity rates of abdominal sepsis from colon-related injuries remain anywhere from 16 to 33% in various military and civilian studies [4–10].

Prior to World War I, mortality rates from bowel injury approached 100% as management of injuries was largely nonoperative. In fact, laparotomy was largely condemned as a treatment option [11]. By World War II, advances in causality transport and prehospital care led to abandonment of nonoperative management in favor of laparotomy and primary repair of the injured colon [12, 13]. This led to a decrease in the overall battlefield mortality but was still associated with a considerable risk of repair failure, sepsis, and death.

The next shift in the management of colorectal trauma management occurred following the publication of Ogilvie's classic analysis of the management of colon wounds from the North African campaign of 1942 [14]. Ogilvie strongly advocated either fecal diversion of all colonic injuries or repair/resection with proximal diversion. This approach led to a drastic decrease in mortality rates compared to World War I [14, 15]. In fact, the US surgeon general adopted proximal diversion as a formal policy directive for the treatment of all colonic injuries [15, 16]. During the Korean and Vietnam war era, the management of colonic injuries became more anatomically based. Selected right-sided injuries underwent resection and primary anastomosis versus routine colostomy formation for left-sided injuries [17].

For rectal injuries, the principles of wide local washout in addition to proximal diversion were adopted during World War II [17, 18]. This led to a significant decrease in mortality from pelvic sepsis. This approach was further modified during the Korean and Vietnam wars with the addition of distal rectal washout and presacral drain placement. This led to the "4 Ds" of rectal trauma: direct repair, divert, drain, and distal washout.

The more recent combat conflicts in Iraq and Afghanistan over the past decade have led to several published series [2, 3, 19]. The overall trend now is that the majority of colonic injures are being managed with primary repair or resection and anastomosis. Despite this paradigm shift, approximately one-third of patients still underwent diversion in the management of colon-related injuries. An important factor in recent decades is the introduction of the principles of damage control surgery. This has allowed a delay in decision-making as

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it relates to anastomosis versus proximal diversion in the unstable patient. Combat damage control data assessing primary repair versus anastomosis have demonstrated comparable and acceptable morbidity rates [19, 20].

Colon Trauma

Epidemiology

Most injuries to the colon are due to penetrating abdominal trauma, with gunshot injuries the most common cause followed by stabbing and impalement. After the small bowel, the colon is the most commonly injured organ in penetrating abdominal trauma [21]. Blunt colonic injuries are less common and account for <10% of injuries found at laparotomy. Lap belt use, particularly without the concomitant use of the shoulder harness, increases the risk of visceral injury. Most colonic injuries secondary to blunt trauma result in superficial injuries from small hematomas or serosal tears. However, a third will have full-thickness colon perforation [22]. Mesenteric tears and ischemic necrosis of the colon should be suspected in injuries secondary to rapid deceleration. In rare cases, colonic injuries can present in a delayed presentation secondary to a colonic wall hematoma or contusion. Blast injuries such as explosions are more likely to lead to injuries to hollow viscera than solid organs, with the colon being the most susceptible. Sometimes, these injuries can present without external signs of abdominal trauma [23].

The American Association for the Surgery of Trauma has now published a grading scale for colonic injuries (Table 42.1) [23]. This is useful in predicating possible complications and evaluation of different therapeutic interventions.

Diagnosis

In penetrating abdominal trauma to the anterior abdominal wall, prompt abdominal exploration accurately identifies the majority of colonic injuries. The highest level of suspicion should be for gunshot wounds to the trunk that have passed from anterior to posterior or crossed the midline from side to side. Perineal or trans-pelvic gunshot wounds should be assumed to have a rectal injury until proven otherwise. For those undergoing a trial of nonoperative management, serial abdominal examinations and computed tomography (CT) scan evaluation with IV contrast are useful both for visualizing injuries and for reconstructing the projectile tract and assessing the structures at risk [24].

Wounds to the flank and back can lead to colonic injuries despite the absence of initial peritoneal irritation or hemodynamic instability. CT scan with triple contrast is useful for delineating such injuries, with 90% sensitivity and 96% specificity [25]. However, it is unclear whether a "triple-contrast" CT scan provides any more sensitivity or specificity versus standard CT with IV contrast only. In most cases, we have found that standard CT is adequate and avoids the inherent delays of administering oral and rectal contrast.

Diagnosis of colonic injury following blunt trauma can be difficult. This is particularly challenging in patients who are unevaluable secondary to drug or alcohol intoxication or the presence of concomitant brain or spinal cord trauma. CT scan remains the diagnostic modality of choice looking for the presence of free air, unexplained free peritoneal fluid, or thickened colonic wall. The presence of free intraperitoneal air mandates exploration for perforated hollow viscus. Free intraperitoneal fluid in the absence of solid organ injury should significantly raise the index of suspicion for bowel injury and mandate either surgical exploration or close serial examinations and possible repeat imaging. Diagnostic peritoneal lavage and laparoscopy have little utility in the contemporary evaluation of patients with suspected colonic injury. Laparoscopy could be useful in stable patients with back, flank, or pelvic wounds. Some of the key aspects of the initial evaluation of colorectal trauma are summarized in Table 42.2.

Table 42.1 Time from injury to surgical management in American wars

Grade	Injury description
I	A. Contusion or hematoma without devascularization B. Partial-thickness laceration
II	Laceration ≤50% of circumference
III	Laceration >50% of circumference
IV	Transection of the colon
V	Transection of the colon with segmental tissue loss

Management

Preoperative Consideration

Once the decision has been made for operative intervention for a suspected colorectal injury, the basic principles of emergency surgery and Advanced Trauma Life Support (ATLS) apply. Attention should be paid to hypothermia prevention and management with active warming devices. The possibility of ongoing bleeding should be anticipated. Emergency-release blood products should be standing by, and type and cross should be performed as soon as possible. A Foley catheter should be placed barring any signs of urethral injury. Antibiotics should be administered as soon as there is evidence of the injury or a decision for laparotomy has been made. The optimal goal is to administer antibiotics 30–60 minutes prior to skin incision. Re-dosing of antibiotics should be performed if the surgery is prolonged or in

Table 42.2 Key elements of the initial trauma evaluation for colorectal trauma

History	Physical examination	Diagnostic and imaging studies
Abdominal pain or complaints	Overall impression ("sick" or "not sick")	Chest x-ray – free air, elevated or blurred diaphragm
Allergies and medications	Vital signs	FAST exam – free fluid in the abdomen or pelvis
Prior abdominal surgery: particularly any prior bowel surgery, hernia repairs, mesh implantation, and aortoiliac surgery	Focused abdominal exam: tenderness, distension, rebound, guarding, bruising, "seat-belt sign." Identify all prior incisions and any hernias	CT scan of the abdomen/pelvic: diagnostic study of choice in most patients. No oral contrast required for initial study. Consider follow-up CT with oral contrast or "triple contrast" for equivocal initial study or concerning clinical picture
Major comorbidities: vasculopathy, congestive heart failure, high-dose steroid use, immunosuppressants	Location of all open penetrating wounds	"Triple-contrast" CT scan: may be useful for penetrating flank or back wounds with suspicion for retroperitoneal colonic injury, but usually standard CT is adequate
Injury mechanism (from high to low risk): Penetrating, missile Penetrating, stab Blunt, high velocity Blunt, low velocity	Logroll and full back/flank exam	Abdominal x-rays: not useful as routine study in blunt trauma. Can be very useful in gunshot wounds for identifying location of fragments and estimating trajectories. Place radiolucent markers on all external wounds
	Pelvic and perineal exam	Diagnostic peritoneal lavage: mainly of historical interest but can be used with equivocal CT findings (i.e., free fluid with no solid organ injury) in patients with unreliable exam
	Digital rectal exam (DRE)	Anoscopy, rigid proctoscopy: penetrating perineal trauma, open pelvic fracture, positive DRE, any other suspicion for rectal injury

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cases where blood loss and transfusion are approaching one whole blood volume. Antibiotics need to only be continued for 24 hours, and there is no benefit of continuing them any longer, even in the face of large-volume contamination [26]. The only exception to this would be the patient with a delayed presentation of a colonic injury, where there is now sepsis and an established intraabdominal infection.

Timing of Injury and Operative Decisions

Most traumatic colorectal injuries will present within the first few hours, and a short delay (2–8 hours) should not impact management decisions. However, occasionally there may be a significant delay to either diagnosis or intervention in a patient with a major colorectal injury. This can result in severe morbidity or mortality. These scenarios may occur in settings where there is a failure to recognize peritoneal signs or imaging findings at initial presentation, the presence of factors that compromise the abdominal exam (i.e., head injury or intoxication), or the masking of peritoneal signs by medications (i.e., steroids) or other patient factors. Generally, delays of more than 8–12 hours in the setting of fecal contamination will alter both the anatomy and the patient physiology, potentially altering surgical decision-making.

As a general principle, in the setting of fecal contamination and peritonitis as a result of delay to operation, there should be a much more liberal use of proximal diversion as opposed to primary anastomosis. However, this decision should be individualized based on the patient's age and comorbidities, the physiologic status during surgery, the location and severity of injury, and the local anatomic factors. Factors that can alter the operative approach in these cases include:

1. Hemodynamic instability secondary to septic shock from fecal contamination
2. Staple line compromise secondary to bowel wall induration and edema
3. Presence of significant bowel distension
4. Mesenteric thickening and shortening that can limit colostomy creation

Operative Management: When to Repair, Resect, or Divert

Several factors go into the decision to repair, resect, or divert. Classically, the teaching has been to categorize injuries as either destructive (>50% of bowel circumference or devascularized) or nondestructive. The recommendation for destructive injuries is to resect the injured area, whereas primary repair is recommended for nondestructive wounds. However, several other factors must be considered. These are outlined

in Table 42.3. Important factors include not only the size of the injury but the numbers and locations.

Injuries secondary to high-velocity gunshot wounds require that the wound edges be debrided back to healthy tissue before closure. It is important to remember that missile injuries can cause extensive tissue damage or even direct thermal injury (Fig. 42.1), which will often lead to breakdown of the closure if the edges have not been adequately debrided. Another important factor is the status of the mesentery, as this will determine the adequacy of the blood supply to the area. The classic "bucket-handle" deformity is a large tear in the mesentery without injury to the colon wall, which may occur in blunt trauma from rapid deceleration. The bowel will often appear uninjured but should be resected due to the large area of devascularization and the potential for delayed perforation or anastomotic leak (Fig. 42.2).

Table 42.3 Factors to guide primary repair versus resection for colon surgery

Primary repair	Resection
Small size (nondestructive)	Destructive (>50% circumference or devascularized)
Single injuries or multiple with adequate spacing	Multiple injuries with short spacing
Clean margins (after debridement of edges)	Inflamed or necrotic edges
Minimal or no mesenteric injury	Large mesenteric hematoma or laceration
Tension-free closure	Cannot be closed without tension
Healthy surrounding bowel	Major edema, inflammation, bowel wall hematoma
No major pathology present	Major pathology present (cancer, diverticulitis, etc.)
Closure leaves widely patent lumen	Closure would narrow lumen (>25%)
Low-velocity wound	High-velocity wound
At risk for short gut syndrome with resection	Adequate bowel length after resection
No adjacent pancreatic injury or leak	Pancreatic injury/leak adjacent to injury

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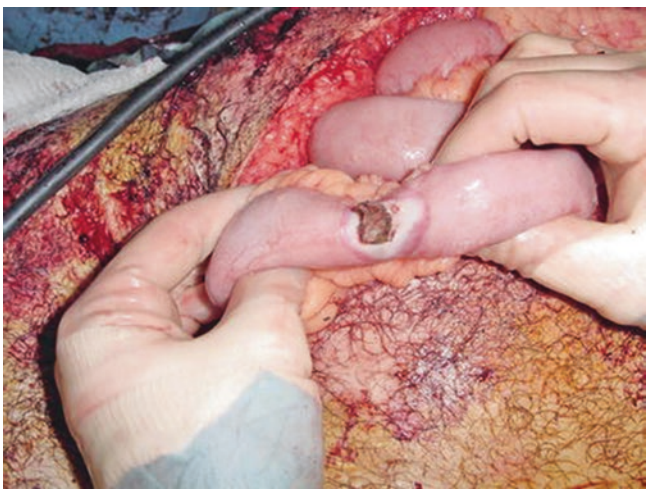

Fig. 42.1 Missile wound to the bowel with small perforation but significant thermal injury to the surrounding bowel wall. This injury should be completely debrided and then repaired or resected. (Reprinted [adapted] from Complexities in Colorectal Surgery (p. 524, Fig. 34.3) by Steele SR, Maykel JA, Champagne BJ, Orangio GR, editors. New York; 2014. Copyright © 2014 Springer Nature)

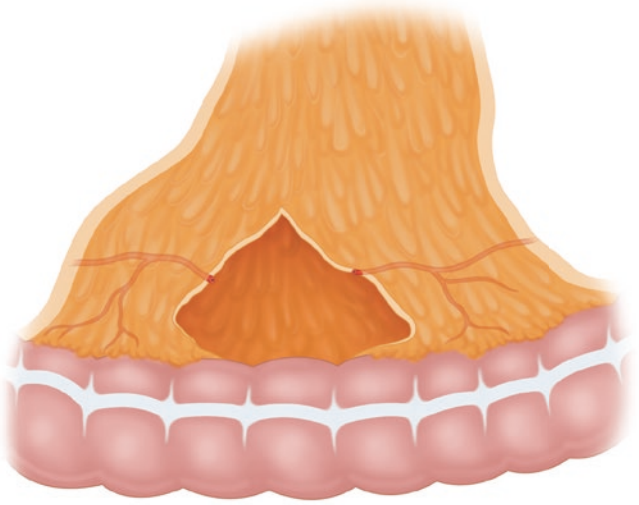

Fig. 42.2 Large tear of the mesenteric border of the bowel ("bucket-handle" deformity) from blunt deceleration forces. This usually requires resection of the now devascularized bowel segment to avoid subsequent ischemic complications

While each individual colon and rectal injury type and location may have an associated "textbook" answer for the most appropriate operation to perform, this often does not consider the wide variety of presentations, number of injuries, presence of associated injuries, and patient physiology.

Evidence and Practice Guidelines

In 1979, Stone [26] performed the first reported trial of patients randomized to exteriorization or colostomy versus primary repair for small colonic injuries (n = 268). This study demonstrated a tenfold reduction in the incidence of complications with primary repair and a significantly increased hospital stay and cost associated with colostomy. Several years later, studies by Chappuis [27], Sasaki [28], and Gonzalez [29] together randomized more than 300 patients to primary repair or colostomy. These studies showed that primary repair or anastomosis was safe and effective; in fact, they reported fewer complications in the repair group as compared to those who underwent proximal diversion (Table 42.4).

Table 42.4 Mortality rate of penetrating colorectal trauma in American wars

	Primary repair		Colonic diversion	
Study	No. of patients	Rate of abdominal septic complications (%)	No. of patients	Rate of abdominal septic complications (%)
Chappuis et al. [27]	28	14.3	28	17.9
Sasaki et al. [28]	43	2.3	28	28.6
Gonzalez et al. [29]	89	18	87	21
Total	100	13.1	143	21.7

A further randomized study by Kamwendo [30] in 2002 confirmed the safety of primary repair. This study was important in that it included patients with delayed presentation, contamination, associated injuries, and shock. In fact, similar to the outcomes of prior studies, it showed that primary repair/anastomosis was superior to colostomy even in the high-risk patients with contamination. In a sense, the colon trauma literature largely mirrors the diverticulitis literature, with better outcomes consistently reported with resection and primary anastomosis versus resection and colostomy or proximal colostomy alone.

Multiple other prospective observational trials have also added valuable evidence upon which to base recommendations [4, 7, 31–34]. The majority of these support the use of primary repair or anastomosis without diversion for all types of colonic injury. This has led to the abandonment of the dogma that right- and left-sided injuries should be treated differently and that left-sided injuries mandated a colostomy.

The American Association for the Surgery of Trauma (AAST) conducted a multicenter randomized prospective trial of diversion vs. resection and anastomosis for destructive colonic injuries that was published in 2001 [1]. In this study, there were 297 patients; 66% were managed with primary anastomosis and 33% by diversion. Colon-related mortality was 1.3%, all in the diversion group. Anastomotic leak rate was 6.6% with zero mortality. Risk factors for abdominal complications were severe fecal contamination, transfusion of more than four units of blood within the first 24 hours, and inappropriate antibiotic selection. If all three factors were present, the rate of abdominal complications reached 60%. The authors concluded that resection with anastomosis is the treatment of choice in all destructive colonic injuries regardless of severity of injury.

However, the low incidence of severe (destructive, high-velocity, etc.) colonic injuries in this trial does limit the conclusion about the potential benefit of fecal diversion in select high-risk cases. These findings have also been misinterpreted by some as indicating that colostomy should be performed in patients with certain risk factors (severe contamination, transfusion requirement, etc.). In actuality, these factors increased the risk for abdominal complications regardless of whether ostomy or primary anastomosis was performed and should not be used as independent criteria for performing a colostomy.

The evolution of damage control laparotomy (DCL) for devastating abdominal trauma has led to a significant reduction in morbidity and mortality. Abbreviated laparotomy and resuscitation in the intensive care unit help to avoid, or more rapidly correct, the lethal triad of coagulopathy, acidosis, and hypothermia [35]. The management of colonic injuries in these situations has evolved as well. Early in the DCL era, colostomy was considered the treatment of choice. However, several studies supported selected repair or resection and delayed anastomosis after DCL, citing the potential ability to inspect the suture or staple line at subsequent operations [36–38]. Others voiced more caution in this patient population, particularly if there was a persistent need for vasopressors [39]. In 2009, Weinberg's retrospective review showed DCL patients that had resection with anastomosis had higher rates of complications compared to colostomy [40]. In 2011, Ott reported an enteric leak rate of 27% for patient who had a DCL, with higher leak rates associated with transfusion requirements and left-sided colonic injuries [41].

More recently, however, several studies have refuted the higher rates of complications for delayed anastomosis in patients that undergo DCL [42]. A recent multicenter retrospective cohort study performed across three Level I centers by Tatebe in 2017 indicated that DCL was not associated with increased enteric leaks, fistula, SSI, or intraperitoneal abscess despite nearly two-third having delayed repair. However, the study was underpowered, and a prospective trial was still recommended [43].

The Eastern Association for the Surgery of Trauma published its initial guidelines for the management of penetrating colonic injuries in 1998 [44]. More recently, in 2018, a meta-analysis was performed, and the guidelines were updated. The most recent guidelines recommend repair or repair and anastomosis in low-risk patients (no signs of shock, hemorrhage, severe contamination, or delay to surgical intervention). In high-risk civilian trauma patients (delay >12 hours, shock, associated injury, transfusion >6 units of blood, contamination, or left-sided colonic injuries), including those who undergo DCL, the society *conditionally* recommends that colon repair or resection and anastomosis be performed rather than mandatory colostomy except in patients with the most severe injuries [45].

Technical Considerations

In managing traumatic injuries, the surgeon is often faced with the need to make decisions rapidly with imperfect and incomplete information, often in suboptimal and chaotic settings. The patient should be widely prepped and draped, including the lateral abdominal wall in case a colostomy or ileostomy is needed. For the unstable or actively bleeding patient, a generous midline incision should be made at the start to allow rapid access to all quadrants of the abdomen. For the stable patient, a smaller laparotomy incision can be considered and may be extended based on the injuries that are identified. If a large amount of hemoperitoneum is discovered on entering the abdominal cavity, even in the "stable" patient, then all attempts at a "minilaparotomy" should be abandoned, and the incision should be extended from the xiphoid to several centimeters above the pubic symphysis.

During the initial exploration for penetrating trauma, it is important to optimize the operative exposure and visualization. This can often be obtained by taking a few minutes to set up a self-retaining retractor of choice. Gross spillage should be controlled with quick suturing or stapling as soon as exsanguinating hemorrhage is stopped. This does not have to be a definitive resection or repair. In penetrating trauma, paracolic and retroperitoneal hematomas should be fully explored. Primary repair can be safely accomplished utilizing a number of methods. There is little difference between single- and double-layered suture techniques, with attention to careful suture placement and complete defect closure more important than how many layers are performed. Perforations that are within a few centimeters of each other are best treated by removing the intervening bridge of tissue and performing a single repair (Fig. 42.3) or resecting the involved segment. There is little difference between stapled and sutured anastomosis in terms of leak rates, anastomotic complications, or function. There is no need for colonic lavage even with left-sided anastomosis. In general, ileocolostomy is associated with fewer leaks than colocolostomy.

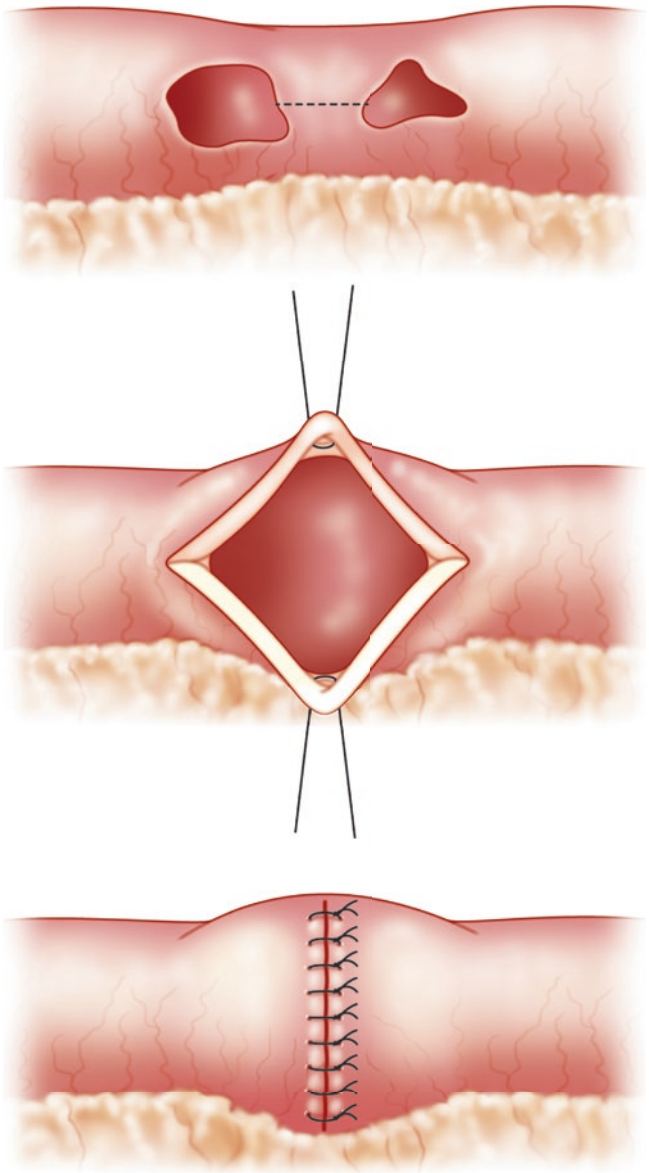

Fig. 42.3 The intervening bridge of tissue between two closed perforations can be removed, and the resulting single defect can be closed transversely

Should DCL be necessary, the colon can be left in discontinuity at the initial exploration. The key concept of DCL is to perform an abbreviated laparotomy that addressed only active bleeding and control of gastrointestinal contamination. The classic indications for DCL are alteration in patient physiology marked by acidosis, hypothermia, and coagulopathy. Detailed exploration and reconstruction are deferred to a later time. Other indications include the presence of multiple complex injuries that will require prolonged surgical reconstruction and the presence of questionably viable bowel that will need a second-look operation. The abdomen is temporarily closed, and resuscitation is continued in the intensive care unit. Once restoration of normothermia and correction of acidosis and coagulopathy are accomplished, the patient is returned to the operating room for further treatment. Every attempt should be made to close the abdomen early, as earlier closure has been shown to decrease complication rates. There is also no optimal or standard time interval between operations that should be utilized. This decision should be based on the patient's injuries and response to resuscitation, and not a predetermined time interval. We strongly recommend avoiding intervals longer than 48 hours in the presence of stapled-off bowel, as this inevitably leads to proximal dilation, edema, and increased fluid requirements.

In most cases, there are multiple intraoperative decisions that need to be made quickly which will have a significant impact on both short-term and long-term outcomes. Table 42.5 provides a summary of these key decisions with

Table 42.5 Key intraoperative management issues and decision in colorectal trauma

Key decision	Factors to consider	Technical issues/pearls
Primary repair or resection?	Size of injury Shape of injury (linear, round/stellate) Single or multiple Tissue quality Mesentery status (rents, hematomas, devascularized segment)	Debride injury or burned tissue Connect close injuries rather than leaving "bridges" Evacuate large mesenteric hematomas Close mesenteric tears Resect segment with "bucket-handle" mesenteric defect
Damage control?	Patient stability Transfusion requirement Acid/base getting better or worse? Multiple injuries? Another reason for a "second look" (i.e., borderline bowel visibility)	Make decision early in case Proceed if patient improving; terminate if getting worse Vacuum-assisted temporary closure works best Usually no need for other drains
Anastomosis or ostomy?	Patient baseline status (age, comorbidities, meds) Physiologic status Quality of the tissues Other injuries and proximity to anastomosis Body habitus, ability to properly site an ostomy	Consider difficulty and risk of ostomy takedown Be wary of anastomosis with an associated pancreatic injury! Obesity increases difficulty and complications with ostomy
Anastomosis: hand-sewn or stapled?	Operative time Other injuries to address Personal experience and comfort Tissue quality, edema Anatomic area and bowel alignment Available equipment	No difference in leak or complication rates in most series Hand-sewn potentially more secure with suboptimal tissue quality, bowel wall edema Laparoscopic staplers great for pelvis, hard to reach areas, or sharp angles
Ostomy: loop, end, or others?	High-risk anastomosis that needs protection? Need access to distal bowel segment? Body habitus Mesentery – shortened, edematous	Loop may reach the skin easier with obesity or shortened mesentery May not get complete fecal diversion with a loop Remember the "end-loop" option (see text) Use an ostomy bar if any tension or obese patient Wrap ostomy in Seprafilm® for easier takedown
Leave a drain?	No indication for routine drainage of bowel anastomosis Widely drain any other adjacent injuries (pancreas, bladder, etc.) Other reasons: associated abscess cavity, control ascites in cirrhotic patient	Avoid direct contact of drain with anastomosis Larger sump drains usually not beneficial Make exit site remote from incision and any ostomy
Place a feeding tube?	Degree of bowel injuries and surgery Estimated need for prolonged NPO status Estimated inability to take oral nutrition Need for feeding access as well as gastric decompression? Pancreatic or duodenal injury?	Generally avoid making additional holes in the bowel in the trauma setting Stamm gastrostomy relatively safe and secure Higher complications with jejunostomy tubes with little benefit Consider intraoperative placement of nasojejunal tube

the associated factors and technical pearls that should be considered. This table is by no means all-inclusive but does highlight many of the common decisions.

Rectal Trauma

Epidemiology

Rectal injuries, while infrequent, are associated with a higher risk of missed or delayed diagnosis, as well as a significant risk of morbidity and mortality. These injuries are most often seen in the setting of penetrating trauma in the civilian population. Gunshot wounds account for greater than 80% of these injuries [3]. Accidental or intentional impalement, iatrogenic endoscopic and urologic injuries, and rectal foreign bodies account for the rest. In the military setting, rectal traumatic injuries occur at a higher rate and are typically more destructive, as they are often due to higher-velocity missile or blast mechanism [46].

Diagnosis

A high degree of suspicion is required to avoid the significant morbidity and mortality that can occur with a missed or delayed diagnosis. While the overall incidence of these injuries is low, certain injury patterns or mechanisms should

raise suspicion and prompt particular attention to the anorectal evaluation. Any penetrating trauma to the buttock, groin, proximal thighs, perineum, or sacra area should raise concern for an associated anorectal injury. Additionally, any trans-pelvic gunshot wound should be assumed to have a rectal injury until proven otherwise. Also, any injuries to any of the other closely associated organs or structures such as the bladder, uterus, vagina, or iliac vessels should prompt an evaluation for concomitant rectal injuries. In blunt trauma, an isolated anorectal injury is rare and is almost always associated with other major pelvic/perineal injuries and a high-velocity mechanism. Any pelvic fractures, particularly an "open-book" fracture, or those with major posterior pelvic/sacral disruption, can cause rectal injury from bone fragments or shearing forces (Fig. 42.4). Additional scenarios that are risks for blunt rectal trauma include straddle-type injuries and any fall with perineal impalement.

The presence of gross blood on digital rectal examination is highly suggestive of rectal injury and should mandate further evaluation. However, this exam finding lacks adequate sensitivity or specificity and should not be considered a definitive test to rule in or rule out a rectal injury. Sigmoidoscopy, either rigid or flexible, should be performed and has an expected diagnostic accuracy of 80–95% [47]. Care must be taken not to worsen a potential defect during the exam by aggressive scope advancement or insufflation [48]. A careful endoscopic exam with full 360-degree circumferential inspection must be performed, as often the signs of injury can be subtle. Visualization of a full-thickness defect of the rectal wall is relatively uncommon, and frequently the only endoscopic finding is a small hematoma at the site of injury.

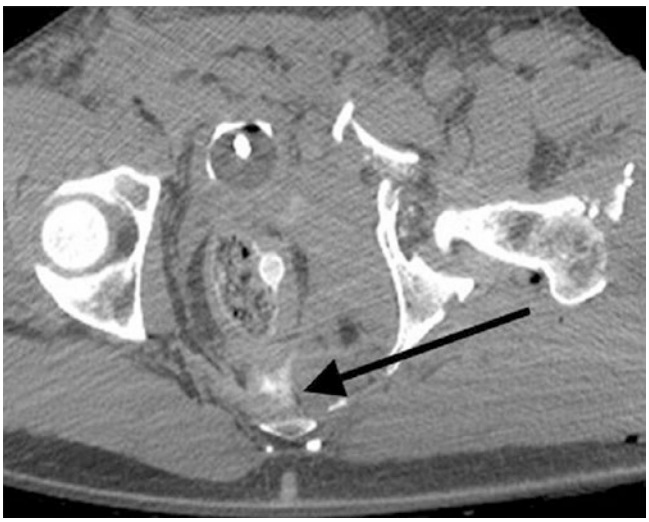

Fig. 42.4 Computed tomography showing rectal injury with contrast extravasation from a severe pelvic fracture

Table 42.6 AAST organ injury grading scale for injury to the rectum

Grade	Type of injury	Description of injury
I	Hematoma	Contusion or hematoma without devascularization
	Laceration	
II	Laceration	Laceration <50% of circumference
	Laceration	
III	Laceration	Laceration ≥50% of circumference
IV	Laceration	Full-thickness laceration with extension into the perineum
V	Vascular	Devascularized segment

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Computed tomography (CT) is now the most common radiologic adjunct in the trauma setting. It is often ordered with only IV contrast. However, should a rectal injury be suspected, the use of triple-contrast CT imaging (IV, oral, and rectal) can improve its diagnostic accuracy [49, 50]. The American Association for the Surgery of Trauma (AAST) has defined injuries to the rectum based on the degree of injury thickness and extent of circumference involved (Table 42.6) [51]. Similar to colonic injuries, rectal injuries are classified as either "destructive" or nondestructive." Any injury involving greater than 50% of the circumference of the bowel wall or with associated mesenteric injury that compromises the perfusion of the segment of bowel is considered "destructive."

Anatomic Considerations

The anatomy of the rectum is unique. The proximal anterior and lateral portions of the upper two-third of the rectum are covered with peritoneum, while the posterior surface is extraperitoneal. The distal third of the rectum lies completely extraperitoneal. This portion of the rectum is surrounded by a thick connective tissue and fat layer which contains the neurovascular supply. Since the dissection required to expose the extraperitoneal rectum is much more extensive and difficult compared to the intraperitoneal portion, the optimal operative strategy in rectal injuries differs vastly between intraperitoneal and extraperitoneal injuries.

It is also important to have a clear understanding of the anatomic locations and relationships of other key pelvic structures and organs in the operative exposure and repair of a rectal injury. These structures include the bladder anteriorly, the sacrum and sacral venous plexus posteriorly, and the iliac vessel and ureters posterolaterally. In males, the prostate and seminal vesicles and, in females, the uterus and vagina will also be found anteriorly.

Management of Intraperitoneal Rectal Injuries

These injuries have historically been managed like that of a distal left colon, with near-universal use of a diverting colostomy even for relatively small isolated injuries. However, there is little reason to treat these injuries any differently than injury to other portions of the colon, and a diverting ostomy should no longer be considered mandatory or "standard of care." The use of primary repair without diversion is a safe option in most nondestructive injuries in hemodynamically stable patients. A larger, more destructive injury to the intraperitoneal rectum should be managed with segmental resection of the injured portion. Following segmental resection, a decision for anastomosis versus ostomy must be made.

Using the same risk scaling approach described earlier in the chapter, we recommend an ostomy without anastomosis or an anastomosis with a protective proximal stoma in high-risk and select moderate-risk patients. Low-risk patients and select moderate-risk patients can safely undergo primary anastomosis as described previously for colonic injuries. Another important factor to consider is the location of the resection that is required. In general, if the resection has to be carried out down to the mid or lower third of the rectum, we recommend an anastomosis with a protective loop ileostomy. Subsequent elective return to the operating room and ileostomy reversal can be done as early as 4–6 weeks after the initial surgery. This can almost always be performed as a local procedure without the need for a repeat laparotomy.

Management of Extraperitoneal Rectum

Classically the teaching for the management of extraperitoneal rectal injuries has involved the "4 Ds": diversion, direct repair, distal washout, and drain placement. In reality, very few patients require all four (or even three) of these interventions, and the mainstay of care for most rectal extraperitoneal rectal injuries should be primary repair (if easily accessible) and proximal diversion. The most important of Ds will be proximal diversion as primary repair of an extraperitoneal rectal injury can be challenging due to its location, presence of bleeding, and proximate anatomic structures. Whether an end or loop colostomy is performed depends on the extent of the injury, associated injuries, body habitus, and operative approach. Creation of a loop colostomy as opposed to an end colostomy has been shown to provide appropriate fecal diversion and avoids the added risk of complicated takedown procedures [52, 53]. As with the loop ileostomy, a loop colostomy can frequently be reversed via a local procedure without the need for repeat laparotomy.

It is recommended that direct repair of extraperitoneal injuries be performed only when they are easily accessible without significant dissection or if the injury is encountered during the exposure of an associated injury [54]. While injuries to the proximal extraperitoneal rectum can be carried out via abdominal mobilization, a very distal injury will be best approached from inside the rectum.

Another option that can be considered is to resect the damaged segment, perform a primary anastomosis, and protect it with a diverting loop ileostomy [55]. While there may be some debate as to whether a loop ileostomy provides adequate diversion for a distal anastomoses, a modification of it to create a stapled end-loop ileostomy (or colostomy), with the distal stapled end buried in the subcutaneous tissue for future identification can be considered (Fig. 42.5) [56, 57]. This modification will provide complete fecal diversion and obviate the need for a future laparotomy when it comes to time for reversal.

When it comes to the other 2 Ds, distal washout and drain placement need only to be used infrequently. When there is a large volume of retained stool in the rectal vault and the injury has been controlled or excluded, then a distal washout can be performed. Similarly, presacral drainage has lost significant support over the years, and in fact it is not necessary in the vast majority of the cases. A prospective trial in 1998 randomized patients with extraperitoneal rectal injury to presacral drain placement versus no drain and found that there was no benefit of presacral drains in reducing infectious complications [58]. Some still advocate for the use of a presacral drain for those injuries that are inaccessible and cannot be repaired or that have a heavy degree of presacral contamination. This should be done in conjunction with a diverting ostomy [59, 60]. Figure 42.6 shows the location of a properly placed presacral drain. This can be placed by making a curved transverse incision posterior to the anus and bluntly dissecting the presacral space to the level of the injury.

Similarly, distal washout of the rectum has not shown to have any benefit in the routine management of penetrating civilian rectal trauma. Those supporting distal rectal washout claim that removal of remaining stool in the defunctionalized rectal vault will decrease the risk of sepsis. Others argue that forceful irrigation of liquid into the rectal vault will only increase the amount of local spillage and can push fecal material into otherwise unaffected tissue planes. Overall, the authors of this chapter do not routinely employ distal rectal washout in the setting of rectal trauma.

Guidelines

The Eastern Association for the Surgery of Trauma (EAST) has released practice guidelines for the management of nondestructive extraperitoneal rectal injuries. They *conditionally* recommend *for* proximal diversion and *against* presacral drainage and distal rectal washout. Keep in mind that these

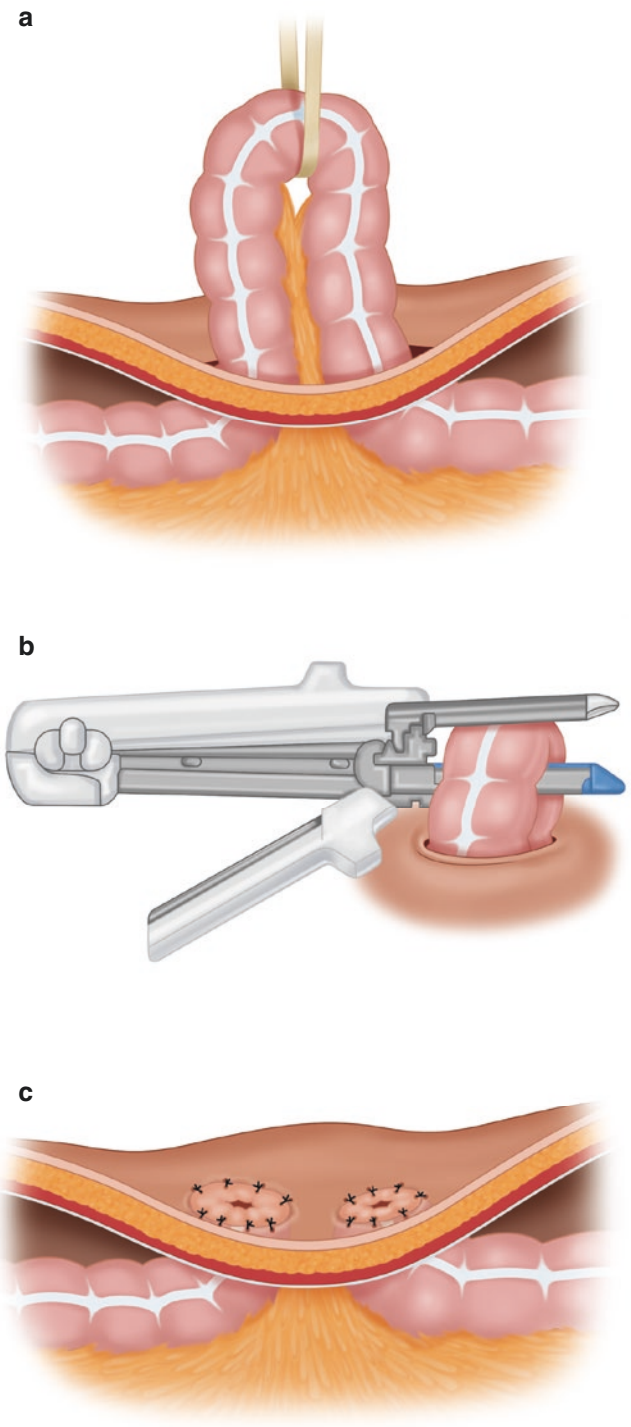

Fig. 42.5 Technique for end-loop ostomy (colon or ileum). (**a**) Loop of the bowel is delivered, (**b**) the bowel is divided at the site of the planned ostomy, and (**c**) proximal end is matured, and the distal stapled end is secured in the subcutaneous position for easy future access and restoration of continuity

recommendations are based on evidence graded as "very low" by the committee [61]. However, this represents the best currently available evidence and synthesis of the disparate literature on this topic.

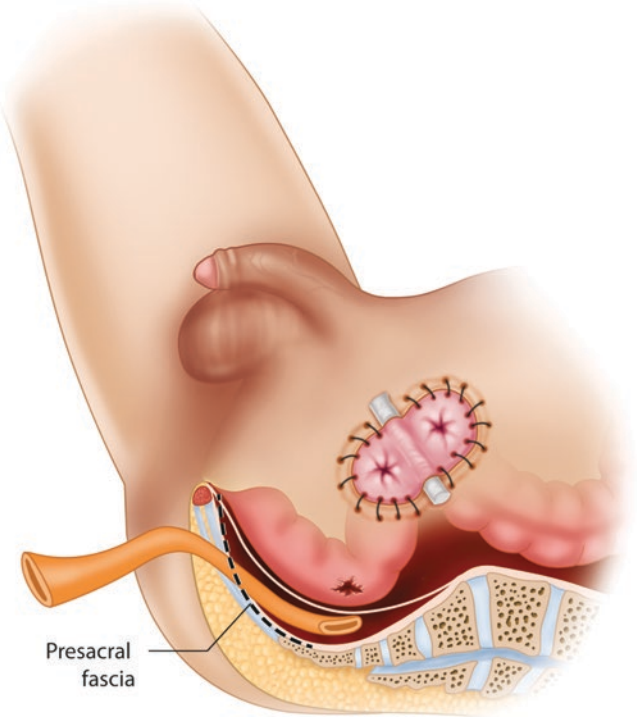

Fig. 42.6 Placement of drains in the presacral space, anterior to Waldeyer's fascia, up to the level of colorectal injury. (Reprinted (adapted) from Fundamentals of Anorectal Surgery (Chap. 29, Fig. 28.2) by Beck DE, et al. (eds). 2019. Copyright © 2019 Springer Nature)

The American Association for the Surgery of Trauma [62] published a recent large multicenter study of traumatic rectal injuries in 2017. This analysis of 758 rectal injuries is the largest in the literature and provides additional support for the current trends outlined above. For intraperitoneal rectal injuries, those managed with a diverting colostomy had twice the complication rate (22% vs. 10%) compared to those managed with primary repair or primary anastomosis without diversion. For the extraperitoneal rectal injuries, the majority were managed with proximal diversion with or without direct repair of the injury. On multivariate analysis, the use of distal rectal washout and presacral drainage were independent risk factors for increased abdominal complications (odds ratios of 3.4 and 2.6, respectively) [62].

We recommend that if the injury is limited and easily accessible with minimal dissection with either transanal or abdominal exposure, then primary repair with or without loop colostomy diversion should be performed. Destructive or inaccessible injuries should be diverted with loop colostomy. Distal rectal washout and presacral drainage are not routinely recommended but can be considered in highly select indications.

Anal Trauma

Epidemiology

While non-obstetric trauma to the anus or sphincter is rare, the onset of the recent wars in Iraq and Afghanistan has led to an increase in perianal and pelvic wounds due to ground-level improvised explosive devices (IEDs). These injuries are often seen in conjunction with other massive destructive injures to the perineum, extremities, and trunk. In the civilian trauma setting, the majority of anal trauma is seen with penetrating injuries to the perineum and straddle or impalement injuries or in association with complex open pelvic fractures.

Diagnosis

The diagnosis of anal injuries is usually readily apparent on history and physical exam during the secondary survey. If the patient is awake and able to respond appropriately, then a history of perineal trauma can usually be elicited as well as any current complaints of anal or perianal pain or pressure. The perineum and anus should be evaluated thoroughly; the majority of clinically significant injuries are readily diagnosed by visual inspection. The perineum should be carefully inspected and palpated. The sphincter tone and voluntary function should be assessed with a digital rectal examination. Females should undergo a vaginal exam as well.

If an injury is suspected or identified, a careful examination in the operating room should be done to assess for involvement of the anal sphincters. Gentle anoscopy/proctoscopy should be performed both to evaluate the anal canal and look for associated rectal injury. Particular care should be taken in patients with obesity as even major injuries can be remained hidden until the buttocks and any redundant tissue is adequately retracted to expose the perianal area. It is also critical to obtain a detailed history (as possible) from the patient regarding any prior trauma, preexisting anal/perineal problems, and existing problems with fecal continence. These factors may have significant impact on the evaluation and subsequent management decisions.

Management

Minor injuries to the anal canal can be treated with either local wound care alone or a transanal debridement back to healthy tissue and primary suture repair. Care must be taken to preserve the anal sphincter mechanism to the extent possible and to avoid narrowing of the anal orifice or canal. Simple lacerations to the anal canal involving the sphincter muscles can be repaired primarily with absorbable suture. In all anal injuries, it is critical to clearly identify and document the exact size of the wound, the location relative to the anal verge and dentate line, and the presence and extent of injury to any related structures such as the urethra, penis or scrotum, vagina, bladder, pelvic nerves, bony pelvis/sacrum, and spine/spinal cord.

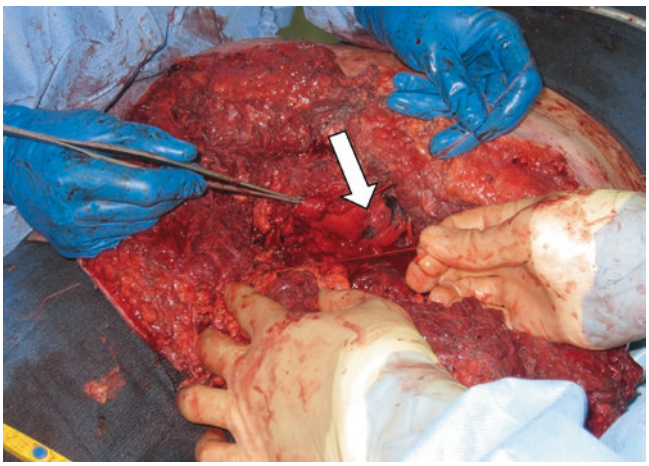

Fig. 42.7 Massive perineal blast wound with destruction of the sphincter complex and exposed distal rectum (arrow). These patients warrant immediate operative intervention to prevent exsanguination, perform debridement, and in this case perform diverting colostomy. (Reprinted (adapted) from Fundamentals of Anorectal Surgery (Chap. 29, Fig. 28.4) by Beck DE, et al. (eds). 2019. Copyright © 2019 Springer Nature)

Massive injures to the perineum can result in significant loss of tissue and complex wounds (Fig. 42.7). Nonviable tissue should be debrided to healthy tissue, but excessive debridement should be avoided at the first operation in order to minimize the loss of sphincter muscle and maximize future options for wound closure. The cut ends of the sphincter muscles should be tagged with sutures for future repair if not repaired at the initial operation. A colostomy is usually indicated in complex perineal wounds involving the anal sphincters and should be performed as early as possible. Although relatively uncommon, large destructive wounds (as seen with military blast injuries) with injury to both the anus and extraperitoneal rectum may require a proctectomy to control contamination and pelvic sepsis.

A vacuum-assisted wound closure device can be used on the perineum while serial debridement is ongoing (Fig. 42.8). It is imperative to investigate the genitourinary tract as many patients will have combined injuries. Older studies have shown good functional outcomes with delayed sphincter repair [63]. Anorectal manometry has been shown to predict functional outcome and should be performed prior to colostomy reversal. Due to the complex nature of these injuries and the local anatomy, we recommend early involvement of a multidisciplinary team including a colorectal surgeon to

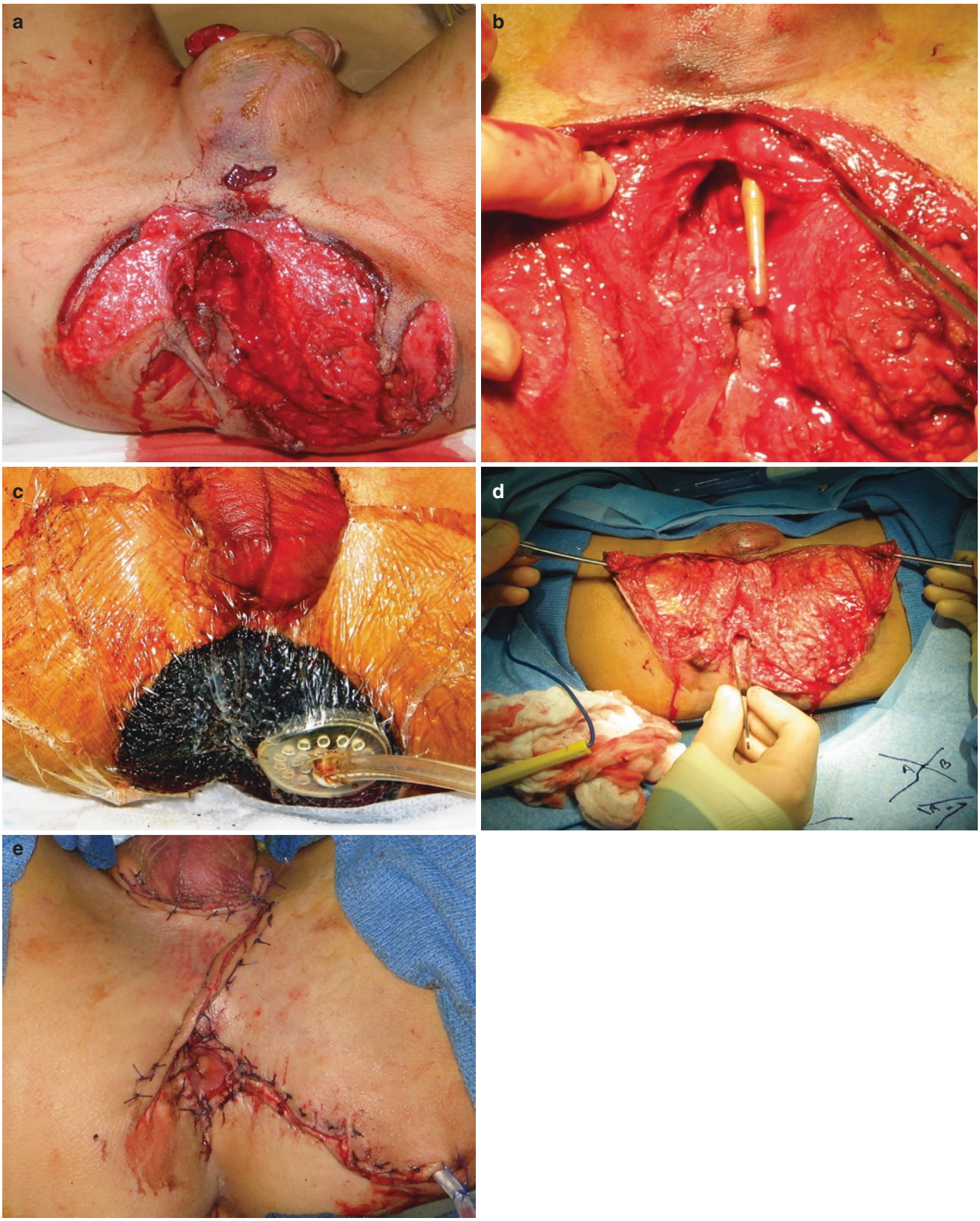

Fig. 42.8 (**a**–**e**). Destructive perineal and anal injury. (**a**) Mortar fragment entered the right hemiscrotum and exited the perineum, causing a massive injury. (**b**) Urethral transection was repaired through the perineum. (**c**) Serial debridements and wound vacuum-assisted closure changes created a healthy wound bed. (**d**) Flaps were constructed to facilitate closure. (**e**) After sphincteroplasty, the final wound closure. Colostomy was closed 6 weeks later and patient had excellent continence

assist with planning and subsequent management. The use of pelvic floor physical therapy with sphincter exercises and biofeedback can improve tone and squeeze mechanics, with improvement of continence in the setting of minor traumatic sphincter injuries [63, 64]. Those individuals with poorly or non-functioning sphincter complexes (or preexisting incontinence) are usually best served with a permanent colostomy.

References

1. Demetriades D, Murray JA, Chan L, Ordonez C, Bowley D, et al. Penetrating colon injuries requiring resection: diversion or primary anastomosis? An AAST prospective multicenter study. J Trauma. 2001;50(5):765–75.
2. Steele SR, Wolcott KE, Mullenix PS, Martin MJ, Sebesta JA, et al. Colon and rectal injuries during Operation Iraqi Freedom: are there any changing trends in management or outcome? Dis Colon Rectum. 2007;50(6):870–7.
3. Cho SD, Kiraly LN, Flaherty SF, Herzig DO, Lu KC, Schreiber MA. Management of colonic injuries in the combat theater. Dis Colon Rectum. 2010;53(5):728–34.
4. George SM Jr, Fabian TC, Voeller GR, Kudsk KA, Mangiante ED, Britt LG. Primary repair of colon wounds: a prospective trial in nonselected patients. Ann Surg. 1989;209(6):728–33; 733–34.
5. Chappuis CW, Frey DJ, Dietzen CD, Panetta TP, Buechter KJ, Cohn I Jr. Management of penetrating colon injuries: a prospective randomized trial. Ann Surg. 1991;213(5):492–7.
6. Demetriades D, Charalambides D, Pantanowitz D. Gunshot wounds of the colon: role of primary repair. Ann R Coll Surg Engl. 1992;74(6):381–4.
7. Ivatury RR, Gaudino J, Nallathambi MN, Simon RJ, Kazigo ZJ, Stahl WM. Definitive treatment of colon injuries: a prospective study. Am Surg. 1993;59(1):43–9.
8. Gonzalez RP, Merlotti GJ, Holevar MR. Colostomy in penetrating colon injury: is it necessary? J Trauma. 1996;41(2):271–5.
9. Demetriades D, Murray JA, Chan L, et al. Penetrating colon injuries requiring resection: diversion or primary anastomosis? An AAST prospective multicenter study. J Trauma. 2001;50(5):765–75.
10. Hatch Q, Causey M, Martin M, et al. Outcomes after colon trauma in the 21st century: an analysis of the U.S. National Trauma Data Bank. Surgery. 2013;154(2):397–403.
11. MacCormac W. Some points of interest in connection with the surgery of war. Br Med J. 1895;ii:278–84.
12. Bennett JD. Abdominal surgery in war – the early story. J R Soc Med. 1991;84(9):554–7.
13. Derby AC. Wounds of the abdomen. Part 1: in war. Can J Surg. 1988;31(4):213–8.
14. Ogilvie WH. Abdominal wounds in the Western Desert. Bull US Army Med Dep. 1946;6(4):435–45.
15. Edwards DP. The history of colonic surgery in war. J R Army Med Corps. 1999;145(2):107–8.
16. Office of the Surgeon General: Circular Letter No. 178; 1943.
17. Perry WB, Brooks JP, Muskat PC. The history of military colorectal trauma management. Semin Colon Rectal Surg. 2004;15(2):70–9.
18. Welch CE. War wounds of the abdomen. N Engl J Med. 1947;237(6):187–94.
19. Vertrees A, Wakefield M, Pickett C, Greer L, Wilson A, Gillern S, et al. Outcomes of primary repair and primary anastomosis in war-related colon injuries. J Trauma. 2009;66(5):1286–91; discussion. 91–3.
20. Sambasivan CN, Underwood SJ, Cho SD, Kiraly LN, Hamilton GJ, Kofoed JT, et al. Comparison of abdominal damage control surgery in combat versus civilian trauma. J Trauma. 2010;69 Suppl 1:S168–74.
21. Demetriades D, Velmahos G, Cornwell E III, et al. Selective nonoperative management of gunshot wounds to the anterior abdomen. Arch Surg. 1997;132(2):178–83.
22. Ross SE, Cobean RA, Hoyt DB, et al. Blunt colonic injury—a multicenter review. J Trauma. 1992;33(3):379–84.
23. Moore EE, Cogbill TH, Malangoni MA, et al. Organ injury scaling II, pancreas, duodenum, small bowel, colon, and rectum. J Trauma. 1990;30(11):1427–9.
24. Velmahos GC, Constantinou C, Tillou A, et al. Abdominal computed tomographic scan for patients with gunshot wounds to the abdomen selected for nonoperative management. J Trauma. 2005;50(5):1155–60.
25. Goldberg SR, Anand RJ, Como JJ, Dechert T, Dente C, Luchette FA, et al. Prophylactic antibiotic use in penetrating abdominal trauma: an Eastern Association for the Surgery of Trauma practice management guideline. J Trauma Acute Care Surg. 2012;73(5 Suppl 4):S321–5.
26. Stone HH, Fabian TC. Management of perforating colon trauma: randomization between primary closure and exteriorization. Ann Surg. 1979;190(4):430–6.
27. Sasaki LS, Allaben RD, Golwala R, et al. Primary repair of colon injuries: a prospective randomized study. J Trauma. 1995;39(5):895–901.
28. Gonzalez PR, Falimirski ME, Holevar MR. Further evaluation of colostomy in penetrating colon injury. Am Surg. 2000;66(4):342–6.
29. Kamwendo NY, Modiba MC, Matlala NS, Becker PJ. Randomized clinical trial to determine if delay from time of penetrating colonic injury precludes primary repair. Br J Surg. 2002;89(8):993–8.
30. Musa O, Ghildiyal JP, Pandey MC. 6 year prospective clinical trial of primary repair versus diversion colostomy in colonic injury cases. Indian J Surg. 2010;72(4):308–11.
31. Cornwell EE 3rd, Velmahos GC, Berne TV, Murray JA, Chahwan S, Asensio J, et al. The fate of colonic suture lines in high-risk trauma patients: a prospective analysis. J Am Coll Surg. 1998;187(1):58–63.
32. Edwards DP. Prospective audit of multiple penetrating injuries to the colon: further support for primary closure. J R Coll Surg Edinb. 1997;42(1):62.
33. Thomson SR, Baker A, Baker LW. Prospective audit of multiple penetrating injuries to the colon: further support for primary closure. J R Coll Surg Edinb. 1996;41(1):20–4.
34. Crookes B. An evidence-based approach to damage control laparotomy for trauma. In: Cohn SM, editor. Acute care surgery and trauma: evidence based practice. 1st ed. London: Informa; 2009.
35. Miller PR, Chang MC, Hoth JJ. Colonic resection in the setting of damage control laparotomy: is delayed anastomosis safe? Am Surg. 2007;73(6):606–9.
36. Georgoff P, Perales P, Laguna B, et al. Colonic injuries and the damage control abdomen: does management strategy matter? J Surg Res. 2013;181(2):293–9.
37. Kashuk JL, Cothren CC, Moore EE, et al. Primary repair of civilian colon injuries is safe in the damage control scenario. Surgery. 2009;146(6):663–70.
38. Weinberg JA, Griffin RL, Vandromme MJ, et al. Management of colon wounds in the setting of damage control laparotomy: a cautionary tale. J Trauma. 2009;67(4):929–35.
39. Weinberg JA, Griffin RL, Vandromme MJ, Melton SM, George RL, Reiff DA, Kerby JD, Rue LW 3rd. Management of colon wounds in the setting of damage control laparotomy: a cautionary tale. J Trauma. 2009;67(5):929–35.
40. Ott MM, Norris PR, Diaz JJ, Collier BR, Jenkins JM, Gunter OL, Morris JA Jr. Colon laparotomy: recommendations from 174 trauma colectomies. J Trauma. 2011;70(3):595–602.

41. Smith IM, Beech ZK, Lundy JB, Bowley DM. A prospective observational study of abdominal injury management in contemporary military operations: damage control laparotomy is associated with high survivability and low rates of fecal diversion. Ann Surg. 2015;261(4):765–73.
42. Tatebe LC, Jennings A, Tatebe K, Handy A, Prajapati P, Smith M, Do T, Ogola GO, Gandhi RR, Duane TM, Luk S, Petrey LB. Traumatic colon injury in damage control laparotomy – a multicenter trial: is it safe to do a delayed anastomosis. J Trauma Acute Care Surg. 2016;82(4):742–9.
43. Cayten CG, Fabian TC, Garcia VF, Ivatury RR, Morris JA. Penetrating colon injuries, management of. J Trauma. 1987;27(11):1237–9.
44. Cullinane DC, Jawa RS, Corno JJ, Moore AE, Morris DS, et al. Management of penetrating intraperitoneal colon injuries: a meta-analysis and practice management guidelines from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg. 2019;86(3):505–15.
45. Demetriades D, Murray JA, Chan LS, et al. Hand sewn versus stapled anastomosis in penetrating colon injuries requiring resection: a multicenter study. J Trauma. 2002;52(1):117–21.
46. Ivatury RR, Lieata J, Gundunz Y, et al. Management options in penetrating rectal injuries. Am Surg. 1991;57(1):50–5.
47. Herzig DO. Care of the patient with anorectal trauma. Clin Colon Rectal Surg. 2012;25:210–3.
48. Anderson SW, Soto JA. Anorectal trauma: the use of computer tomography scan in diagnosis. Semin Ultrasound CT MR. 2008;29(6):472–82.
49. Shanmuganathan K, Mirvis SE, Chiu WC, Killeen KL, Hogan GJ, Scalea TM. Penetrating torso trauma: triple-contrast helical CT in peritoneal violation and organ injury - a prospective study in 200 patients. Radiology. 2004;231:775–84.
50. Moore EE, Cogbill TH, Malangoni MA, Jurkovich GJ. Scaling system for organ specific injuries. Available at: http://www.aast.org/library/traumatools/injuryscoringscales.aspx.
51. Burch JM, Feliciano DV, Mattox KL. Colostomy and drainage for civilian rectal injuries: is that all? Ann Sug. 1989;209:600–11.
52. Rombeau JL, Wilk PJ, Turnbull J, Fazio VW. Total fecal diversion by the temporary skin-level loop transverse colostomy. Dis Colon Rectum. 1978;21:223–6.
53. Hoyt DB, Lekawa ME. Trauma of the colon and rectum. In: Beck DE, Roberts PL, Saclarides TJ, Senagore AJ, Stamos MJ, Wexner SD, editors. The ASCRS textbook of colon and rectal surgery. 2nd ed. New York: Springer; 2007.
54. Martin MJ, Beekley A. Front line surgery: a practical approach. 1st ed. New York: Springer; 2011.
55. van der Sluis FF, Schouten N, de Graaf PW, Karsten TM, Stassen LP. Temporary end ileostomy with subcutaneously buried efferent limb: results and potential advantages. Dig Surg. 2010;27(5):403–8.
56. Prasad ML, Pearl RK, Orsay CP, Abcarian H. End-loop ileocolostomy for massive trauma to the right side of the colon. Arch Surg. 1984;119(8):975–6.
57. Gonzalez RP, Falimirski ME, Holevar MR. The role of presacral drainage in the management of penetrating rectal injuries. J Trauma. 1998;45(4):656–61.
58. McGrath V, Fabian TC, Croce MA, Minard G, Pritchard FE. Rectal trauma: management based on anatomic distinctions. Am Surg. 1998;64:1136.
59. Weinberg JA, Fabian TC, Magnotti LJ, et al. Penetrating rectal trauma: management by anatomic distinction improves outcome. J Trauma. 2006;60:508–14.
60. Bosarge PL, Como JJ, Fox N, Falck-Ytter Y, Haut ER, Robinson BRH, McGwin GJ, Conzalez RP. Management of penetrating extraperitoneal rectal injuries: an Eastern Association for the Surgery of Trauma practice management guideline. J Trauma Acute Care Surg. 2016;80(3):546–51.
61. Engel AF, Kamm MA, Hawley PR. Civilian and war injuries of the perineum and anal sphincters. Br J Surg. 1994;81:1069–73.
62. Brown CVR, Teixeira PG, Furay E, Sharpe J, Musonza T, et al. Contemporary management of rectal injuries at level 1 trauma centers: the results of an American Association for the Surgery of Trauma multi-institutional study. J Trauma. 2017 [Podium paper]. https://doi.org/10.1097/TA.0000000000001739.
63. Critchlow JF, Houlihan MJ, Landolt CC, Weinstin ME. Primary sphincter repair in anorectal trauma. Dis Colon Rectum. 1985;28(12):945–7.
64. McCune WS. War wounds of the rectum and anal sphincter. Surgery. 1948;23:653–64.

Inflammatory Bowel Disease: Pathobiology

43

Benjamin D. Shogan and Pokala Ravi Kiran

Key Concepts

- The pathophysiology of IBD is incompletely understood but thought to be multifactorial and a complex interaction between genetic, environmental, microbial, and immune factors.
- While hundreds of susceptibility genetic loci have been identified to increase the risk of disease, all identified loci individually contribute only a small percentage of the expected heritability in IBD.
- The significantly increasing incidence of IBD in developing urban countries worldwide lends strong evidence that environmental factors may play the dominate role in its pathogenesis.
- The composition of the gut microbiota is significantly different in patients with IBD and has increased colonization of *Fusobacterium* and members of the Proteobacteria phylum and decreased colonization of Firmicutes and Bacteroidetes. Yet, no single organism has been identified to be solely responsible for the development of IBD.

Introduction

Inflammatory bowel disease (IBD) is a disorder characterized by chronic relapsing intestinal inflammation. The incidence of both Crohn's disease and ulcerative colitis has gradually increased since the Second World War, especially in northern Europe and North America, where the highest incidence rates have been reported. Other areas with traditionally low disease prevalence, such as Asia and Africa, have reported increasing numbers in more recent years.

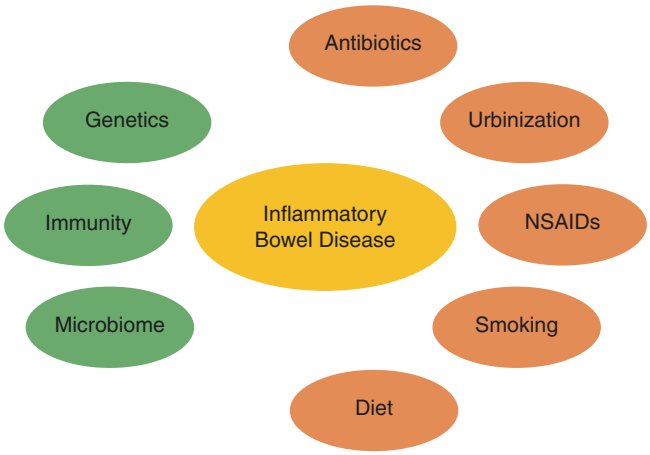

Fig. 43.1 The pathophysiology of IBD consists of host factors (green) and environmental factors (orange)

These shifts in the risk of developing IBD within a relatively short time period provide evidence for the importance of exposure to environmental factors in disease pathogenesis. The greater risk for CD in Ashkenazi Jews regardless of geographic location or time period suggests ethnic differences in the genetic predisposition to IBD.

Various theories have been espoused as to the underlying cause of IBD. A complex interaction between genetic, environmental, and microbial factors, which promote the associated immune responses in susceptible individuals, appears responsible for the pathogenesis (Fig. 43.1). Advances in genetics and immunology have allowed the identification and delineation of contributory mechanisms in IBD.

These factors variably influence the development of IBD as well as its manifestations. While Crohn's disease and ulcerative colitis behave differently, they have some similarities and differences in phenotypic manifestations. This is congruent with the underlying genetic and immunologic mechanisms involved, which also demonstrate similarities and differences in their characteristics. Environmental factors

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such as urbanization, diet, and smoking, as well as medications such as NSAIDs, may also have an impact. In this chapter, we will review the current evidence on the pathobiology of IBD including both host and environmental factors.

Host Factors

Genetics

Population-based studies suggest that genetic factors contribute to IBD. There is an eight- to tenfold greater risk of IBD among relatives of UC and CD [1]. 15% of patients with Crohn's have an affected family member with IBD, and twin studies for CD have shown 50% concordance in monozygotic twins compared to <10% in dizygotics. In contrast, the concordance rate in monozygotic twins is 10–15% in UC. Thus, non-genetic factors may have a more important role in UC than in CD. Similarly, family studies suggest that a child has a 26-fold increased risk for developing CD when another sibling already has the condition while the risk is increased 9 times in the case of UC [2].

Most cases of genetic susceptibility are polygenic, but there is a spectrum of rare genetic disorders that can contribute to early-onset IBD. Monogenic defects have been found to alter intestinal immune homeostasis through many mechanisms. While a variety of genetic factors have been identified in IBD, there remains an important role for microbial and environmental factors. Epigenetic factors can further mediate interactions between environment and genome and could affect the development and progression of IBD. Epigenomics is an emerging field, and future studies could provide new insight into the pathogenesis of IBD.

Conventional IBD is a group of polygenic disorders in which hundred(s) of susceptibility loci contribute to the overall risk of disease. While genetic components are important factors involved in disease pathogenesis, identified genetic factors account for only a small proportion of the disease variance: 13.1% for CD and 8.2% for UC. More than 50% of IBD susceptibility loci have also been associated with other inflammatory and autoimmune diseases.

Monogenic defects are rare but can lead to early-onset (younger than 5 years) and very early-onset (younger than 2 years) CD and cause severe disease manifestations. These defects lead to disruption of the epithelial barrier and the epithelial response, as well as reduced clearance of bacteria by neutrophil granulocytes and other phagocytes. Other single-gene defects induce hyperinflammation or autoinflammation, or disrupted T- and B-cell selection and activation, due to defects in IL-10 signaling or dysfunctional regulatory T-cell activity. Defects in IL-10 or one of the subunits of its receptors cause extensive inflammation of the colon and perianal region. Next-generation sequencing (NGS) through whole exome sequencing (WES) has allowed the identification of single variants in very early-onset IBD.

Progress in genetic testing and DNA sequencing has allowed many genome-wide association studies, which have identified new single-nucleotide polymorphisms (SNPs). Nucleotide-binding oligomerization domain-containing protein 2 (NOD2) was the first susceptibility gene for CD that was discovered in 2001. This gene codes for a protein that acts as an intracellular receptor for bacterial products in monocytes and transduces signals leading to NFkB activation. The activation of NOD2 with muramyl dipeptide induces autophagy in dendritic cells. Dendritic cells from CD patients with NOD2 gene defects are deficient in autophagy induction and also show reduced localization of bacteria in autophagolysosomes. Two other autophagy-related genes, *IRGM* and *ATG16L1*, may have an important role in immune responses in IBD. Genetic variants that have been found to confer an increased risk of CD indicate the importance of innate immunity, autophagy, and phagocytosis in its pathogenesis. Other genes, like *IL23R* and *PTPN2*, are also associated with autoimmune disease, suggesting another aspect of Crohn's disease pathogenesis.

Epigenetics refers to mitotically heritable changes in gene expression via changes in structure and function of chromatin without alterations in DNA sequence. DNA methylation, histone modification, RNA interference, and the positioning of nucleosomes are some epigenetic mechanisms and are important in the interaction between environment and genome. Hypermethylation of gene promoters is associated with IBD patients; differences in DNA methylation status between normal and inflamed tissues from CD and UC patients have been identified.

MicroRNAs (miRNAs) are endogenous small non-coding single-stranded RNA molecules acting as post-transcriptional regulators of gene expression. MiRNAs have an important role in the development, regulation, and differentiation of the innate and adaptive immune system and are strongly implicated in the pathogenesis of many common diseases, including IBD. A lot of miRNAs have been discovered, but little is known of their function. In the intestinal tract, miRNAs are involved in tissue homeostasis, intestinal cell differentiation, and the maintenance of intestinal barrier function. CD and UC patients have unique miRNA expression profiles in their target organs as well as peripheral blood. Thus, identification of distinct miRNA expression profiles may provide an early method to determine a patient's disease course and a target of future treatments.

Immunity

The mucosal immune system is essential for establishing and controlling intestinal inflammation and injury. The role of

immunity in the causation and development of IBD is still evolving. The normal intestinal milieu consists of a complex interplay of genetic, microbial, and environmental factors that lead to mucosal immune and nonimmune responses. At rest and even in non-diseased states, there exists controlled mucosal inflammation regulated by a delicate balance of cytokines Th1, Th17, Th2, Th3, Th9, and Treg cells. In IBD, there is an imbalance whereby the adaptive immune system responds to self-antigens, leading to chronic inflammation and damage. Defects in innate immune functions of the epithelial barrier, pathogen recognition, and autophagy as well as adaptive immune dysfunction, particularly in T-cell activation, differentiation, and function, have all been implicated.

The first layer of defense against pathogens in the intestinal mucosa is the epithelium that faces the luminal surface. Paneth cells, which produce antimicrobial peptides, are located in this layer. Next is the lamina propria, where macrophages and dendritic cells are located and are responsible for the innate immune response. Dendritic cells have cytoplasmic extensions interdigitated among the epithelial cells to sample the luminal contents and then present antigens to T cells in the lamina propria and underlying lymphoid follicles. T and B cells and Peyer's patches form the adaptive immune system.

In the normal physiological state, gut-associated lymphoid tissue (GALT) constituted by Peyer's patches, lymphoid follicles, and mesenteric lymph nodes provides local intestinal immunity. Since there are a disproportionate number of microorganisms in the normal gut, a delicate balance of the innate and adaptive immunity is critical to avoiding an immune response, and a loss of this balance may be responsible for IBD. Alterations in autophagy, which is a cellular process related to the degradation of intracellular pathogens, antigen processing, regulation of cell signaling, and T-cell homeostasis that results in reduced clearance of pathogens, may contribute to the onset of inflammatory disorders in susceptible subjects [3, 4]. There is some evidence that problems with tolerance to self-antigens in the intestinal mucosa may lead to IBD [5, 6].

Macrophages and dendritic cells identify the molecular patterns of microorganisms by using pattern recognition receptors (PRR), such as toll-like receptors (TLR) and nucleotide-binding oligomerization domains (NOD). NOD2 is an intracellular microbial sensor that acts as a potent activator and regulator of inflammation. Mutations in the caspase recruitment domain-containing protein 15 (CARD-15) gene encoding the NOD2 protein have been identified in CD. Deficiency in NOD2 impacts the immune response in the lamina propria leading to chronic inflammation.

An internal imbalance in the cytokines in the intestinal mucosa has also been described in IBD. Such an imbalance may impact the intensity and duration of the inflammatory response in susceptible individuals. Various cytokines such as interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and transforming growth factor-beta (TGF-β) are implicated. UC is often described as Th2-mediated disease and CD as a Th1 condition, but the underlying mechanisms may be interrelated and more complex. Recent data suggest that IL-17 and IL-22, cytokines that initiate and amplify the local inflammatory signs and promote the activation of counter-regulatory mechanisms targeting intestinal epithelium cells, are related to the induction of colitis.

IL-2, released by macrophages and dendritic cells in the intestinal mucosa, activates signal transducer and activator of transcription (STAT) 4 in memory T lymphocytes, stimulating the production of IFN-γ. IFN-γ triggers the production of inflammatory cytokines in cells of the innate immune system, contributing to the increase of the inflammation present in colitis. IL-9 that regulates intestinal epithelial cells has also been implicated. The role of the other cytokines in IBD is as follows: IL-1 activates T cells to produce IL-8 and IL-6; IL-6 helps differentiate Th17 and Treg cells; IL-12 promotes the differentiation of Th1 cells; IL-23 stimulates the production of IL-17 and TNF-α and IL-6, while TNF-α acts on Th2 surface receptors promoting the proliferation of macrophages and inhibits Treg cells.

Intestinal Microbiome

Over the last decade, the importance of the intestinal microbiome in health and disease has become very apparent. The introduction of 16S rRNA next-generation sequencing has allowed researchers the ability to investigate how perturbations of microbes may lead to disease. Not surprising, there has been an abundance of research investigating the role of intestinal bacteria on the development of IBD.

It has been well shown that the composition of the gut microbiota in IBD patients significantly differs from healthy controls. As a whole, the microbiota of IBD patients shows less diversity and richness [7]. Increased abundance of certain pathogens is also found in patients with IBD. For example, *Fusobacterium* and members of the Proteobacteria phylum (Enterobacteriaceae, *Escherichia coli*) are commonly found to be increased in IBD patients compared to controls [8–10]. Conversely, patients with IBD have been consistently found to have decreased members of the Firmicutes (e.g., *Faecalibacterium prausnitzii*, *Ruminococcus*, *Oscillibacter*) and Bacteroidetes phyla [7, 11].

In addition to microbial composition, metagenomics has been used to provide insight into the functional characteristics of the microbiome. Interestingly, the dysbiosis seen in IBD patients is not seen in unaffected twins and relatives, suggesting that these changes are related to the disease state or environment effects, rather than underlying genetics [12, 13].

Table 43.1 Microorganisms associated with the development of IBD

Bacteria	Viruses	Fungus
Enterobacteriaceae	Caudovirales	*Saccharomyces cerevisiae*
Mycobacterium avium	*Synechococcus* phage S	*Candida albicans*
Escherichia coli	*Retroviridae* family	
Faecalibacterium prausnitzii		
Ruminococcus spp.		
Oscillibacter spp.		
Bacteroidetes		

Although cultivation of single organisms has been associated with active IBD, there is limited evidence that implicates individual organisms as the sole driver of IBD (Table 43.1). For example, *Mycobacterium avium* can induce granulomatous enteritis in animals and has been investigated as an inducer of Crohn's disease [14]. However, a clear link between *Mycobacterium avium* inducing granulomas and IBD in human patients remains unproven [15]. Colombel found that adherent-invasive *E. coli* strains colonized ileal lesions in patients with Crohn's disease. These strains demonstrated a cytolytic effect in cell culture by production of alpha-hemolysin and were hypothesized to promote Crohn's disease by increasing intestinal permeability. Yet, the fact that these strains were found in 33% of healthy controls demonstrates that they alone are not sufficient to cause disease [16].

Global metabolic changes associated with bacterial compositional alterations likely play a role in the development of IBD. Metagenomics has shown an increased prevalence of certain virulence factors in IBD patients, such as endotoxins and hemolysins [17]. Morgan analyzed both the compositional and functional differences in 231 patients with IBD compared to healthy controls [18]. They reported that while only 2% of the bacterial composition was different (at the genus level), 12% of the metabolic pathways were different between IBD patients and controls. Patients with IBD had increased virulence and secretion pathways as well as major oxidative stress pathways. Other studies have demonstrated significant decreases in microbial metabolism such as short-chain fatty acids and amino acid production [19].

The role of viruses and fungi in the pathogenesis of IBD has been receiving increasing attention. Similar to bacteria, certain patterns have emerged in patients with IBD compared to healthy controls. A comprehensive analysis of the virome in IBD patients has been performed [20]. The authors demonstrated significant expansions of certain virions including Caudovirales bacteriophages. Others have found associations of *Synechococcus* phage S and the *Retroviridae* family of viruses in IBD patients [21]. Interestingly, some studies have shown these virome changes are independent of IBD-associated bacterial composition changes. In a similar fashion, Sokol characterized the fungal microbiota in 235 patients with IBD [22]. They found increased abundance of multiple fungal species including *S. cerevisiae* and *C. albicans*. Additionally, they reported that *Basidiomycota* abundance was associated with IBD flares.

While these microbiota changes have consistently been demonstrated in patients with IBD, whether they are driving the disease or are a consequence of inflammation remains uncertain. For example, inflammation decreases the oxygen tension of the intestinal mucosa, preventing the growth of aerotolerant taxa [23]. Alternatively, the changing oxygen level can promote anaerobic microorganisms and dysbiosis [24]. Further studies are needed to understand the interplay between dysbiosis and inflammation and determine which may be driving the pathogenesis of IBD.

Antibiotics

Antimicrobial agents have a strong influence on the composition and diversity of gut microbiome. Multiple studies have demonstrated that within the first few days following antibiotic administration, there are a profound and immediate decrease in diversity and significant shift of the bacterial community structure [25]. While the microbiome begins to reconstitute to its initial state after antibiotics are stopped, in some cases the microbiome remains altered [26].

Given this large influence of antibiotics on the microbiome, researchers have investigated if antibiotic exposure is a risk factor for the development of IBD. In a Canadian case-control study, 294 children diagnosed with IBD were compared to 2377 controls [27]. The authors found that patients who were diagnosed with otitis media (a proxy for antibiotic use) were 2.8-fold more likely to have IBD (95% CI 1.5–5.2; $p = 0.001$) compared to controls. In a similar study, antibiotic prescriptions were significantly associated with both the development of ulcerative colitis and Crohn's disease [28]. In a recent meta-analysis, 8 case-control and 3 cohort studies including 7208 patients with IBD were analyzed. Antibiotic exposure was significantly associated with Crohn's disease (OR 1.74, 95% CI 1.35–2.23), but not with ulcerative colitis (OR 1.08, 95% CI 0.91–1.27). While all antibiotics, except for penicillin, were associated with Crohn's disease, metronidazole and fluoroquinolones were most significantly associated with IBD overall. Taken together, the evidence strongly supports antibiotics to be a risk factor for the development of IBD, further implicating the microbiome as a major driver of IBD.

Environmental Factors

Urbanization

Since its discovery in the late 1800s, IBD has long been thought to be a disease of Caucasian people of European descent; IBD continues to be most prevalent in wealthy Western countries, with a prevalence of ~0.5% in North America and Europe [29, 30]. Because of new diagnoses and the low mortality rate in IBD patients, the prevalence of IBD in these countries is increasing [31]. While IBD was rare in developing nations during the twentieth century, the emergence and increasing incidence of IBD in developing countries in Asia, Africa, South America, and the Middle East is now well documented (Fig. 43.2) [32]. For example, in Brazil the incidence of ulcerative colitis increased to 4.5 cases per 100,000 people in 2005 from 1.0 per 100,000 between 1986 and 1990 [33]. Similarly, in the 1960s–1980s, IBD was barely recognized in Hong Kong, while now the incidence ranges from 1.3 to 2.1 per 100,000 patients [34].

Industrialization and urbanization in developing countries is associated with a multitude of factors including changes in lifestyle, diet, smoking habits, pollution, and healthcare delivery. In fact, Benchimol found that growing up in a rural environment was significantly protective of later development of IBD (IRR 0.58, 95% CI 0.43–0.73). Thus, the emergence and increasing incidence of IBD in these developing countries worldwide provides strong evidence that environmental factors play a large role in pathogenesis. While it is not possible to isolate all environmental changes associated with urbanization, herein we will review the influence of certain lifestyle changes on the development of IBD.

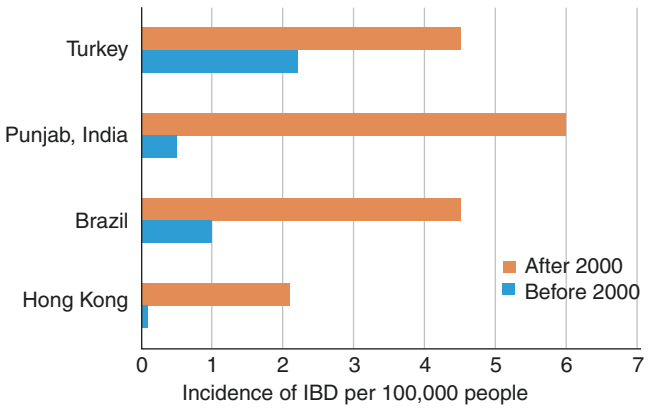

Fig. 43.2 The incidence of IBD is significantly increased over the last two decades in developing countries

Smoking

The divergent findings of smoking as a risk factor for Crohn's disease, yet potentially protective for ulcerative colitis, have been appreciated since the early 1980s. Both passive and active smoking is associated with a twofold increased risk of development of Crohn's disease (OR 1.76; 95% CI 1.4–2.2) [35]. Additionally, smoking portends a significantly increased risk of fistula formation, strictures, and need for surgery [36]. On the other hand, it is well accepted that smoking is protective against ulcerative colitis. In a meta-analysis of 13 articles investigating the association of smoking on IBD, the authors reported that current smokers have a significantly lower incidence of ulcerative colitis compared to controls (OR 0.58; 95% CI 0.45–0.75) [35].

How smoking promotes IBD is unclear. Smoking changes the microvasculature, which can contribute to inflammation via decreased perfusion and recruitment of immune cells. This can increase oxidative stress which subsequently affects gut barrier function, mucus production, and microbiome changes [37, 38]. How these molecular changes promote Crohn's disease but protect against ulcerative colitis is uncertain. Ananthakrishnan studied nicotine metabolism in 634 patients with Crohn's disease and 401 with ulcerative colitis. They found that certain genetic polymorphisms in nicotine-metabolizing enzymes, such as CYP2A6, and GSTP1, were associated with the development of Crohn's diseases and protection against ulcerative colitis [39]. Thus, a genetic predisposition may exist as to the effects of smoking on the pathophysiology of IBD.

NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) have long been associated with the development or exacerbation of IBD, although the literature shows conflicting results. Long recently retrospectively studied 791 patients from a prospectively collected database with IBD patients that were in remission [40]. They reported that Crohn's disease patients with NSAID use more than five times per month had a greater risk of active disease (RR 1.65; 95% CI 1.12–2.44), while no effect was seen in patients with ulcerative colitis (RR 1.25; 95% CI 0.81–1.92). Ananthakrishnan reported that NSAID use at least 15 times per month increased the risk of development of both Crohn's disease and ulcerative colitis [41].

Low-dose NSAID does not appear to promote IBD. In 426 Crohn's disease patients and 203 ulcerative colitis patients, low-dose NSAID (<200 mg/day and used less than daily) was not associated with an increase in disease activity. High-dose NSAID use was associated with a higher numeri-

cal disease activity score in Crohn's patients, but was not associated with an increase in disease flares in Crohn's or ulcerative colitis patients. Takeuchi studied the effect of NSAIDs in patients with quiescent IBD. Patients were given either acetaminophen, naproxen, diclofenac, or indomethacin for 4 weeks and then assessed for recurrence [42]. The authors reported a 17–28% recurrence rate in both Crohn's disease and ulcerative colitis patients within 9 days of administration of NSAIDs, but no recurrence was seen with acetaminophen.

Given these mixed results, a recent systematic review and meta-analysis of publications between 1983 and 2016 examined the association between acetaminophen and NSAIDs on the risk of disease exacerbation [43]. Pooled analysis of 18 publications found that NSAID use was not associated with exacerbation of Crohn's disease (OR, 1.42, 95% CI, 0.65–3.09) or ulcerative colitis (OR, 1.52, 95% CI, 0.87–2.63). Similar findings were observed with acetaminophen.

Multiple mechanisms have been suggested as to how NSAIDs can promote IBD. NSAIDs inhibit cyclooxygenase (such as COX-1 and COX-2) and prevent accumulation of prostaglandins. Cyclooxygenases and prostaglandins play a critical role in epithelial wound healing, mucosal defense, and immune modulation within the colon [44–46]. For instance, using a model of dextran sulfate sodium (DSS)-induced colitis, inhibition of COX-1 and COX-2 resulted in significantly decreased amounts of mucosal prostaglandins and exacerbation of DSS colitis [47]. Of the many pathways impacted by COX inhibition, increased mucosal permeability has most often been suggested as the main pathogenic factor. Animal models of IL-10-deficient mice (a common animal model for colitis) given 4 weeks of NSAID treatment had a 75% reduction of PGE_2 and developed colitis, with infiltration of the lamina propria by macrophages and CD4+ T-cells [48]. Collectively, while the literature is mixed, there is a biological basis to support the notion that NSAIDs influence the pathobiology of IBD.

Diet

A recent Cochrane review concluded that the effects of dietary interventions on Crohn's disease and ulcerative colitis are uncertain [49]. However, observational studies have shown associations between dietary patterns and the risk of being newly diagnosed with Crohn's disease and ulcerative colitis, as well as the exacerbation of symptoms. Greater consumption of meat and animal products has been associated with the onset of Crohn's disease and ulcerative colitis, whereas greater consumption of fruits and vegetables had a lower incidence. Some hypotheses used to explain the impact on diet on IBD suggest a direct alteration of the microbiome. Dietary antigens may also influence the immune response of the gut. Alternatively, diet may directly affect the mucosal barrier or indirectly affect immune function by influencing the composition of gut enzymes, bile acids, and hormones. Some diet-based therapies have been shown to impact IBD, particularly in CD. Studies are underway to further elucidate the role of diet on the pathogenesis of IBD.

Pouchitis Pathobiology

Pouchitis is a common complication in patients who undergo restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA). The incidence of pouchitis depends upon the indication for surgery; pouchitis occurs in approximately 50% of patients with ulcerative colitis but rarely if ever it occurs in patients with familial adenomatous polyposis [50–52]. While the pathogenesis of pouchitis remains unclear, the finding that the incidence is dependent upon the primary diagnosis strongly suggests an underlying genetic component. Carter found that patients who carried the +2018 single-nucleotide polymorphism in interleukin-1 were at a significantly higher risk for the development of pouchitis (relative risk 3.1; 95% CI 1.2–7.8) [53].

Similarly, Sehgal investigated the association of NOD2 mutations to the development of pouchitis [54]. They reported that mutations in NOD2 were significantly higher in patients with severe pouchitis compared to either asymptomatic IPAA patients or patients with IPAA complications such as abscess or fistula. Genetic changes have also been linked to immune alterations in patients with pouchitis. Increased expression of toll-like receptors 2 and 4 is seen in patients with pouchitis [55]. Additionally, aberrant expression of defensing-1 and increased expression of defensing-5 is expressed in IPAA patients when compared to normal ileum [56, 57].

The reservoir function of an IPAA promotes fecal stasis, leading to adaptation and metaplasia of the mucosa from small bowel to colon-like mucosa [58]. Similarly, the pouch bacteria move closer to a colonic-like microbiome after pouch creation [59]. Because fecal stasis promotes bacterial overgrowth, the influence of microbiome changes on pouchitis has been investigated. McLaughlin investigated the colonizing bacterial community of the pouch in patients with ulcerative colitis and familial adenomatous polyposis [60]. Interestingly, they found a significant decrease in Bacteroidetes and significant increases in Proteobacteria in patients with ulcerative colitis compared to polyposis patients. Additionally, bacterial diversity, which is a marker of bacterial health, was significantly increased in polyposis patients, compared to ulcerative colitis patients.

Functional characteristics of the host in relation to microbiome changes have also been studied in IPAA patients. Investigators have found that the most strongly microbe-associated transcriptomic pattern is enrichment with activation of the interleukin-12 pathway and complement cascade

genes. Collectively, the investigations to date suggest that pouchitis is a multifactorial disease resulting from immune and microbial changes in a genetically susceptible host.

References

1. Cho JH, Brant SR. Recent insights into the genetics of inflammatory bowel disease. Gastroenterology [Internet]. 2011;140(6):1704–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21530736.
2. Uhlig HH, Schwerd T, Koletzko S, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology [Internet]. 2014;147(5):990–1007.e3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25058236.
3. Deretic V, Saitoh T, Akira S. Autophagy in infection, inflammation and immunity. Nat Rev Immunol [Internet]. 2013;13(10):722–37. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24064518.
4. Pabst O, Mowat AM. Oral tolerance to food protein. Mucosal Immunol [Internet]. 2012;5(3):232–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22318493.
5. Faria AMC, Weiner HL. Oral tolerance. Immunol Rev [Internet]. 2005;206:232–59. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16048553.
6. Faria AMC, Weiner HL. Oral tolerance: therapeutic implications for autoimmune diseases. Clin Dev Immunol [Internet]. 2006;13(2–4):143–57. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17162357.
7. Manichanh C, Rigottier-Gois L, Bonnaud E, et al. Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. Gut [Internet]. 2006;55(2):205–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16188921.
8. Seksik P, Rigottier-Gois L, Gramet G, et al. Alterations of the dominant faecal bacterial groups in patients with Crohn's disease of the colon. Gut [Internet]. 2003;52(2):237–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12524406.
9. Mangin I, Bonnet R, Seksik P, et al. Molecular inventory of faecal microflora in patients with Crohn's disease. FEMS Microbiol Ecol [Internet]. 2004;50(1):25–36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19712374.
10. Tahara T, Shibata T, Kawamura T, et al. Fusobacterium detected in colonic biopsy and clinicopathological features of ulcerative colitis in Japan. Dig Dis Sci [Internet]. 2015;60(1):205–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25102986.
11. Sokol H, Pigneur B, Watterlot L, et al. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc Natl Acad Sci U S A [Internet]. 2008;105(43):16731–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18936492.
12. Joossens M, Huys G, Cnockaert M, et al. Dysbiosis of the faecal microbiota in patients with Crohn's disease and their unaffected relatives. Gut [Internet]. 2011;60(5):631–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21209126.
13. Willing BP, Dicksved J, Halfvarson J, et al. A pyrosequencing study in twins shows that gastrointestinal microbial profiles vary with inflammatory bowel disease phenotypes. Gastroenterology [Internet]. 2010;139(6):1844–1854.e1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20816835.
14. Timms VJ, Daskalopoulos G, Mitchell HM, Neilan BA. The association of Mycobacterium avium subsp. paratuberculosis with inflammatory bowel disease. PLoS One [Internet]. 2016;11(2):e0148731. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26849125.
15. Liverani E, Scaioli E, Cardamone C, Dal Monte P, Belluzzi A. Mycobacterium avium subspecies paratuberculosis in the etiology of Crohn's disease, cause or epiphenomenon? World J Gastroenterol [Internet]. 2014;20(36):13060–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25278700.
16. Darfeuille-Michaud A, Neut C, Barnich N, et al. Presence of adherent Escherichia coli strains in ileal mucosa of patients with Crohn's disease. Gastroenterology [Internet]. 1998;115(6):1405–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9834268.
17. Moustafa A, Li W, Anderson EL, et al. Genetic risk, dysbiosis, and treatment stratification using host genome and gut microbiome in inflammatory bowel disease. Clin Transl Gastroenterol [Internet]. 2018;9(1):e132. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29345635.
18. Morgan XC, Tickle TL, Sokol H, et al. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. Genome Biol [Internet]. 2012;13(9):R79. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23013615.
19. McIlroy J, Ianiro G, Mukhopadhya I, Hansen R, Hold GL. Review article: the gut microbiome in inflammatory bowel disease-avenues for microbial management. Aliment Pharmacol Ther [Internet]. 2018;47(1):26–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29034981.
20. Norman JM, Handley SA, Baldridge MT, et al. Disease-specific alterations in the enteric virome in inflammatory bowel disease. Cell [Internet]. 2015;160(3):447–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25619688.
21. Pérez-Brocal V, García-López R, Vázquez-Castellanos JF, et al. Study of the viral and microbial communities associated with Crohn's disease: a metagenomic approach. Clin Transl Gastroenterol [Internet]. 2013;4:e36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23760301.
22. Sokol H, Leducq V, Aschard H, et al. Fungal microbiota dysbiosis in IBD. Gut [Internet]. 2017;66(6):1039–48. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26843508.
23. Glover LE, Lee JS, Colgan SP. Oxygen metabolism and barrier regulation in the intestinal mucosa. J Clin Invest [Internet]. 2016;126(10):3680–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27500494.
24. Lewis JD, Chen EZ, Baldassano RN, et al. Inflammation, antibiotics, and diet as environmental stressors of the gut microbiome in pediatric Crohn's disease. Cell Host Microbe [Internet]. 2015;18(4):489–500. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26468751.
25. Ananthakrishnan AN, Bernstein CN, Iliopoulos D, et al. Environmental triggers in IBD: a review of progress and evidence. Nat Rev Gastroenterol Hepatol [Internet]. 2018;15(1):39–49. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29018271.
26. Dethlefsen L, Huse S, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. PLoS Biol [Internet]. 2008;6(11):e280. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19018661.
27. Shaw SY, Blanchard JF, Bernstein CN. Association between early childhood otitis media and pediatric inflammatory bowel disease: an exploratory population-based analysis. J Pediatr [Internet]. 2013;162(3):510–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23084703.
28. Shaw SY, Blanchard JF, Bernstein CN. Association between the use of antibiotics and new diagnoses of Crohn's disease and ulcerative colitis. Am J Gastroenterol [Internet]. 2011;106(12):2133–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21912437.
29. Büsch K, Ludvigsson JF, Ekström-Smedby K, Ekbom A, Askling J, Neovius M. Nationwide prevalence of inflammatory bowel disease in Sweden: a population-based register study. Aliment Pharmacol Ther [Internet]. 2014;39(1):57–68. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24127738.
30. Stone MA, Mayberry JF, Baker R. Prevalence and management of inflammatory bowel disease: a cross-sectional study from central England. Eur J Gastroenterol Hepatol [Internet].

2003;15(12):1275–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14624149.
31. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet (London, England) [Internet]. 2018;390(10114):2769–78. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29050646.
32. Kaplan GG. The global burden of IBD: from 2015 to 2025. Nat Rev Gastroenterol Hepatol [Internet]. 2015;12(12):720–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26323879
33. Victoria CR, Sassak LY, de Carvalho Nunes HR. Incidence and prevalence rates of inflammatory bowel diseases, in midwestern of São Paulo State, Brazil. Arq Gastroenterol [Internet]. 2009;46(1):20–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19466305.
34. Zheng JJ, Zhu XS, Huangfu Z, Gao ZX, Guo ZR, Wang Z. Crohn's disease in mainland China: a systematic analysis of 50 years of research. Chin J Dig Dis [Internet]. 2005;6(4):175–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16246226.
35. Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin Proc [Internet]. 2006;81(11):1462–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17120402.
36. Gajendran M, Loganathan P, Catinella AP, Hashash JG. A comprehensive review and update on Crohn's disease. Dis Mon [Internet]. 2018;64(2):20–57. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28826742.
37. Hatoum OA, Heidemann J, Binion DG. The intestinal microvasculature as a therapeutic target in inflammatory bowel disease. Ann N Y Acad Sci [Internet]. 2006;1072:78–97. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17057192.
38. Ananthakrishnan AN. Epidemiology and risk factors for IBD. Nat Rev Gastroenterol Hepatol [Internet]. 2015;12(4):205–17. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25732745.
39. Ananthakrishnan AN, Nguyen DD, Sauk J, Yajnik V, Xavier RJ. Genetic polymorphisms in metabolizing enzymes modifying the association between smoking and inflammatory bowel diseases. Inflamm Bowel Dis [Internet]. 2014;20(5):783–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24651583.
40. Long MD, Kappelman MD, Martin CF, Chen W, Anton K, Sandler RS. Role of nonsteroidal anti-inflammatory drugs in exacerbations of inflammatory bowel disease. J Clin Gastroenterol [Internet]. 2016;50(2):152–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26485106.
41. Ananthakrishnan AN, Higuchi LM, Huang ES, et al. Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis: a cohort study. Ann Intern Med [Internet]. 2012;156(5):350–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22393130.
42. Takeuchi K, Smale S, Premchand P, et al. Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol [Internet]. 2006;4(2):196–202. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16469680.
43. Moninuola OO, Milligan W, Lochhead P, Khalili H. Systematic review with meta-analysis: association between acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) and risk of Crohn's disease and ulcerative colitis exacerbation. Aliment Pharmacol Ther [Internet]. 2018;47(11):1428–39. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29620794.
44. Miyoshi H, VanDussen KL, Malvin NP, et al. Prostaglandin E2 promotes intestinal repair through an adaptive cellular response of the epithelium. EMBO J [Internet]. 2017;36(1):5–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27797821.
45. Newberry RD, Stenson WF, Lorenz RG. Cyclooxygenase-2-dependent arachidonic acid metabolites are essential modulators of the intestinal immune response to dietary antigen. Nat Med [Internet]. 1999;5(8):900–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10426313.
46. Wallace JL, McKnight W, Reuter BK, Vergnolle N. NSAID-induced gastric damage in rats: requirement for inhibition of both cyclooxygenase 1 and 2. Gastroenterology [Internet]. 2000;119(3):706–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10982765.
47. Tanaka K-I, Suemasu S, Ishihara T, Tasaka Y, Arai Y, Mizushima T. Inhibition of both COX-1 and COX-2 and resulting decrease in the level of prostaglandins E2 is responsible for non-steroidal anti-inflammatory drug (NSAID)-dependent exacerbation of colitis. Eur J Pharmacol [Internet]. 2009;603(1–3):120–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19101538.
48. Berg DJ, Zhang J, Weinstock JV, et al. Rapid development of colitis in NSAID-treated IL-10-deficient mice. Gastroenterology [Internet]. 2002;123(5):1527–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12404228.
49. Limketkai BN, Iheozor-Ejiofor Z, Gjuladin-Hellon T, et al. Dietary interventions for induction and maintenance of remission in inflammatory bowel disease. Cochrane Database Syst Rev [Internet]. 2019;2:CD012839. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30736095.
50. Lohmuller JL, Pemberton JH, Dozois RR, Ilstrup D, van Heerden J. Pouchitis and extraintestinal manifestations of inflammatory bowel disease after ileal pouch-anal anastomosis. Ann Surg [Internet]. 1990;211(5):622–7; discussion 627–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2339922.
51. Sandborn WJ. Pouchitis following ileal pouch-anal anastomosis: definition, pathogenesis, and treatment. Gastroenterology [Internet]. 1994;107(6):1856–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7958702.
52. Bullman S, Pedamallu CS, Sicinska E, et al. Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer. Science [Internet]. 2017;358(6369):1443–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29170280.
53. Carter MJ, Di Giovine FS, Cox A, et al. The interleukin 1 receptor antagonist gene allele 2 as a predictor of pouchitis following colectomy and IPAA in ulcerative colitis. Gastroenterology [Internet]. 2001;121(4):805–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11606494.
54. Sehgal R, Berg A, Hegarty JP, et al. NOD2/CARD15 mutations correlate with severe pouchitis after ileal pouch-anal anastomosis. Dis Colon Rectum [Internet]. 2010;53(11):1487–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20940596.
55. Scarpa M, Grillo A, Pozza A, et al. TLR2 and TLR4 up-regulation and colonization of the ileal mucosa by Clostridiaceae spp. in chronic/relapsing pouchitis. J Surg Res [Internet]. 2011;169(2):e145–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21601883.
56. Kiehne K, Brunke G, Wegner F, Banasiewicz T, Folsch UR, Herzig K-H. Defensin expression in chronic pouchitis in patients with ulcerative colitis or familial adenomatous polyposis coli. World J Gastroenterol [Internet]. 2006;12(7):1056–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16534846.
57. Masters SL, Simon A, Aksentijevich I, Kastner DL. Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease (*). Annu Rev Immunol [Internet]. 2009;27:621–68. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19302049.
58. de Silva HJ, Millard PR, Soper N, Kettlewell M, Mortensen N, Jewell DP. Effects of the faecal stream and stasis on the ileal pouch mucosa. Gut [Internet]. 1991;32(10):1166–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1955172.
59. Kohyama A, Ogawa H, Funayama Y, et al. Bacterial population moves toward a colon-like community in the pouch after total proctocolectomy. Surgery [Internet]. 2009;145(4):435–47. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19303993.
60. McLaughlin SD, Walker AW, Churcher C, et al. The bacteriology of pouchitis: a molecular phylogenetic analysis using 16S rRNA gene cloning and sequencing. Ann Surg [Internet]. 2010;252(1):90–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20562611.

IBD Diagnosis and Evaluation

44

Mantaj S. Brar and Helen MacRae

Key Concepts

- Crohn's disease may present in a wide variety of ways depending on site of disease and phenotype.
- Multiple scoring and grading systems are in use to assess disease-related activity.
- Extraintestinal manifestations are common and may be the presenting sign of diagnosis in ~ 1/4 of patients with IBD.
- Pathologists are commonly unable to distinguish between UC and CD on endoscopic biopsies.

Inflammatory Bowel Disease Epidemiology

Inflammatory bowel disease (IBD) was arguably first described by Matthew Baillie in 1793 [1]. It is a chronic idiopathic condition with genetic predilection and environmental triggers [2–4]. The highest prevalence of IBD is in North America and Europe (~0.3–0.7%) [5, 6]. While the incidence in these populations has stabilized, that of newly industrialized countries has been increasing over the last 30 years [5, 6]. Immigration from low-prevalence areas to Europe and North America has been associated with increased incidence of IBD, both in immigrants and in their children, highlighting the importance of environmental triggers in the pathogenesis of IBD [7, 8].

Clinical Presentation of IBD

Given the varied disease distribution and severity, IBD can present in a myriad of ways and must be in the differential diagnosis of a variety of clinical scenarios. Patients can present with a change in bowel frequency (either increased or decreased); crampy abdominal pain, with or without blood in the stool; tenesmus; urgency; incontinence; food intolerance(s); anorexia; and/or weight loss. Symptoms can be subtle and may be related primarily to extraintestinal manifestations of their disease. Some patients present in a very delayed fashion and have internalized their chronic bowel symptoms, while others present with acute severe colitis as the first manifestation of their disease. When evaluating a patient with gastrointestinal symptoms, a careful history must be taken to evaluate the chronicity of symptoms, family history of IBD, as well as risk factors for infectious colitis or enteritis, such as recent travel, sick contacts, and recent antibiotic use. In addition, a thorough past medical history and medication history are important, especially with respect to NSAID exposure, previous radiation therapy, or immunosuppression. Lastly, a thorough review of systems may elucidate extraintestinal manifestations of IBD. Taken together, these components of the history will assist in narrowing the differential diagnosis and aid in selection of the appropriate diagnostic tests.

IBD Phenotypes

Due to the lack of known etiologic causes and "gold standard" diagnostic tests, IBD phenotypes are based on the distribution of inflammation, macroscopic appearance of the bowel, and histologic findings. Although two classic phenotypes of Crohn's disease (CD) and ulcerative colitis (UC) are often presented, this dichotomization of the vast spectrum of disease may prove with time and greater understanding of the underlying etiology of IBD, to represent an oversimplification of IBD subtypes. However, appropriate patient selection for surgical intervention is predicated on establishing the IBD phenotype of the patient.

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Crohn's Disease

First described in 1932, Crohn's disease was initially described as a chronic inflammatory condition of the terminal ileum leading to the development of strictures and fistulas [9]. Although the terminal ileum is the most common site of involvement, Crohn's disease can involve any part of the GI tract from the mouth to the anus and may have areas of involved bowel interspersed with spared areas (skip lesions). In addition, inflammation in Crohn's disease may involve all layers of the bowel wall with possible progression to fistula development, stricture formation, or perforation. Macroscopically, in addition to bowel wall thickening, Crohn's disease can be accompanied by *creeping fat*, or mesenteric adipose tissue extending beyond the mesenteric border around the inflamed intestine. Although traditionally thought to be a consequence of the inflammation of the bowel wall, there are emerging hypotheses that the mesentery is an active mediator of local inflammatory changes and may contribute to stricture formation and postoperative recurrence [10, 11].

Ulcerative Colitis

In contrast to Crohn's disease, the hallmark of ulcerative colitis is mucosal inflammation that involves the distal rectum and extends proximally in a continuous manner to involve the colon while sparing the small intestine, upper GI tract, and anus (see Table 44.1). However, there are specific scenarios where patients with UC may not have this distribution of disease. For example, patients with inflammation extending to the cecum may also have inflammation for a short distance of the terminal ileum ("backwash ileitis"); a patch of non-contiguous cecal inflammation (i.e., cecal patch) is occasionally observed in UC patients with more distal disease. Patients who receive topical enema therapy or have a partial response to medical therapy may be observed to have relative rectal sparing and/or discontinuous inflammation [12–14]. However, it remains controversial whether complete rectal sparing (without treatment) represents a subtype of UC rather than CD, in the absence of other features of CD [14, 15]. Patients who present with severe acute ulcerative colitis or fulminant colitis may have inflammation that extends beyond the mucosa or through the colon wall which may lead to perforation. These patients also have "skip" lesions or relative sparing of portions of the colon as the disease develops. The presence of these findings should prompt further evaluation, and a review by an experienced pathologist of available histology to ensure diagnosis of UC rather than CD is favored, as the surgical options following colectomy rely on appropriate phenotypic diagnosis.

Table 44.1 Features distinguishing Crohn's disease from ulcerative colitis

	Crohn's disease	Ulcerative colitis
Distribution Ileal involvement Perianal disease	Any part of the GI tract Often Common	Distal rectum and extending proximally to involve the colon Limited to backwash ileitis Rare – in the setting of cryptoglandular disease
Bowel wall involvement	Full thickness	Mucosal inflammation; unless fulminant colitis
Creeping fat	Present	Not present
Skip lesions	Often	Rare – but may be the consequence of treatment response
Fistulas	Possible	Rare
Deep ulceration/ fissures	Common	Only in fulminant colitis
Strictures	Common	Rare

IBD-Unclassified (IBD-U) and Indeterminate Colitis

In approximately 10% of adult-onset IBD and up to 30% of pediatric-onset IBD, a clear diagnosis between UC and CD cannot be established despite clinical, endoscopic, imaging, and histological evaluation [16–19]. Prior to colectomy, these patients should be labelled as IBD-unclassified (IBD-U). Following colectomy and pathological review of the specimen, the term indeterminate colitis (IC) is employed if no classic phenotypic diagnosis can be made [18, 20]. Although this label represents a heterogenous group of patients, they generally have a milder disease course and require less medical therapy than those diagnosed with UC [16]. Approximately a quarter of patients labelled with IBD-U will ultimately be reclassified in the first 5 years following diagnosis, with 2/3 of them being diagnosed with UC [16].

PSC-IBD

Primary sclerosing cholangitis (PSC) is a chronic liver disease characterized by bile duct inflammation and often progresses to stricture formation within the bile ducts. While ~3/4 of PSC patients will also be diagnosed with IBD (predominately UC), approximately 2–4% of IBD patients will develop PSC [21, 22]. Despite the strong association with IBD, the exact mechanisms of interplay between IBD and PSC remain poorly understood, with little genetic correlation between the two entities and conflicting evidence on the role of intestinal microbiota [21–24]. In addition to conventional UC (or less often CD) associated with PSC, there appears to be a distinct phenotype among IBD patients with PSC (PSC-

IBD). PSC-IBD has been characterized as pancolitis with rectal sparing, right- greater than left-sided inflammation, higher rates of backwash ileitis, milder symptoms despite endoscopic activity, and a higher medical treatment response rate [22, 23, 25]. Importantly, patients with PSC and colonic IBD also have an increased risk of developing IBD-associated mucosal dysplasia and colorectal cancer [22]. Although it has been previously observed that PSC progression is independent of IBD activity, recent reports suggest that timing of colectomy is associated with the risk of liver transplant for PSC, and ileoanal pouch reconstruction may be associated with poor graft survival after liver transplantation for PSC – suggesting a possible link between gut and liver inflammation [22, 26–29].

Extraintestinal Manifestations

Involvement of other organ systems occurs in 1/3 to 1/2 of all IBD patients during their disease course, and importantly, 1/4 of patients with extraintestinal manifestations (EIMs) present with extraintestinal symptoms prior to their IBD diagnosis [30, 31]. The pathogenesis of EIMs is poorly understood and may be related to genetic risk (associations with HLA subtypes have been described) and dysregulated adaptive immunity [30]. The most common EIM is joint involvement, which occurs in up to 40% of IBD patients, while cutaneous, biliary, and ocular are also common sites of EIMs [30–32]. While some EIMs follow the course of intestinal inflammatory burden, others do not, and there is some uncertainty about the relationship in others (see Table 44.2) [30–32]. During the assessment of a patient with suspected IBD, a review of the common EIM symptoms/diagnosis is necessary and may aid in the diagnosis. In addition, decisions regarding medical and surgical therapy may rely on an accurate EIM diagnosis, especially PSC in light of the increased risk of malignancy.

Table 44.2 Common extraintestinal manifestations of IBD, stratified by organ system and relationship to intestinal inflammation [30–32]

Organ system	Associated with intestinal activity	Unclear association with intestinal activity	No association with intestinal activity
Mucocutaneous	Oral aphthous ulcers (10%) Erythema nodosum (10–15%)	Pyoderma gangrenosum (1–5%)	
Joints		Peripheral arthropathy (5–20%)	Ankylosing spondylitis (5–20%)
Ophthalmologic	Episcleritis (2–3%)	Uveitis (2–6%)	
Biliary		PSC (5–8%)	

In addition to EIMs, there are several common manifestations of IBD activity and treatment that may warrant evaluation and treatment, such as anemia, osteopenia, cholelithiasis, nephrolithiasis, tubulointerstitial nephritis, and venous thromboembolism [31].

Diagnostic Evaluation of Suspected IBD

After thorough history, assessment of vital signs, and physical examination of the abdomen, skin examination, inspection of the orbits, and perineal examination with digital rectal exam, a number of preliminary investigations are relevant to the workup of suspected IBD.

Laboratory Investigations and Stool Tests

Laboratory investigations include a complete blood count, electrolyte, creatinine, liver enzyme, bilirubin, and iron studies. In addition, inflammatory markers such as C-reactive protein (CRP) should be drawn given their correlation with disease severity (in CD more than in UC); however, it must be noted that elevations in CRP are not specific enough to rule out infectious or other causes of colitis and CRP may be normal in up to 30% of patients with active CD [33–36]. Erythrocyte sedimentation rate, despite extensive use, has limited clinical utility in establishing a diagnosis of IBD [37]. In the first presentation of diarrhea, stool cultures and examination for ova and parasites are necessary, as well as *C. difficile* toxin assay if there has been any recent hospitalization or antibiotic use. If there is a history of anal receptive intercourse, consider anal swabs for STIs and nucleic acid amplification testing for *Chlamydia* [38]. The use of serological markers pANCA and ASCA individually have limited diagnostic utility for IBD given their low sensitivity; however, the combination of +pANCA and -ASCA serology has been demonstrated to have a sensitivity and specificity of 70% and 93%, respectively, for differentiating UC from CD once the diagnosis of IBD has been established [39, 40].

The measurement of fecal calprotectin is often employed to evaluate the burden of inflammation in IBD patients and may aid in the initial evaluation of patients with suspected IBD. Fecal calprotectin is a neutrophil cytosolic protein which is released during cellular degranulation in response to intestinal inflammation, and can be elevated in IBD, infectious colitis, cancer, and diverticulitis, and in response to NSAID or proton pump inhibitors [41]. There are variable cutoffs for elevated fecal calprotectin reported in the literature, and normal values vary by age (higher in children and the elderly), limiting the generalizability of reported diagnostic utility [33, 42]. Several meta-analyses have demonstrated a pooled sensitivity of 93–95% and specificity of

90–96%; the high negative predictive value suggests that patients may be able to avoid invasive testing in the setting of a fecal calprotectin level <50 mcg/g [33, 42].

Diagnostic Imaging

Diagnostic imaging studies are commonly employed in the diagnosis and staging of IBD. Abdominal X-rays have limited clinical utility in the evaluation of IBD except perhaps in acute severe colitis where the findings of a toxic megacolon or perforation would mandate urgent colectomy. In the absence of severe colitis, the utility of imaging studies for the evaluation of UC (other than to rule out small bowel CD) is limited. In contrast, given the varied distribution of disease and possible involvement of endoscopically difficult-to-reach jejunum and proximal ileum, as well as the higher risks of complicated disease in CD, imaging is a key component of evaluation of these patients. The goals of imaging are to accurately characterize the distribution of inflammation, determine the relative contributions of inflammation and fibrosis within strictures, and exclude penetrating complications such as abscess and fistula.

Computed tomography

In the acute care setting, conventional intravenous and oral contrast-enhanced computed tomography (CT) is often employed given its broad availability. CT can be useful in detecting moderate to severe small bowel or colonic inflammation, intraabdominal or perianal abscess, and bowel obstruction with characterization of transition points and evaluation of enteric fistulas [43, 44]. With the added administration of large-volume, low-density, or neutral contrast, in addition to intravenous contrast, CT enterography (CTE) allows for increased detection of mucosal inflammation and increased wall thickness, better characterization of strictures, and visualization of extraintestinal findings, such as abscesses, with high resolution (see Figs. 44.1 and 44.2)

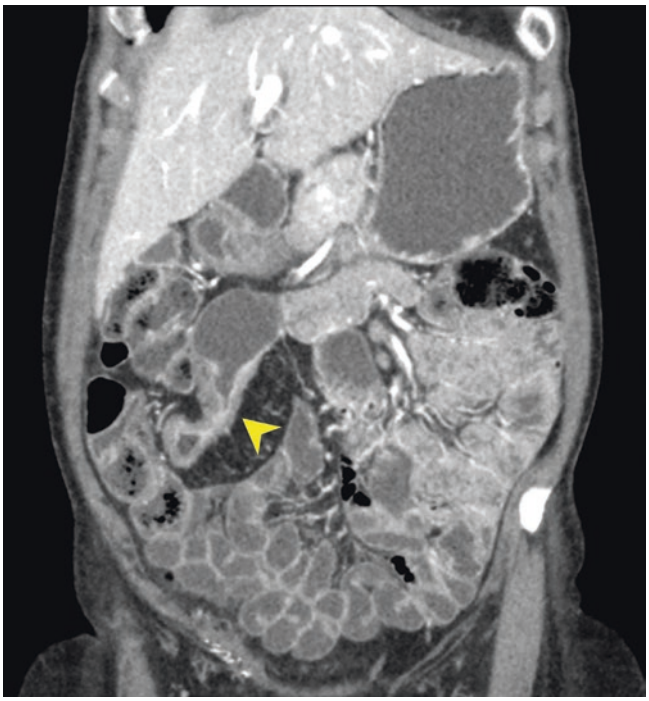

Fig. 44.2 CT enterography coronal images demonstrating an ileal stricture with pre-stenotic dilation in a patient with Crohn's disease

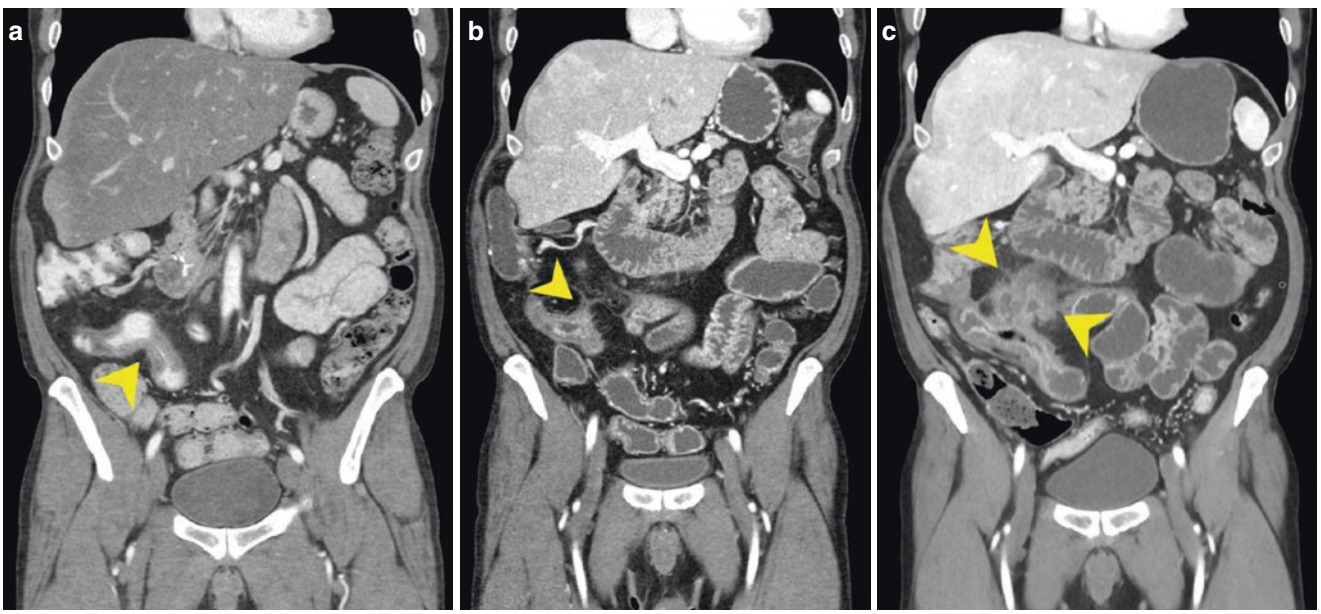

Fig. 44.1 Serial CT enterography coronal images for a patient with Crohn's disease with progression from (**a**) structuring disease to (**b**) early penetrating disease and to (**c**) complicated disease with localized perforation with mesenteric abscess

[43, 45, 46]. Specifically, the findings of luminal stenosis, increased wall thickness, and pre-stenotic dilation have been highly correlated with the severity of fibrosis within surgical specimens [43–45]. Given the concerns regarding cumulative radiation exposure with CT among CD patients, new protocols delivering a lower dose of radiation have been developed using iterative reconstruction algorithms resulting in dose reductions between 34 and 74% with inconsequential loss in image fidelity and diagnostic utility [45, 47].

Ultrasound

Given the high cumulative exposure to ionizing radiation among IBD patients, particularly those with CD, there has been increasing utilization of ultrasound (US) and magnetic resonance (MR) imaging [48]. Transabdominal small bowel US is a low-cost, radiation-free technique used primarily to assess small bowel involvement and characterize strictures [43, 49]. In a multicenter cohort study, among those newly diagnosed with CD, transabdominal US had a 66% sensitivity and 88% specificity for assessing extent of small bowel disease and 92% sensitivity and 91% specificity for the presence of small bowel disease [49]. In a smaller study, transabdominal US was demonstrated to have a 100% sensitivity and a 63% specificity for intermediate to severe fibrosis in surgical specimens [50]. Newer US techniques such as intravenous contrast-enhanced US and US elastography have demonstrated accuracy in small series, but further evidence is required to demonstrate a benefit over conventional US [43]. Transperineal and transanal US for the assessment of perianal fistulas and abscesses have demonstrated high sensitivity for detecting fistulas and abscesses in a meta-analysis of small series (>90%) and, thus, may have a role in following patients with known perianal disease given the lower cost compared to MR [51, 52].

Magnetic Resonance Imaging

Magnetic resonance enterography (MRE) has quickly become the preferred cross-sectional imaging modality of the small intestine in many centers; despite the issues of cost and availability of modern MR technology, utilization has increased with time [48]. In a multicenter cohort study, it was demonstrated that MRE had a low sensitivity for detection of colonic disease or extent of disease (64% and 22%, respectively) but high specificity (93% and 96%, respectively) – similar to that of US [49]. However, the sensitivity and specificity of MRE were significantly higher than US for both small bowel disease detection (97% and 96%) and extent of small bowel disease (80% and 95%) [49]. Novel MR techniques, such as diffusion-weighted imaging, magnetization transfer, and delayed enhancement MRE, may further enhance the accuracy of MR at determining the amount of fibrosis within a small bowel stricture [43, 44, 53, 54].

In several small series correlating these novel MRI techniques with surgical specimens, sensitivity for the detection of fibrostenotic disease was 86–96% and the specificity 89–100% (see Figs. 44.3 and 44.4) [3, 43, 44, 54]. However, these newer MR techniques require standardization of protocols, definitions of cutoff values for fibrosis, larger series for validation, and possibly comparative studies to determine the technique with the optimal diagnostic accuracy [43, 44]. MR

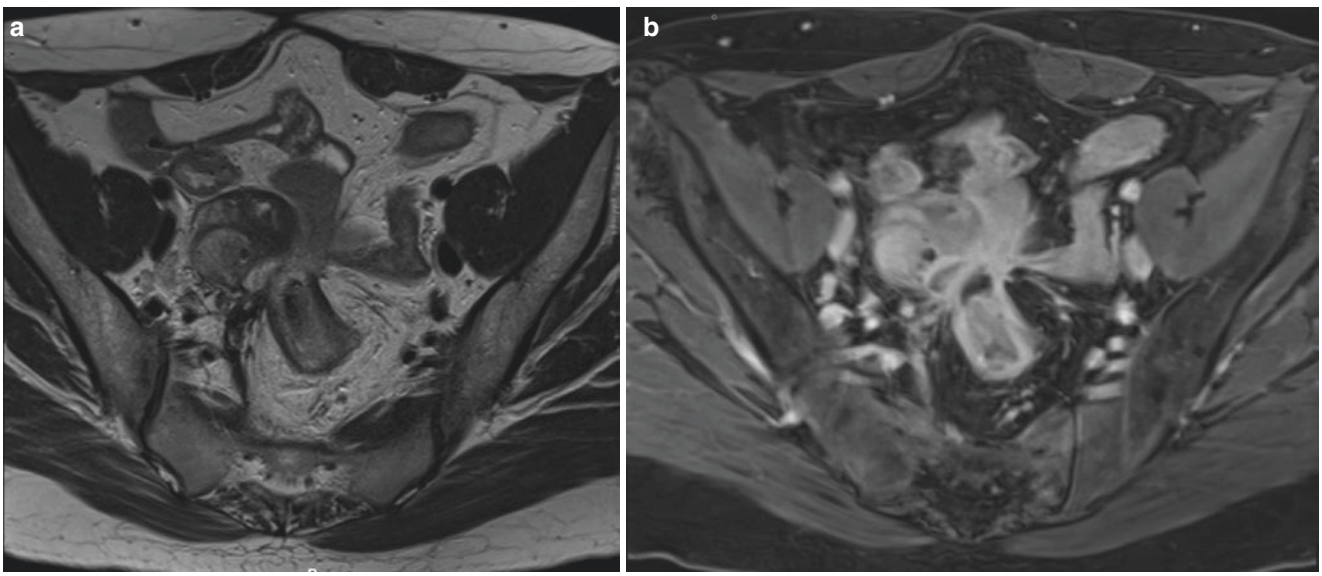

Fig. 44.3 MR enterography demonstrating penetrating ileal disease with a complex stellate fistula involving the sigmoid colon on (**a**) T2-weighted and (**b**) post-gadolinium axial images

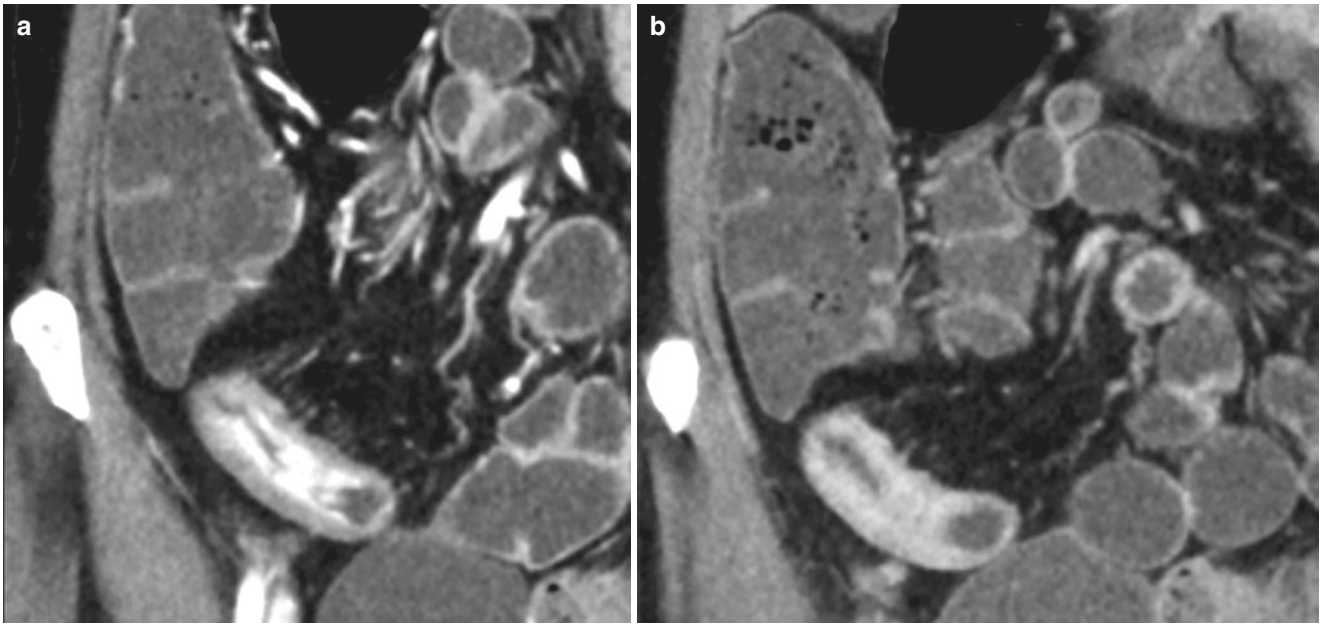

Fig. 44.4 Delayed enhancement MR enterography coronal images demonstrating (**a**) mucosal enhancement on initial imaging and (**b**) increased wall enhancement on delayed images which correlates to the amount of fibrosis

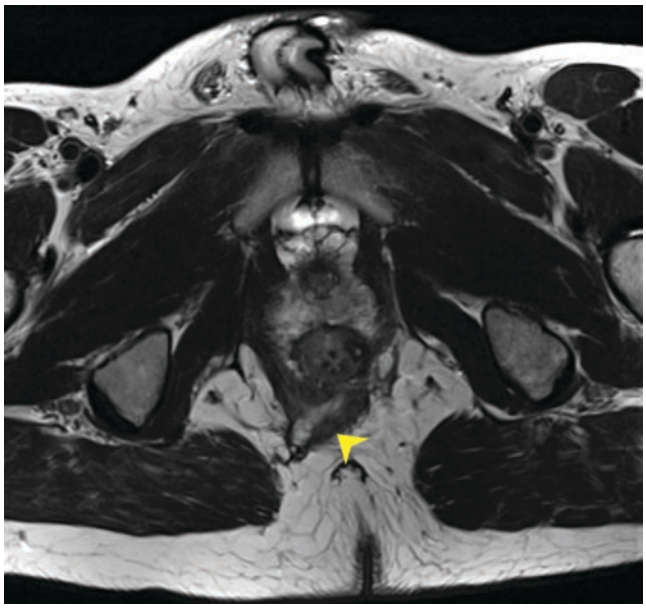

Fig. 44.5 MR pelvis axial T2-weighted images demonstrating a transsphincteric fistula tract

pelvis is the gold standard imaging investigation for those being evaluated for perianal Crohn's disease. It has demonstrated high sensitivity and specificity (80–100%) for the detection of fistula tracts and abscesses and modest specificity with respect to detection of the internal opening of a fistula tract (69%) (see Fig. 44.5) [55, 56].

Endoscopy

Colonoscopy with terminal ileal intubation is the gold standard diagnostic test in patients presenting with symptoms suggestive of IBD involving the colon and/or terminal ileum. A minimum of two representative biopsies should be taken from the terminal ileum; ascending, transverse, descending, and sigmoid colon; and rectum, retrieved in separate vials and reviewed by a GI pathologist, if available [57, 58]. Several endoscopic scores have been developed and are reviewed later in this chapter. These scores should be employed (using that most common in local practice) to improve communication across care providers. Standard terminology should also be employed to describe the endoscopic findings (see Table 44.3) [57]. In the setting of severe acute colitis, due to the extent of inflammation present and the risk of perforation, flexible sigmoidoscopy with biopsies is sufficient to establish a diagnosis and exclude other causes of colitis [57]. Upper GI endoscopy is not required for the assessment of adult patients with suspected IBD, unless symptoms specific to the upper GI tract are present [57]. In the setting of possible isolated small bowel Crohn's disease with spared terminal ileum on colonoscopy, patients may require capsule endoscopy or double-balloon or push enteroscopy, to establish a diagnosis if cross-sectional imaging studies are inconclusive or in the setting of occult small bowel bleeding [57, 59].

Table 44.3 Description and definitions of endoscopic lesions in IBD [57]

Finding	Description
Loss of vascular pattern	Loss of normal mucosal appearance without well-demarcated, arborizing capillaries
Erythema	Reddened mucosa
Granularity	Mucosal pattern produced by a reticular network of radiolucent foci of <1 mm of diameter with a sharp light reflex
Friability	Bleeding or intramucosal hemorrhage before or after the passage of the endoscope
Erosion	A definite discontinuation of mucosa <3 mm
Aphthous ulcer	White depressed center surrounded by a halo of erythema
Ulcer	Any lesion of the mucosa of unequivocal depth, with or without reddish halo; may be circular, linear, stellate, or serpiginous
Stenosis	Narrowing of the lumen
Inflammatory polyps (aka pseudopolyps)	Raised polypoid lesions, usually small, glistening; usually in areas of healed inflammation
Cobblestoning	Mucosal pattern with raised nodules, resembling the paving of a "Roman" road

Histology

Histopathologic assessment of endoscopic biopsies are a critical component in the workup of a patient with suspected IBD, as it can help exclude other diagnoses and assist with assigning a phenotypic diagnosis. The microscopic appearance of UC on endoscopic biopsies is characterized by crypt architectural distortion, with a diffuse transmucosal inflammatory infiltrate with cryptitis and crypt abscess, while in CD, the findings often show focal and often discontinuous chronic inflammation and focal crypt distortion, and there may be granulomas present (see Table 44.4 for all histological features) [58]. Given that there is no pathognomonic histological feature of either UC or CD, pathologists may not be able to accurately discriminate between the two classic phenotypes based on histology. Therefore, histology remains only a component of the diagnostic and phenotypic assessment, with only modest accuracy, even among expert GI pathologists (64–74%) [58]. However, histologic examination of specimens from colonoscopy is valuable in excluding other causes of colitis, such as Cytomegalovirus (CMV), microscopic and collagenous colitis, and, less so, infectious colitis [58].

Genetic Studies

Over 240 loci have been identified via genome-wide studies that are associated with IBD. Despite the strong evidence of a genetic contribution to the development of IBD based on twin studies, the clinical utility of genetic testing is limited for the diagnosis of IBD given the heterogenous disease presentation and phenotypes [60]. Current guidelines only recommend genetic testing in the setting of suspected monogenic disorders (such as IL-10 receptor mutations), in those with very early-onset (<5 years old), young patients with aggressive/refractory IBD, or to assess for mutations related to thiopurine metabolism (in TPMT and NUDT15 genes) when initiating thiopurine treatment [61–63].

Table 44.4 Histological findings in IBD [57]

	Ulcerative colitis	Crohn's disease
Crypt architectural irregularity	Diffuse (continuous)	Focal (discontinuous)[a]
Chronic inflammation	Diffuse (continuous), decreases proximally	Focal (discontinuous)[a], variable
Patchiness	Uncommon	Common
Localization	Superficial, transmucosal, occ. submucosal	Transmural
Serositis	Absent (except in fulminant colitis)	Present
Lymphoid aggregates	Frequent in mucosa and submucosa	Common, transmural
Granulomas	Absent (except in ruptured cysts)	Present
Acute inflammation	Diffuse (continuous)	Focal (discontinuous)[a]
Crypt epithelial polymorphs	Diffuse (continuous)	Focal (discontinuous)[a]
Crypt abscesses	Common	Uncommon
Mucin depletion	Present, pronounced	Uncommon, mild
Neuronal hyperplasia	Rare	Common
Muscular hypertrophy	Absent	Present
Paneth cell metaplasia	Present	Uncommon
Pyloric gland metaplasia	Rare	Present

[a]Discontinuous histological findings are often identified in Crohn's disease; however, continuous findings may also be observed

Classification and Grading of IBD

Given the diversity of clinical presentation and severity of IBD, classification and stratification of patients are exceedingly important for clinical decision-making, communication between health professionals, and monitoring of response and for research purposes. The Montreal classification and the Paris classification (for pediatric patients) remain the most well-accepted classification systems and have been demonstrated to have high inter-observer agreement [20, 64–66]. As IBD is a chronic disease, it is important to recognize that patient's disease course and behavior may change

over time and their classification may need to be modified. CD patients are classified by the age of diagnosis, disease sites, behavior, and presence of growth delay for children (see Table 44.5) [65, 66]. In UC, patients are classified by the extent of the inflammation and severity of inflammation (determined by the ACG guidelines and the Pediatric Ulcerative Colitis Activity Index; see Table 44.6) [65–68].

Endoscopic Scores

In addition to clinical classification systems, several IBD phenotype-specific endoscopic scores have been developed to assist in consistent grading of disease severity and to assess endoscopic response. In UC, the endoscopy subscore of the Mayo score is the most frequently employed in clinical practice (see Table 44.7 and Fig. 44.6); however, this score is a very simple four-point scale that only measures severity of colitis in the most inflamed segment of the colon/rectum, and inter-rater variability has been shown to be moderate [69, 70]. Over 15 other scores have been developed to summarize both the endoscopic severity of the inflammation and its extent, including the Modified Mayo Endoscopic Score (MMES), which employs the sum of Mayo score in all five segments of the colon, multiplied by the number of segments visualized, divided by the number of segments inflamed (see Table 44.7) [70, 71]. Despite being well correlated to disease activity and disease response, further validation of this score is required before wide clinical use [70, 71]. Based on current literature, there is insufficient evidence to recommend a single index in UC, and clinicians should employ the index that is most commonly used locally to improve communication with the other members of the treatment team [70].

In Crohn's disease, the simplified endoscopic activity score for Crohn's disease (SES-CD) is the most commonly employed in clinical practice and in research, has excellent inter-observer agreement, and demonstrates greater responsiveness than the more complex Crohn's disease endoscopic index of severity (CDEIS) [72–74]. The SES-CD consists of scoring the terminal ileum, right colon, transverse colon, left colon, and rectum in the domains of ulceration, ulcerated

Table 44.5 Montreal and Paris classification of Crohn's disease [65, 66]

	Montreal	Paris
Age at diagnosis	A1 < 17 years A2 17–40 years A3 > 40 years	A1a <10 years A1b 10–17 years A2 17–40 years A3 > 40 years
Location	L1 terminal ileum L2 colon L3 ileocolon L4 upper GI[a]	L1 distal 1/3 ileum L2 colon L3 ileocolon L4a upper disease prox. to the ligament of Treitz[a] L4b upper disease distal to the ligament of Treitz and proximal to distal 1/3 ileum[a]
Behavior	B1 nonstricturing, nonpenetrating B2 stricturing B3 penetrating p perianal disease modifierΔ	B1 nonstricturing, nonpenetrating B2 stricturing B3 penetrating B2B3 both penetrating and structuring disease p perianal disease modifierΔ
Growth delay		G0 no growth delay G1 growth delay

Δp may be added to B1–B3 (i.e., B1p)
[a]L4 and L4a/b may be added to L1–L3 (i.e., L2 + L4); upper GI is defined as any disease proximal to the terminal ileum

Table 44.7 Endoscopic evaluation in ulcerative colitis, the endoscopic subscore of the Mayo score, and the Modified Mayo Endoscopic Score (MMES) [71, 77]

	0	1	2	3
Mayo endoscopic subscore	Normal or inactive disease	Erythema Decreased vascular pattern Mild friability	Marked erythema Absent vascular pattern Friability Erosions	Ulcerations Spontaneous bleeding
MMES	Sum of Mayo score for all 5 colon segments[a] (max 15) × length of inflamed segment during withdrawal (in dm) ÷ number of segments[a] inflamed (>0 Mayo score, max 5)			

[a]Segments = rectum, sigmoid, descending, transverse, and ascending colon

Table 44.6 Montreal and Paris classification of ulcerative colitis [65, 66]

	Montreal	Paris
Extent	E1 ulcerative proctitis E2 left-sided UC (distal to splenic flexure) E3 extensive UC (proximal to pancolitis)	A1a <10 years A1b 10–17 years A2 17–40 years A3 > 40 years
Severity	S0 clinical remission S1 mild UC (≤4 BM/day, no systemic toxicity, normal ESR) S2 moderate UC (≥ 5 BM/day, mild signs of systemic toxicity) S3 severe UC (≥ 6 bloody BM/day, evidence of toxicity)	S0 never severe S1 ever severe[a]

[a]Severity defined by Pediatric Ulcerative Colitis Activity Index >65 [68]

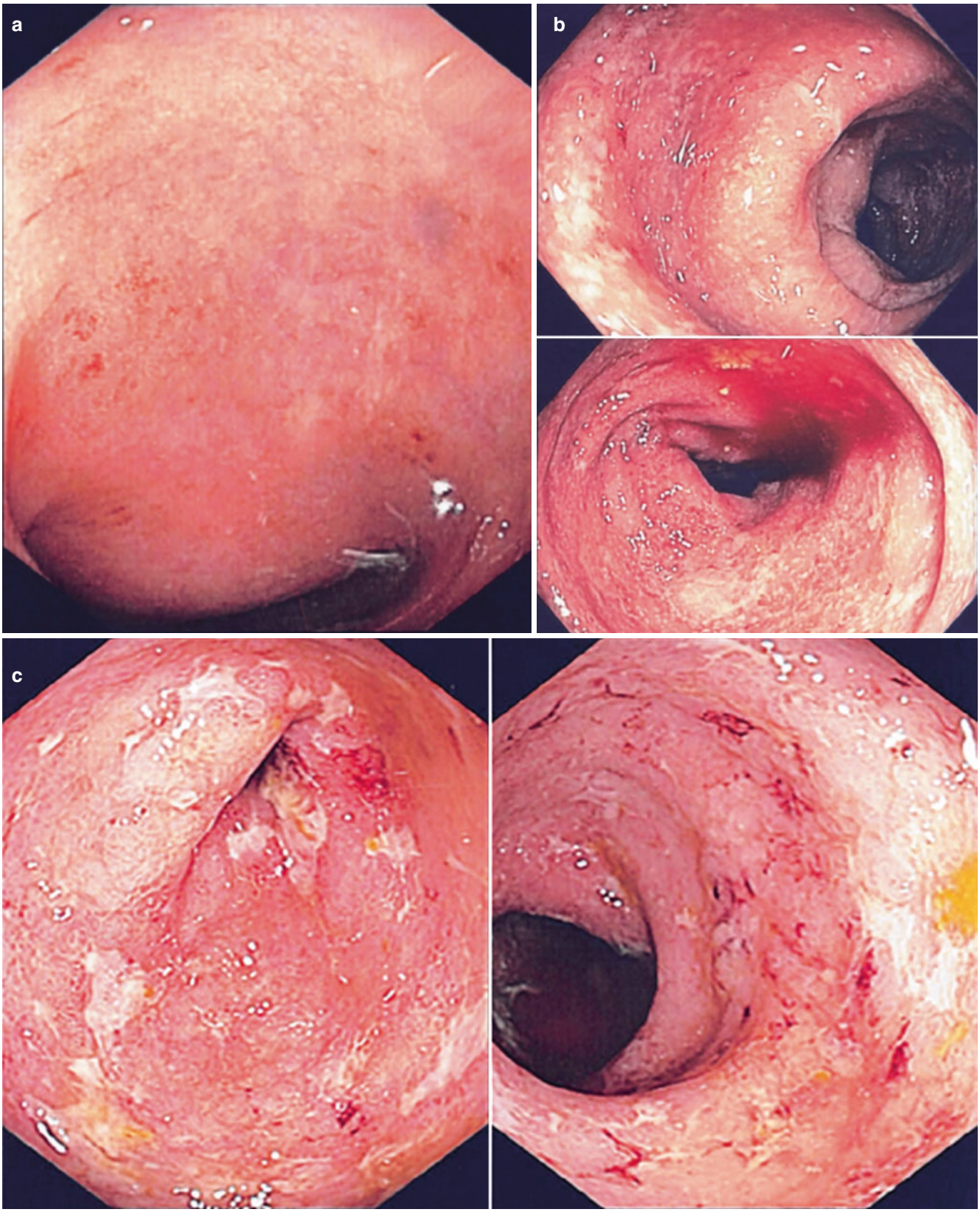

Fig. 44.6 Representative examples of Mayo endoscopic subscore for grading of colitis: (**a**) Mayo 1, (**b**) Mayo 2, and (**c**) Mayo 3 colitis

Table 44.8 The simplified endoscopic activity score for Crohn's disease (SES-CD) [73]

Domain	0	1	2	3
Size of ulcers	None	Aphthous (<5 mm)	Large (5–20 mm)	Very large (>20 mm)
Ulcerated surface	None	<10%	10–30%	>30%
Affected surface	Unaffected	<50%	50–75%	>75%
Presence of narrowings	None	Single, passable	Multiple, passable	Cannot be passed

Each segment (terminal ileum, right colon, transverse colon, left colon, and rectum) receives a score for each domain, and the sum of all the domain scores for all the segments is the total SES-CD

Table 44.9 Rutgeerts score to assess recurrent disease in the neoterminal ileum following an ileocolic resection

i0	i1	i2	i3	i4
No lesions	≤5 aphthous ulcers	>5 aphthous ulcers with normal intervening mucosa, skip areas of larger lesions confined to ileocolonic anastomosis	Diffuse aphthous ileitis with diffusely inflamed mucosa	Diffuse inflammation with large ulcers, nodules, and/or stenosis

i2 and greater are classified as endoscopic recurrence [75]

surface, affected surface, and presence of narrowing; each domain is scored from 0 to 3, and the sum of all domains for all five segments comprises the SES-CD for that patient (see Table 44.8) [73]. For patients who have previously had an ileocolic resection, the Rutgeerts score is commonly employed to grade the extent of inflammation within the terminal ileum and has been strongly associated with risk of symptomatic recurrence; however, it has been shown to have only modest inter-rater reliability (see Table 44.9 and Fig. 44.7) [75, 76].

At the time of endoscopy, it may assist the physician to accurately and systematically evaluate the extent of endoscopic disease by printing the commonly employed endoscopic indices directly on the synoptic colonoscopy report form, as done at our institution.

Activity Scores

In addition to endoscopic scores, several activity scores have been reported for grading the severity of IBD. For patients with UC, the Mayo score is often described in the literature and includes an assessment of stool frequency, rectal bleeding, a physician's global assessment, and the endoscopic subscore (see above) to generate a score from 0 to 12 [77]. Despite its simplicity, the Mayo score is rarely employed in routine clinical practice, and patients are more often described as having mild, moderate, or severe colitis based on Truelove and Witt's criteria (see Table 44.6) [78]. In addition, UC patients are often characterized by their response to treatment: medically/steroid refractory, steroid dependent, medically responsive, or in remission.

In Crohn's disease, the Crohn's disease activity index (CDAI) is often employed in clinical trials with a score of <150 consistent with remission; however, it is not used in routine clinical practice given the complexity in calculating the score itself [79, 80]. In contrast, the Harvey-Bradshaw index is a simplified score for CD and involves assessment of the patient's general well-being, abdominal pain, number of bowel movements per day, presence of an abdominal mass, and complications of Crohn's disease (see Table 44.10) [81]. This index is highly correlated with the CDAI, is easier to administer, and is used more broadly in the clinical setting (see Table 44.10) [80, 81].

More recently, there have been over 20 new patient-reported outcome measures (PROMs) that have been described in the literature, some of which include patient responses only (such as IBD-10), while others combine scores with laboratory investigations such as CRP or fecal calprotectin (such as Monitor IBD At Home questionnaire (MIAH)) and/or clinical assessment (such as HB-PROp/c) [82–85]. Although these indices have demonstrated accuracy in predicting endoscopic activity and correlation with other indices, they require external validation and direct comparative analyses in a single cohort to assess superiority of one over the other [82–85].

Surveillance Endoscopy in IBD

There is ample evidence based on population-based cohorts, cohort, and case-control studies that patients with IBD are at an increased risk of colorectal cancer (CRC) [86–90]. CRC in the setting of IBD is associated with a younger age of diagnosis, and patients have a higher risk of death (even after adjustment for stage) [86–88, 91]. Among IBD patients, those with an earlier onset of disease, longer duration of disease, active inflammation, colonic strictures, PSC, and a family history of CRC are at a higher risk of CRC [86, 89, 92]. The evidence for endoscopic surveillance for dysplasia and CRC is based solely on low-quality observational data, but surveillance has been consistently associated with a decreased risk of CRC, a lower stage of CRC when diagnosed, and a lower risk of death from CRC [93, 94].

Society guidelines recommend surveillance for all UC patients and CD patients with colonic involvement (but excluding patients with a history of proctitis alone) and to commence colonoscopy surveillance at 8 years following symptom onset or at diagnosis if PSC is present. Ideally, sur-

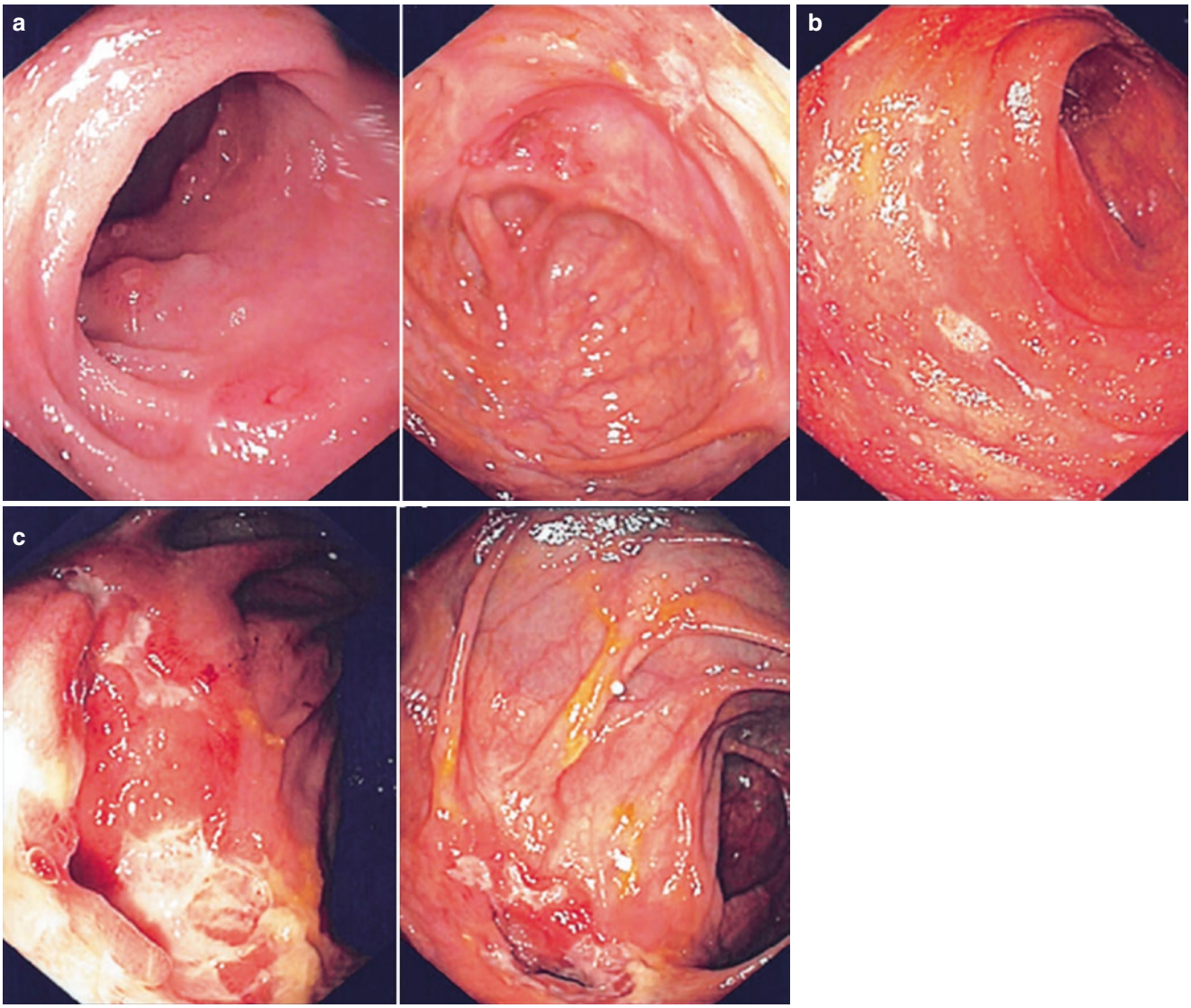

Fig. 44.7 Representative examples of Rutgeerts score for grading neoterminal ileal recurrence: (**a**) i2, (**b**) i3, and (**c**) i4

veillance should occur when the disease is in remission to increase the reliability of histopathology findings of dysplasia [61, 62, 92]. Chromoendoscopy may improve dysplasia detection compared to standard-definition colonoscopy; however, data are inconsistent with respect to the added value of chromoendoscopy in addition to high-definition colonoscopy [62, 95–97]. Two recent RCTs have demonstrated no added benefit of chromoendoscopy in detecting colitis-associated dysplasia [96, 97]. Therefore, guidelines recommend high-definition colonoscopy with chromoendoscopy if local expertise exists [61, 62, 92].

Based on current evidence, there is a lack of consensus on the incremental yield of random colonic biopsies in addition to targeted biopsies of abnormal mucosal findings [61, 62, 92]. Therefore, until further data are available, four random biopsies should be taken every 10 cm and reviewed by a GI pathologist [61, 62, 92]. Patients at high risk (PSC, family history of CRC, stricture, or dysplasia) should undergo annual surveillance colonoscopy, while those with intermediate risk (including those with active mucosal inflammation) should undergo surveillance colonoscopy in 1–3 years; and those at low risk should undergo surveillance colonoscopy every 3–5 years [61, 62, 92].

Based on the SCENIC guidelines, the terminology used to describe endoscopically detected dysplastic lesions in IBD patients has evolved [98]. The term dysplasia-associated lesion or mass (DALM) is no longer being employed, and lesions should be described based on the visibility, morphology, border, and presence of ulceration (see Table 44.11) [98, 99].

Table 44.10 Harvey-Bradshaw index for Crohn's disease activity [81]

Domain	Score
General well-being	0 = very well 1 = slightly below par 2 = poor 3 = very poor 4 = terrible
Abdominal pain	0 = none 1 = mild 2 = moderate 3 = severe
Number of liquid stools per day	# of liquid stools/day
Abdominal mass	0 = none 1 = dubious 2 = definite 3 = definite and tender
Complications	1 point for each of: Arthralgia Uveitis Erythema nodosum Aphthous ulcers Pyoderma gangrenosum Anal fissure New fistula Abscess

Table 44.11 SCENIC guidelines for reporting dysplastic lesions identified on colonoscopy surveillance [98]

Terms	Definitions
Visible dysplasia Invisible dysplasia	Dysplasia identified on targeted biopsies from a lesion visualized at colonoscopy Dysplasia identified on random biopsies without a visible lesion
Polypoid Pedunculated Sessile	Protruding into lumen >2.5 mm Stalk present No stalk; entire base is contiguous with mucosa
Nonpolypoid Superficially elevated Flat Depressed	No or little (<2.5 mm) protrusion above the mucosa Protrusion <2.5 mm No protrusion above the mucosa Any portion depressed below the level of the mucosa
Distinct border Indistinct border	Discrete border can be distinguished from surrounding mucosa Border cannot be distinguished from surrounding mucosa
Ulcerated	Ulceration (fibrinous-appearing base with depth) within the lesion

References

1. Actis GC, Pellicano R, Fagoonee S, Ribaldone DG. History of inflammatory bowel diseases. J Clin Med. 2019;8:1970.
2. Kuhnen A. Genetic and environmental considerations for inflammatory bowel disease. Surg Clin North Am. 2019;99:1197–207.
3. Dragasevic S, Stankovic B, Milosavljevic T, et al. Genetic and environmental factors significant for the presentation and development of inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2017;29:909–15.
4. Ng SC, Woodrow S, Patel N, Subhani J, Harbord M. Role of genetic and environmental factors in British twins with inflammatory bowel disease. Inflamm Bowel Dis. 2012;18:725–36.
5. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2018;390:2769–78.
6. Kaplan GG, Bernstein CN, Coward S, et al. The impact of inflammatory bowel disease in Canada 2018: epidemiology. J Can Assoc Gastroenterol. 2019;2:S6–S16.
7. Misra R, Limdi J, Cooney R, et al. Ethnic differences in inflammatory bowel disease: results from the United Kingdom inception cohort epidemiology study. World J Gastroenterol. 2019;25:6145–57.
8. Benchimol EI, Mack DR, Guttmann A, et al. Inflammatory bowel disease in immigrants to Canada and their children: a population-based cohort study. Am J Gastroenterol. 2015;110:553–63.
9. Crohn BBG, Ginzburg L, Oppenheimer GD. Regional ileitis: a pathological and clinical entity. JAMA. 1932;99:1323–9.
10. Mao R, Kurada S, Gordon IO, et al. The mesenteric fat and intestinal muscle interface: creeping fat influencing stricture formation in Crohn's disease. Inflamm Bowel Dis. 2019;25:421–6.
11. Coffey CJ, Kiernan MG, Sahebally SM, et al. Inclusion of the mesentery in ileocolic resection for Crohn's disease is associated with reduced surgical recurrence. J Crohns Colitis. 2018;12:1139–50.
12. Zimmer V, Emrich K. The cecal patch: a signature skip lesion in ulcerative colitis. Tech Coloproctol. 2020;24:213–4.
13. Dendrinos K, Cerda S, Farraye FA. The "cecal patch" in patients with ulcerative colitis. Gastrointest Endosc. 2008;68:1006–7; discussion 7.
14. Joo M, Odze RD. Rectal sparing and skip lesions in ulcerative colitis: a comparative study of endoscopic and histologic findings in patients who underwent proctocolectomy. Am J Surg Pathol. 2010;34:689–96.
15. Glickman JN, Odze RD. Does rectal sparing ever occur in ulcerative colitis? Inflamm Bowel Dis. 2008;14 Suppl 2:S166–7.
16. Burisch J, Zammit SC, Ellul P, et al. Disease course of inflammatory bowel disease unclassified in a European population-based inception cohort: an Epi-IBD study. J Gastroenterol Hepatol. 2019;34:996–1003.
17. Birimberg-Schwartz L, Zucker DM, Akriv A, et al. Development and validation of diagnostic criteria for IBD subtypes including IBD-unclassified in children: a multicentre study from the Pediatric IBD Porto Group of ESPGHAN. J Crohns Colitis. 2017;11:1078–84.
18. Odze RD. A contemporary and critical appraisal of 'indeterminate colitis'. Mod Pathol. 2015;28 Suppl 1:S30–46.
19. Tremaine WJ. Is indeterminate colitis determinable? Curr Gastroenterol Rep. 2012;14:162–5.
20. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006;55:749–53.
21. Kevans D, Tyler AD, Holm K, et al. Characterization of intestinal microbiota in ulcerative colitis patients with and without primary sclerosing cholangitis. J Crohns Colitis. 2016;10:330–7.
22. Mertz A, Nguyen NA, Katsanos KH, Kwok RM. Primary sclerosing cholangitis and inflammatory bowel disease comorbidity: an update of the evidence. Ann Gastroenterol. 2019;32:124–33.
23. Ricciuto A, Kamath BM, Griffiths AM. The IBD and PSC phenotypes of PSC-IBD. Curr Gastroenterol Rep. 2018;20:16.
24. Sabino J, Vieira-Silva S, Machiels K, et al. Primary sclerosing cholangitis is characterised by intestinal dysbiosis independent from IBD. Gut. 2016;65:1681–9.
25. Ricciuto A, Hansen BE, Ngo B, et al. Primary sclerosing cholangitis in children with inflammatory bowel diseases is associated with milder clinical activity but more frequent subclinical inflammation and growth impairment. Clin Gastroenterol Hepatol. 2019;18:1509–1517.e7.

26. Trivedi PJ, Reece J, Laing RW, et al. The impact of ileal pouch-anal anastomosis on graft survival following liver transplantation for primary sclerosing cholangitis. Aliment Pharmacol Ther. 2018;48:322–32.
27. Nordenvall C, Olen O, Nilsson PJ, et al. Colectomy prior to diagnosis of primary sclerosing cholangitis is associated with improved prognosis in a nationwide cohort study of 2594 PSC-IBD patients. Aliment Pharmacol Ther. 2018;47:238–45.
28. Nordenvall C, Olen O, Johan Nilsson P, et al. Restorative surgery in patients with primary sclerosing cholangitis and ulcerative colitis following a colectomy. Inflamm Bowel Dis. 2018;24:624–32.
29. Lindstrom L, Jorgensen KK, Boberg KM, et al. Risk factors and prognosis for recurrent primary sclerosing cholangitis after liver transplantation: a Nordic multicentre study. Scand J Gastroenterol. 2018;53:297–304.
30. Vavricka SR, Schoepfer A, Scharl M, Lakatos PL, Navarini A, Rogler G. Extraintestinal manifestations of inflammatory bowel disease. Inflamm Bowel Dis. 2015;21:1982–92.
31. Garber A, Regueiro M. Extraintestinal manifestations of inflammatory bowel disease: epidemiology, etiopathogenesis, and management. Curr Gastroenterol Rep. 2019;21:31.
32. Ott C, Scholmerich J. Extraintestinal manifestations and complications in IBD. Nat Rev Gastroenterol Hepatol. 2013;10:585–95.
33. Ma C, Battat R, Parker CE, Khanna R, Jairath V, Feagan BG. Update on C-reactive protein and fecal calprotectin: are they accurate measures of disease activity in Crohn's disease? Expert Rev Gastroenterol Hepatol. 2019;13:319–30.
34. Magro F, Gionchetti P, Eliakim R, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. J Crohns Colitis. 2017;11:649–70.
35. Gomollon F, Dignass A, Annese V, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. J Crohns Colitis. 2017;11:3–25.
36. Vermeire S, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? Gut. 2006;55:426–31.
37. Menees SB, Powell C, Kurlander J, Goel A, Chey WD. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. Am J Gastroenterol. 2015;110:444–54.
38. Stoner BP, Cohen SE. Lymphogranuloma venereum 2015: clinical presentation, diagnosis, and treatment. Clin Infect Dis. 2015;61 Suppl 8:S865–73.
39. Zhou G, Song Y, Yang W, et al. ASCA, ANCA, ALCA and many more: are they useful in the diagnosis of inflammatory bowel disease? Dig Dis. 2016;34:90–7.
40. Reese GE, Constantinides VA, Simillis C, et al. Diagnostic precision of anti-Saccharomyces cerevisiae antibodies and perinuclear antineutrophil cytoplasmic antibodies in inflammatory bowel disease. Am J Gastroenterol. 2006;101:2410–22.
41. Ma C, Battat R, Khanna R, Parker CE, Feagan BG, Jairath V. What is the role of C-reactive protein and fecal calprotectin in evaluating Crohn's disease activity? Best Pract Res Clin Gastroenterol. 2019;38–39:101602.
42. Ministro P, Martins D. Fecal biomarkers in inflammatory bowel disease: how, when and why? Expert Rev Gastroenterol Hepatol. 2017;11:317–28.
43. Allocca M, Fiorino G, Bonifacio C, Peyrin-Biroulet L, Danese S. Noninvasive multimodal methods to differentiate inflamed vs fibrotic strictures in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2019;17:2397–415.
44. Bettenworth D, Bokemeyer A, Baker M, et al. Assessment of Crohn's disease-associated small bowel strictures and fibrosis on cross-sectional imaging: a systematic review. Gut. 2019;68:1115–26.
45. Ippolito D, Lombardi S, Trattenero C, Franzesi CT, Bonaffini PA, Sironi S. CT enterography: diagnostic value of 4th generation iterative reconstruction algorithm in low dose studies in comparison with standard dose protocol for follow-up of patients with Crohn's disease. Eur J Radiol. 2016;85:268–73.
46. Yu H, Wang Y, Wang Z, Li J, Lu J, Hu D. Prospective comparison of diffusion-weighted magnetic resonance enterography and contrast enhanced computed tomography enterography for the detection of ileocolonic Crohn's disease. J Gastroenterol Hepatol. 2020;35:1136–42.
47. Kavanagh RG, O'Grady J, Carey BW, et al. Low-dose computed tomography for the optimization of radiation dose exposure in patients with Crohn's disease. Gastroenterol Res Pract. 2018;2018:1768716.
48. Nguyen GC, Low D, Chong RY, Diong C, Chawla T. Utilization of diagnostic imaging and ionization radiation exposure among an inflammatory bowel disease inception cohort. Inflamm Bowel Dis. 2020;26:898–906.
49. Taylor SA, Mallett S, Bhatnagar G, et al. Diagnostic accuracy of magnetic resonance enterography and small bowel ultrasound for the extent and activity of newly diagnosed and relapsed Crohn's disease (METRIC): a multicentre trial. Lancet Gastroenterol Hepatol. 2018;3:548–58.
50. Maconi G, Carsana L, Fociani P, et al. Small bowel stenosis in Crohn's disease: clinical, biochemical and ultrasonographic evaluation of histological features. Aliment Pharmacol Ther. 2003;18:749–56.
51. Lavazza A, Maconi G. Transperineal ultrasound for assessment of fistulas and abscesses: a pictorial essay. J Ultrasound. 2019;22:241–9.
52. Wright EK, Novak KL, Lu C, Panaccione R, Ghosh S, Wilson SR. Transperineal ultrasonography in perianal Crohn disease: a valuable imaging modality. Can J Gastroenterol Hepatol. 2015;29:445–7.
53. Rimola J, Planell N, Rodríguez S, et al. Characterization of inflammation and fibrosis in Crohn's disease lesions by magnetic resonance imaging. Am J Gastroenterol. 2015;110:432–40.
54. Zappa M, Stefanescu C, Cazals-Hatem D, et al. Which magnetic resonance imaging findings accurately evaluate inflammation in small bowel Crohn's disease? A retrospective comparison with surgical pathologic analysis. Inflamm Bowel Dis. 2011;17:984–93.
55. Thipphavong S, Costa AF, Ali HA, Wang DC, Brar MS, Jhaveri KS. Structured reporting of MRI for perianal fistula. Abdom Radiol (NY). 2019;44:1295–305.
56. Siddiqui MR, Ashrafian H, Tozer P, et al. A diagnostic accuracy meta-analysis of endoanal ultrasound and MRI for perianal fistula assessment. Dis Colon Rectum. 2012;55:576–85.
57. Annese V, Daperno M, Rutter MD, et al. European evidence based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis. 2013;7:982–1018.
58. Magro F, Langner C, Driessen A, et al. European consensus on the histopathology of inflammatory bowel disease. J Crohns Colitis. 2013;7:827–51.
59. Riff BP, DiMaio CJ. Exploring the small bowel: update on deep enteroscopy. Curr Gastroenterol Rep. 2016;18:28.
60. Furey TS, Sethupathy P, Sheikh SZ. Redefining the IBDs using genome-scale molecular phenotyping. Nat Rev Gastroenterol Hepatol. 2019;16:296–311.
61. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. Am J Gastroenterol. 2019;114:384–413.
62. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68:s1–s106.
63. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults. Am J Gastroenterol. 2018;113:481–517.

64. Spekhorst LM, Visschedijk MC, Alberts R, et al. Performance of the Montreal classification for inflammatory bowel diseases. World J Gastroenterol. 2014;20:15374–81.
65. Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis. 2011;17:1314–21.
66. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol. 2005;19 Suppl A:5A–36A.
67. Kornbluth A, Sachar DB, Practice Parameters Committee of the American College of G. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2004;99:1371–85.
68. Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. Gastroenterology. 2007;133:423–32.
69. McCurdy JD, Kuenzig ME, Smith G, et al. Risk of venous thromboembolism after hospital discharge in patients with inflammatory bowel disease: a population-based study. Inflamm Bowel Dis. 2020;26:1761–8.
70. Mohammed Vashist N, Samaan M, Mosli MH, et al. Endoscopic scoring indices for evaluation of disease activity in ulcerative colitis. Cochrane Database Syst Rev. 2018;1:CD011450.
71. Lobaton T, Bessissow T, De Hertogh G, et al. The Modified Mayo Endoscopic Score (MMES): a new index for the assessment of extension and severity of endoscopic activity in ulcerative colitis patients. J Crohns Colitis. 2015;9:846–52.
72. Khanna R, Zou G, Stitt L, et al. Responsiveness of endoscopic indices of disease activity for Crohn's disease. Am J Gastroenterol. 2017;112:1584–92.
73. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc. 2004;60:505–12.
74. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut. 1989;30:983–9.
75. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990;99:956–63.
76. Marteau P, Laharie D, Colombel JF, et al. Interobserver variation study of the Rutgeerts score to assess endoscopic recurrence after surgery for Crohn's disease. J Crohns Colitis. 2016;10:1001–5.
77. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317:1625–9.
78. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J. 1955;2:1041–8.
79. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976;70:439–44.
80. Best WR. Predicting the Crohn's disease activity index from the Harvey-Bradshaw index. Inflamm Bowel Dis. 2006;12:304–10.
81. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet. 1980;1:514.
82. de Jong MJ, Roosen D, Degens J, et al. Development and validation of a patient-reported score to screen for mucosal inflammation in inflammatory bowel disease. J Crohns Colitis. 2019;13:555–63.
83. de Jong MJ, Huibregtse R, Masclee AAM, Jonkers D, Pierik MJ. Patient-reported outcome measures for use in clinical trials and clinical practice in inflammatory bowel diseases: a systematic review. Clin Gastroenterol Hepatol. 2018;16:648–63.e3.
84. Zittan E, Kabakchiev B, Kelly OB, et al. Development of the Harvey-Bradshaw index-pro (HBI-PRO) score to assess endoscopic disease activity in Crohn's disease. J Crohns Colitis. 2017;11:543–8.
85. Subramanian S, Asher R, Weston W, et al. Validation of a simple 0 to 10 numerical score (IBD-10) of patient-reported inflammatory bowel disease activity for routine clinical use. Inflamm Bowel Dis. 2016;22:1902–7.
86. Olen O, Erichsen R, Sachs MC, et al. Colorectal cancer in ulcerative colitis: a Scandinavian population-based cohort study. Lancet. 2020;395:123–31.
87. Olen O, Erichsen R, Sachs MC, et al. Colorectal cancer in Crohn's disease: a Scandinavian population-based cohort study. Lancet Gastroenterol Hepatol. 2020;5(5):475–84.
88. Bogach J, Pond G, Eskicioglu C, Seow H. Age-related survival differences in patients with inflammatory bowel disease-associated colorectal cancer: a population-based cohort study. Inflamm Bowel Dis. 2019;25:1957–65.
89. Fornaro R, Caratto M, Caratto E, et al. Colorectal cancer in patients with inflammatory bowel disease: the need for a real surveillance program. Clin Colorectal Cancer. 2016;15:204–12.
90. Castano-Milla C, Chaparro M, Gisbert JP. Systematic review with meta-analysis: the declining risk of colorectal cancer in ulcerative colitis. Aliment Pharmacol Ther. 2014;39:645–59.
91. Taylor CC, Millien VO, Hou JK, Massarweh NN. Association between inflammatory bowel disease and colorectal cancer stage of disease and survival. J Surg Res. 2020;247:77–85.
92. Maaser C, Sturm A, Vavricka SR, et al. ECCO-ESGAR guideline for diagnostic assessment in IBD part 1: initial diagnosis, monitoring of known IBD, detection of complications. J Crohns Colitis. 2019;13:144–64.
93. Clarke WT, Feuerstein JD. Colorectal cancer surveillance in inflammatory bowel disease: practice guidelines and recent developments. World J Gastroenterol. 2019;25:4148–57.
94. Bye WA, Nguyen TM, Parker CE, Jairath V, East JE. Strategies for detecting colon cancer in patients with inflammatory bowel disease. Cochrane Database Syst Rev. 2017;9:CD000279.
95. Bessissow T, Dulai PS, Restellini S, et al. Comparison of endoscopic dysplasia detection techniques in patients with ulcerative colitis: a systematic review and network meta-analysis. Inflamm Bowel Dis. 2018;24:2518–26.
96. Yang DH, Park SJ, Kim HS, et al. High-definition chromoendoscopy versus high-definition white light colonoscopy for neoplasia surveillance in ulcerative colitis: a randomized controlled trial. Am J Gastroenterol. 2019;114:1642–8.
97. Iacucci M, Kaplan GG, Panaccione R, et al. A randomized trial comparing high definition colonoscopy alone with high definition dye spraying and electronic virtual chromoendoscopy for detection of colonic neoplastic lesions during IBD surveillance colonoscopy. Am J Gastroenterol. 2018;113:225–34.
98. Laine L, Kaltenbach T, Barkun A, et al. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastrointest Endosc. 2015;81:489–501.e26.
99. Chiu K, Riddell RH, Schaeffer DF. DALM, rest in peace: a pathologist's perspective on dysplasia in inflammatory bowel disease in the post-DALM era. Mod Pathol. 2018;31:1180–90.

Medical Management of Ulcerative Colitis

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Key Concepts

- The goal of medical therapy for ulcerative colitis is steroid-free clinical remission with mucosal healing.
- 5-ASA medications are the first-line treatment for low-risk patients with mild-to-moderate UC.
- IV corticosteroids are first-line treatment for severe UC flare-ups requiring hospitalization.
- Cyclosporin and infliximab are appropriate second-line agents for patients with steroid refractory severe acute colitis.

Introduction

Appropriate treatment of ulcerative colitis includes a combination of medical and surgical therapies to safely resolve inflammation, lessen symptoms, improve quality of life, and minimize the risk for short- and long-term complications. Therapy is usually guided by the age of the patient, anatomic extent of inflammation, symptom severity, treatment response, and risk for adverse effects. Treatment can be intended to induce remission in patients with active disease or maintain remission in others. Operative intervention is generally reserved for patients with disease-related complications or disease that is refractory to medical therapy, with the latter indication being quite common. Consequently, it is important for the surgeon to understand the indications, dosing, benefits, and risks of the various types of medications used to treat ulcerative colitis.

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Medications

Homeopathic agents, 5-aminosalicylate compounds, glucocorticoids, immunomodulators, and biologic agents/biosimilars are all modalities used for the medical treatment of ulcerative colitis depending upon the clinical scenario. Each drug within these therapeutic groups is distinguished by dosing parameters, short- and long-term side effects, and expected response intervals. Before initiating therapy with any medication, patients should be comprehensively counseled about these characteristics. Moreover, objective criteria for disease response should be initially discussed and then measured after a reasonable time interval. If the desired response is not achieved, prohibitive side effects ensue, or noncompliance transpires, the drug has failed, and another medication/approach should be trialed. When medical management has proven unsuccessful, operative intervention is generally indicated. The continuation of ineffective drug therapy risks the development of further disease complications that may adversely impact surgical outcomes.

Some patients will instead seek an operation before trialing all available medical modalities because they have concerns regarding the alternative drug(s). Interestingly, a survey of outpatients with ulcerative colitis, gastroenterologists, and colorectal surgeons quantified this behavior [1]. Participants were interviewed to measure their inclinations in five scenarios by using a prospective preference measure. When the scenario pitted escalating medical therapy against a proctocolectomy and ileal pouch-anal anastomosis, 80% of gastroenterologists were willing to gamble life expectancy while only 64% of patients, and 49% of colorectal surgeons were willing to similarly gamble. Conversely, 75% of patients were willing to gamble with escalating medical therapy to avoid a proctocolectomy and permanent ileostomy compared to 85% of gastroenterologists and 68% of surgeons.

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Homeopathic Agents

Curcumin

Curcumin (diferuloylmethane), the yellow pigment in the large-leafed herb Indian saffron (i.e., *Curcuma longa*; turmeric, haldi, or haridara in the East; curry powder in the West) has been consumed for centuries to manage a variety of proinflammatory disorders [2]. Its postulated mechanism of action includes suppression of the nuclear factor k-light chain enhancer in B-lymphocytes as well as expression of Th1 and Th2 cytokines. Curcumin has also been reported to possess anti-interleukin (IL)-1 and anti-tumor necrosis factor (TNF) properties, and this makes it an attractive treatment option for inflammatory conditions. A recent meta-analysis of 7 studies with 380 patients (curcumin $n = 188$; placebo $n = 190$) reported a threefold increase in clinical and endoscopic response to curcumin as an adjunct to mesalamine compared to mesalamine plus placebo; only 21 adverse events were reported and all were of mild degree [3].

Probiotics

Probiotics are beneficial microorganisms that can potentially impact the gut's microbiota composition, metabolic activity, and immunomodulation to confer host benefit. These bacteria and fungi can alter microbial diversity through competitive inhibition of other microbes, enhance mucosal barrier function via the production of short-chain fatty acids, and interact with intestinal dendritic cells to instigate an anti-inflammatory response. The microorganisms must be of human origin, nonpathogenic, and able to survive the gastrointestinal transit in order to be beneficial. Although probiotics have not been approved by the US Food and Drug Administration (FDA) to prevent or treat any health condition, a recent meta-analysis suggested that probiotics containing bifidobacteria offer a promising role for the treatment of active ulcerative colitis [4].

5-Aminosalicylate Compounds

A number of 5-aminosalicylate (ASA)-containing compounds are available with active 5-ASA released at various locations throughout the intestinal tract depending on the design of each specific drug. These compounds work by activating a class of nuclear receptors involved in the control of apoptosis, cell proliferation, inflammation, and metabolic function. The gamma forms of the peroxisome proliferator-activated receptors are found at particularly high levels in colon epithelial cells, where their expression appears to be at least partially stimulated by gut bacteria. Sulfasalazine is the original 5-aminosalicylate and is comprised of 5-ASA bound to a sulfapyridine moiety that detaches when the drug is impacted by colonic bacteria.

Other 5-ASA-derivatives, such as mesalamine, are formulated for release in the colon through varied mechanisms including bacterial- and pH-mediated as well as time-dependent release. Patients with limited disease (e.g., proctitis, left-sided disease) may prefer transanal topical therapy (e.g., suppository, enema) because of less frequent dosing, lower cost, and shorter response time compared to oral treatment.

Although sulfasalazine and mesalamine are both associated with side effects, the sulfapyridine moiety of sulfasalazine appears to impart a wider range of more serious adverse events, including symptoms such as gastrointestinal upset and headaches. Rare side effects include bone marrow suppression, fever, hemolytic anemia, hepatitis, hypersensitivity reactions, pancreatitis, pneumonitis, and rash. Patients who take sulfasalazine must also take folic acid (1 mg daily) because the medication depletes folic acid stores. Whereas nausea and headaches are typically dose-dependent and slow titration of the dosage can minimize these problems, sulfasalazine should be discontinued for idiosyncratic drug reactions such as agranulocytosis, pancreatitis, pneumonitis, and skin rash. Conversely, mesalamine is a safe, effective medication, and it is rare for patients to develop side effects; interstitial nephritis can develop, so routine monitoring of kidney function is recommended [5].

Glucocorticoids

Glucocorticoid drugs were first used for the management of ulcerative colitis several decades ago, and their benefit originates from an ability to modulate the immune response, inhibit expression of adhesion molecules, and decrease trafficking of inflammatory cells to the intestine. However, the traditional glucocorticoids are associated with significant short- and long-term adverse effects that limit their usage to management of acute episodes. Budesonide, a glucocorticoid with an extensive first pass liver metabolism was consequently developed because it maximizes the amount of glucocorticoid locally available but theoretically has minimal systemic impact. Three formulations of budesonide currently exist with two standard capsules designed to release the drug in the terminal ileum and right colon and a newer budesonide capsule (i.e., budesonide MMX®) formulated to steadily release the drug throughout the entire colon.

Resistance and dependency are major concerns when treating patients with glucocorticoids. The occurrence and severity of most side effects are related to the dose and duration of treatment. Common findings include abdominal striae, acne, cataracts, fluid retention, glaucoma, hyperglycemia, hypertension, insomnia, mood disturbances, moon facies, and weight gain. Musculoskeletal complications such as myopathy, osteonecrosis, and osteoporosis are additional

side effects. Lastly, adrenal suppression can occur during the course of treatment and contribute to physiologic dependence.

Oral and rectal budesonide formulations are associated with little to no risk. Studies suggest a small alteration in systemic cortisol levels associated with budesonide therapy, but typical steroid-related side effects are only seen with oral budesonide chronically prescribed at high dosages [6].

Immunomodulators

The thiopurines are immunomodulators that can be used to allow glucocorticoid tapering in patients with "steroid-dependent" disease but are not generally employed as monotherapy to induce or maintain remission. Conversely, cyclosporin and tacrolimus are calcineurin inhibitors that can be prescribed in "steroid-refractory" patients to achieve remission; tofacitinib, a nonselective inhibitor of the Janus kinase enzyme, can both induce and maintain remission.

Thiopurines

Azathioprine and 6-mercaptopurine (6-MP) are thiopurines with azathioprine being the precursor of 6-MP. Although their exact mechanism of action in patients with ulcerative colitis is uncertain, they are known to cause immunosuppression by interfering with nucleic acid metabolism in the immunological sequence that follows antigenic stimulation. Genetic polymorphisms of thiopurine methyltransferase (TPMT), the primary enzyme responsible for 6-MP metabolism, have been identified, and drug metabolite levels can be measured. These clinical assays allow monitoring and dosing of the medications according to measurements of the metabolites 6-thioguanine and 6-methylmercaptopurine. Prior to starting thiopurine therapy, TPMT enzyme activity or genotype should usually be determined because the drugs should be avoided in patients with TPMT deficiency. Patients with heterozygous genotype of intermediate activity should begin therapy at reduced doses that are one-half the usual recommendations. If TPMT activity or genotype cannot be assayed in advance of initiating treatment, the drugs should be cautiously dosed at the outset with careful monitoring for leukopenia.

While the most common side effect linked to azathioprine and 6-MP is nausea, adverse events associated with these drugs include liver function abnormalities, leukopenia, and pancreatitis. Pancreatitis typically presents during the first 8 weeks of therapy, and reintroduction of either agent should be avoided because pancreatitis will likely recur. Routine monitoring of complete blood counts is recommended at 1- to 2-week intervals initially and subsequent to a dose change and then at least every 3 months thereafter to detect evidence of acute or delayed bone marrow suppression. Rare hypersensitivity reactions characterized by fever, liver dysfunction, and rash may occur. A slightly increased risk of lymphoma has also been reported [7, 8].

Data related to the risk of serious infections were obtained from a large prospective, observational cohort study of 6273 patients with a mean follow-up of more than 5 years [9]. On multivariate analysis, thiopurine therapy was associated with a trend towards an increase in serious infections (adjusted odds ratio: 1.23; 95% CI, 0.96–1.57). Patients treated with thiopurines had 10 more serious infections per 1000 patients compared with patients who were not managed with thiopurines.

Methotrexate

Methotrexate and its polyglutamate metabolites are folic acid analogues that demonstrate inhibitory activity against many enzymes in the metabolic pathway of folic acid. Chronic low-dose methotrexate therapy inhibits the production of thymidylate, purines, and methionine and leads to the accumulation of adenosine, a potent anti-inflammatory purine nucleoside. These actions decrease formation of antibodies, inhibit cellular proliferation, and reduce the production of inflammatory mediators. Methotrexate is administered each week by oral ingestion (12.5–15 mg) or intramuscular/subcutaneous injection (25 mg). Folic acid (1 mg daily) should be concomitantly prescribed. The most frequent side effects reported with methotrexate are gastrointestinal upset and stomatitis. Leukopenia can also occur but much less frequently than seen with thiopurine therapy. Rare complications of methotrexate therapy include hepatic fibrosis and hypersensitivity pneumonitis.

Calcineurin Inhibitors

Cyclosporine and tacrolimus bind with great affinity to a family of cytoplasmic proteins present in most cells. The resultant drug-receptor complex competitively and specifically inhibits calcineurin, leading to reduced production of interleukin (IL)-2 and a resultant reduction in T lymphocyte proliferation [10]. While both cyclosporine and tacrolimus can be administered by infusion (2–4 mg/kg/day; 0.01–0.02 mg/kg/day, respectively) or ingestion (4–8 mg/kg/day; 0.1–0.2 mg/kg/day, respectively), the serum trough levels achieve target more quickly with an intravenous approach. The principal side effects of these medications include gastrointestinal intolerance, gum hyperplasia, hirsutism, hypertension, renal dysfunction, and tremor [11]. In one cohort, 13.5% of patients treated with cyclosporine and/or tacrolimus had to discontinue treatment because of adverse events with gastrointestinal intolerance and hypertension cited as the most frequent reasons for drug discontinuation [12].

Janus Kinase Enzyme Inhibitors

Janus kinase inhibitors (JAKi) such as tofacitinib are oral, small molecule drugs that bind a group of four membrane-bound receptors and mediate regulation of genes that code for diverse inflammatory proteins through the signal transducer and activator of transcription proteins pathway [13]. Tofacitinib was initially approved (10 mg twice daily by mouth) for patients failing standard treatment (e.g., mesalamines, glucocorticoids) or those exposed to biologic agent(s). However, the indication for ulcerative colitis has been recently limited to adults with moderately to severely active disease who have had an inadequate response or who are intolerant to TNF blockers; there were concerns from rheumatoid arthritis post-marketing clinical trials regarding an increased occurrence of blood clots and death in patients treated with the 10 mg twice-daily dosing. Until further information is available, the lower 5 mg twice daily dose should be used for maintenance when feasible. This medication is also associated with increased risk for infections and hyperlipidemia [14]. No problems related to immunogenicity are expected with tofacitinib because it is a synthetic small molecule JAK inhibitor and not a biologic agent.

Biologic Agents/Biosimilars

Biologic agents have played an increasing and evolving role in the management of ulcerative colitis. All biologic agents approved by the Food and Drug Administration to manage patients with ulcerative colitis (i.e., infliximab, adalimumab, golimumab, vedolizumab, ustekinumab), demonstrate a positive correlation between drug concentrations and favorable therapeutic outcomes. Reactive therapeutic drug monitoring has become the new standard of care for optimizing biologic agent therapies, and some pundits now advocate for proactive therapeutic drug monitoring to enhance therapy with antitumor necrosis factor (TNF) medications [15]. Second, biosimilars have been developed and introduced at a lower cost because patents have expired for some of the original biologic agents. Despite initial concerns, mounting evidence from phase III/IV clinical trials and prospective observations has partially confirmed the short- and long-term efficacy, interchangeability, and safety of biosimilars.

Antitumor Necrosis Factor (TNF) Agents

The anti-TNF medications are designed to block the effects of TNFα, and three such medications (i.e., infliximab, adalimumab, golimumab) are currently approved for the treatment of ulcerative colitis. Infliximab is permitted for the treatment of moderate-to-severe ulcerative colitis that does not respond to standard therapies. Adalimumab is accepted for the treatment of moderate-to-severe disease that does not respond to conventional medications, but its effectiveness for patients who have lost response to or are intolerant of infliximab is uncertain. Golimumab was approved for therapy in patients with moderate-to-severe disease who demonstrate an inadequate response or intolerance to prior treatment or require continuous steroid therapy. Dose optimization of anti-TNF agents through the measurement of serum levels is an important step to complete before switching to another biologic agent [15].

Infliximab (5 mg/kg) is parenterally administered and usually well tolerated. After the initial infusion of infliximab, patients are generally administered another dose 2 and 6 weeks later and then at consistent 8-week intervals. If patients lose their initial response to infliximab, the medication dose can be increased (10 mg/kg), or the interval between infusions can be decreased (every 6 weeks) depending on individual pharmacokinetics. Infusion reactions are not uncommon, and most are successfully managed without discontinuing the infusion or preventing further use of infliximab.

Adalimumab (40 mg) is given as a single subcutaneous injection every other week after an initial induction regimen of four injections the first week and two during the third week. Although adalimumab may prove highly effective in the initial treatment stages, some patients lose response over time, and the medication may need to be administered each week.

Golimumab (100 mg) is indicated for patients who demonstrate an inadequate response or intolerance to prior treatment or require continuous glucocorticoid therapy. The drug is given by subcutaneous injection at weeks 2 and 6 and continued every 4 weeks after an initial induction with two injections.

Side effects associated with the anti-TNF agents are well recognized and include an increased risk of infections, such as tuberculosis, as well as autoimmune reactions, heart failure, liver dysfunction, lymphoma, and multiple sclerosis. Ongoing infection is an absolute contraindication to treatment with any TNF inhibitor. Prior to initiating treatment with an anti-TNF agent, patients should be screened to ensure that they do suffer from occult infection secondary to hepatitis B or tuberculosis.

Integrin Receptor Antagonist

Vedolizumab is monoclonal antibody targeting a specific integrin, $\alpha_4\beta_7$, that reduces lymphocyte trafficking by blocking interactions with mucosal vascular address in cell adhesion molecule (MAdCAM-1) [16]. The medication is indicated for patients with moderate-to-disease who have failed glucocorticoid or immunomodulator therapy. After an initial infusion of vedolizumab (300 mg), patients are administered another dose 2 and 6 weeks later and then at consistent 8-week intervals. If patients have not experienced a therapeutic benefit by 14 weeks of induction therapy or can-

not discontinue glucocorticoids within 6 months of starting therapy, the drug should be discontinued.

In a pooled analysis of 6 randomized controlled trials with 2830 inflammatory bowel disease patients, vedolizumab was associated with a favorable safety profile over an extended treatment period with low incidence rates of serious infections, malignancies, and infusion-related reactions [17].

IL-12 and IL-23 Inhibitor

Ustekinumab is a monoclonal antibody targeting the p40 subunit shared by IL-12 and IL-23. Ustekinumab is approved for use in moderate-to-severe ulcerative colitis; standard dosing includes an initial, weight range-based (260 mg, 390 mg, or 520 mg) infusion followed by 90 mg subcutaneous injections every 8 weeks. Ustekinumab has not been linked to increased rates of adverse events or serious adverse events including major cardiovascular events, malignancy, and mortality.

Disease Severity

The clinical severity of ulcerative colitis is classified as mild, moderate, or severe disease. The definition of mild-to-moderate disease is less than four to six bowel movements per day, mild to moderate rectal bleeding, no signs of systemic toxicity, normal C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR), and absence of features suggestive of high inflammatory activity based upon the Truelove and Witt's criteria (Table 45.1) [18], the Mayo Clinic score (Table 45.2), and the Mayo Clinic endoscopic severity score (Table 45.3) [19]. Moderate disease is defined as more frequent bowel movements (4–6 times per day) that may be loose and bloody, mild anemia not requiring transfusion (hemoglobin >10 g/dL), non-severe abdominal pain, no or minimal signs of systemic toxicity, and maintenance of body weight. Severe disease is defined as frequent, loose bloody stools (>6 per day) with severe cramps and evidence of systemic toxicity (e.g., fever, tachycardia), anemia (hemoglobin <10 g/dL), elevated CRP and/or ESR, and weight loss.

The exact definition of moderate-to-severe disease can vary in the literature depending in which index or scoring system is utilized (e.g., Truelove and Witts severity index, Mayo Clinic score, Montreal classification). Most often, however, patients with moderate-to-severe disease are defined as those dependent on or refractory to glucocorticoids, have severe endoscopic disease activity (presence of ulcers), are at high risk of colectomy based on Truelove and Witts criteria, or have a Mayo Clinic score of 6–12 with an endoscopic subscore of 2 or 3. Similar to severe colitis, acute severe ulcerative colitis (ASUC) is defined as six or more bowel movements per day plus at least one sign of systemic toxicity including tachycardia, fever, anemia

Table 45.1 Truelove and Witts score [18]

	Mild[a]	Moderate	Severe[b]
(1) Frequency of defecation	4 times or less	Intermediate between mild and severe	6 times or more
(2) Bloody stool	(−) or (+)		(+++)
(3) Fever[c]	Absent		37.5 C or higher
(4) Tachycardia[d]	Absent		90/min or more
(5) Anemia	Absent		Hb 10 g/dL or less
(6) ESR	Normal		30 mm/h or more

[a]Rated as "mild" when all six criteria are satisfied
[b]Rated as "severe" when criteria (1) and (2), and either of systemic symptoms (3) and (4) are satisfied, and at least 4 of the 6 criteria are satisfied
[c]Mean evening temperature of 37.5C or a temperature of ≥37.8C at least 2 of 4 days
[d]Mean pulse rate of >90/min

Table 45.2 Mayo score system for ulcerative colitis [19]

Measure	Scoring system
Stool frequency (per day)	0 = normal number of stool for patient
	1 = 1–2 more stools than normal
	2 = 3–4 more stools than normal
	3 = 5 + more stools than normal
Rectal bleeding	0 = no blood seen
	1 = streaks of blood with stool <50% time
	2 = obvious blood with stool most of the time
	3 = passes blood without stool
Findings on endoscopy	0 = normal or inactive disease
	1 = mild disease
	2 = moderate disease
	3 = severe disease
Physician's global assessment	0 = normal
	1 = mild disease
	2 = moderate disease
	3 = severe disease

Table 45.3 Mayo endoscopic severity score [19]

Score	Disease activity	Endoscopic features (descriptors)
0	Normal or inactive	None
1	Mild	Erythema, decreased vascular patter, mild friability
2	Moderate	Marked erythema, absent vascular pater, friability, erosions
3	Severe	Spontaneous bleeding, ulceration

(hemoglobin <10.5 g/dL), or elevated inflammatory markers (ESR >30 mm/hour) [18].

The majority of ulcerative colitis patients fall into the cohort of mild-to-moderate disease with intermittent periods of disease remission or activity. However, some patients who begin in the mild-to-moderate category will transition to moderate-to-severe if they begin having more frequent bowel movements, rectal bleeding, or an increased overall inflammatory burden. Similarly, while most patients in this mild-to-moderate category are at low risk of needing a colectomy, certain features such as age less than 40 years at diagnosis, pancolitis, extraintestinal manifestations, presence of deep ulcers on endoscopy, and elevated inflammatory markers can predict a more aggressive disease course [20]. When these features are present, patients may benefit from more aggressive initial therapy or rapid intensification rather than repeated courses of glucocorticoids. Other risk factors for a more complicated disease course and an increased need for colectomy include the number of hospitalizations related to ulcerative colitis, number of disease flares, need for glucocorticoids, and infection with *Clostridium difficile* or cytomegalovirus [20, 21]. Overall, the cumulative risk of colectomy after 5–10 years of disease is 15–20%, but this can increase to 25–30% in a subset of patients with acute severe ulcerative colitis (ASUC) [22, 23].

Induction of Remission

The treatment goal for patients afflicted with ulcerative colitis is glucocorticoid-free clinical remission with demonstration of complete mucosal healing on endoscopy. Increasing evidence supports the use of histologic remission as a principal endpoint, but this is not yet defined as a primary treatment target [24].

Selecting an appropriate induction agent is becoming increasingly difficult as the number of potential pharmaceuticals approved for the treatment of ulcerative colitis continues to increase. The choice is largely driven by both the American College of Gastroenterology (ACG) and American Gastroenterological Association (AGA) guidelines focused on disease severity and extent and a collection of myriad factors including access to an infusion center, concomitant medication use, insurance coverage, patient characteristics, patient compliance, patient preference, prior therapy for ulcerative colitis, and risk of adverse events [24, 25].

Mild-to-Moderate Disease

5-ASA Compounds (Topical, Oral)

Up to 90% of patients with mild-to-moderate ulcerative colitis are initiated on a 5-aminosalicylate (ASA) compound (e.g., sulfasalazine, mesalamine, diazo-bonded 5-ASA) with or without induction using oral or topical glucocorticoids. Both systemic exposure and therapeutic efficacy are equivalent among the various 5-ASA formulations [26, 27]. The majority of patients treated with 5-ASA compounds achieve clinical and endoscopic remission and are able to continue the same medication to maintain remission [5]. The remaining minority of patients require immunomodulator or biologic agent therapy for long-term disease control [22].

The ACG and AGA guidelines recommend topical mesalamine as first-line treatment for inducing remission in low-risk patients with mild-to-moderate ulcerative proctitis or proctosigmoiditis [24, 25, 28]. Low-risk patients are those with mild-to-moderate symptoms; no systemic symptoms; lack of severe endoscopic disease such as deep ulceration, normal, or mild elevation in CRP and/or ESR; no extraintestinal manifestations; diagnosis at age >40 years; and a normal albumin [20, 21, 28]. Mesalamine comes formulated in a suppository or enema, and the preferred choice should be driven by the extent of disease. A suppository will only reach the rectum, whereas an enema can deliver agent to the splenic flexure in most patients.

Thus, for patients with mild-to-moderate disease isolated to the rectum, a mesalamine suppository (1 gram daily) can be initiated. If the patients do not experience any improvement in symptoms after 2 weeks, the dose should be increased (1 gram twice daily) for 4 weeks followed by a reduction back to daily dosing. For patients with mild-to-moderate disease extending into the sigmoid colon, mesalamine enemas (1 gram daily) are more effective than suppositories. If patients achieve symptomatic relief, the dose can be increased to twice daily or stay as once daily. While some patients may experience relief after only 1 week of treatment, clinical remission usually requires 4–6 weeks of treatment.

When patients tolerating topical mesalamine do not demonstrate any improvement after 4 weeks of therapy, subsequent treatment options include supplementing the existing therapy with a daily topical glucocorticoid, an oral 5-ASA derivative, or an oral glucocorticoid (i.e., budesonide, prednisone) [29–31].

Topical glucocorticoids include formulations as a suppository or an enema delivered once daily, depending on the extent of disease; an enema is used if the inflammation extends further than 18 cm proximal to the anal verge [28]. Symptomatic improvement typified by decreased stool frequency and absence of blood in the stool should be seen within 3–4 weeks of initiating therapy. The use of topical glucocorticoids longer than 8 weeks is not recommended due to potential adverse events with chronic use [32, 33].

With regard to oral 5-ASA agents, the AGA recommends treating patients with extensive mild-to-moderate ulcerative colitis with standard-dose (2–3 grams/day) mesalamine or

diazo-bonded 5-ASA [25]. When low-dose (<2 grams/day) [19, 34–36], standard-dose (2–3 grams/day) [34–40], and high-dose (>3 grams/day) [19, 35, 37, 38, 41] 5-ASA concentrations were compared across 18 randomized control trials (RCTs), all were superior to placebo for the induction of remission. Standard- and low-dose were superior to placebo for the maintenance of remission, with the standard-dose being superior to low-dose mesalamine. A meta-analysis of four RCTs for left-sided ulcerative colitis found that a combination treatment with 5-ASA-containing enemas plus oral 5-ASA derivatives was more effective that oral 5-ASA-containing compounds alone for the induction of remission [42]. If there is more extensive or more active colitis, then higher doses of oral 5-ASA up to 4.8 grams/day may be necessary to achieve remission [43].

In patients who fail to reach remission with appropriately dosed 5-ASA, switching classes of 5-ASA medications is not recommended because there is no difference between formulations with regard to therapeutic benefit [26]. Therefore, the next best treatment strategy is initiating oral glucocorticoids in patients who have not responded to oral 5-ASA-based compounds [26].

Glucocorticoids (Topical, Oral)

In patients who are unresponsive or intolerant to oral and rectal 5-ASA derivatives, the ACG recommends patients with left-sided ulcerative colitis start oral colonic-release budesonide (budesonide MMX®) at 9 mg/day, and patients with extensive ulcerative colitis begin oral systemic glucocorticoids [44]. In a prospective RCT, ulcerative colitis patients achieved clinical remission 17.9%, 13.2%, 12.1%, and 7.4% of the time with budesonide MMX® (9 mg daily), budesonide MMX® (6 mg daily), 5-ASA compound, and placebo, respectively, with statistical significance seen in the higher-dose budesonide MMX® group.

For patients who do not respond to budesonide MMX® or have more extensive disease, oral prednisone at a dose of 40–60 mg should be initiated. A meta-analysis demonstrated that traditional glucocorticoids are more effective than both budesonide and placebo for the induction of remission and prevention of relapse [45]. Most patients will respond within a week of starting treatment and can then begin a taper by 5–10 mg per week after 1 week at a higher dose. This approach prevents possible side effects of long-term use [45]. Once induction is achieved, glucocorticoids should not be used for maintenance of remission due to potential side effects. If patients cannot be tapered within 3 months without symptom relapse to less than 10 mg daily of prednisone (or its equivalent), they are considered to have steroid-dependent ulcerative colitis and typically require escalation to other longer-term maintenance therapy to avoid chronic steroid dependency.

Moderate-to-Severe Disease

Selecting induction therapy for patients with moderate-to-severe ulcerative colitis should account for several factors including access to an infusion center and medical care providers, coverage of medication costs by payers, patient characteristics (e.g., age, comorbidities), patient compliance, patient preferences, prior therapies for ulcerative colitis, risk of adverse events (e.g., infection, malignancy), and plan for long-term maintenance therapy [46]. Due to the complexity of the decision, significant variability in treatment patterns exists among ulcerative colitis patients [47].

5-ASA Compounds (Topical, Oral)

While 5-ASA-based therapy is effective in mild and moderate disease, it is not useful for treating severe disease. One meta-analysis showed that patients with moderately active disease demonstrated benefit with 2.4 grams/day of oral 5-ASA, but glucocorticoid therapy remained more effective for patients with severe disease [48]. Thus, 5-ASA derivatives are not often prescribed for this cohort of patients.

Glucocorticoids

For moderate disease, oral budesonide or colonic-release budesonide (budesonide MMX®) can be used for induction of remission. In both a dose-finding RCT and multicenter RCT of budesonide MMX® (9 mg daily) in mild-to-moderate disease, improved efficacy for induction of combined clinical and endoscopic remission at week 8 as compared to placebo was demonstrated [40]. In addition, patients in the budesonide and control groups experienced similar rates of adverse events.

However, systemic glucocorticoids remain the cornerstone of induction therapy for moderate-to-severe disease of any extent according to both small prospective studies and meta-analyses of these trials, which reported significant benefit with the use of systemic glucocorticoids compared to placebo [40].

Immunomodulators

Thiopurines and methotrexate are slow acting and do not induce remission in moderate-to-severe ulcerative colitis [49–52]. In a multicenter study using methotrexate for induction, an increased number of patients achieved steroid-free remission, but this did not reach statistical significance [53]. For this reason, the ACG and AGA do not recommend immunomodulator monotherapy for the induction of remission [24, 25, 28, 47]. Thus, most patients with moderate-to-severe ulcerative colitis are given a biologic agent or small molecule JAK inhibitor for induction of remission.

Tofacitinib, the only approved small molecule, is a non-selective inhibitor of the Janus kinas enzyme and preferred

Table 45.4 Pivotal trials for induction of UC

Drug	Approval by the FDA for UC	Pivotal studies	Number of patients randomized	Dosage	Measure of induction	Rate of induction/clinical response	Side effects
Infliximab [108]	2005	ACT 1 and 2	364; 364	5 mg/kg and 10 mg/kg	Clinical response: decrease in Mayo score by 3 or 30%	Week 8 ACT 1:69% (5 mg/kg); 61% (10 mg/kg) vs 37% placebo; ACT 2: 64% (5 mg/kg) and 69% (10 mg/kg) vs 29% placebo	Serious events and infection rates were similar between treatment and placebo
Adalimumab [109]	2012	ULTRA 1 and 2	576; 494	160, 80, 40, 40 mg SC	Clinical remission: Mayo score ≤ 2 and no subscore >1 and bleeding subscore of 0	Week 8 16.5% versus 9.3%	Serious events and infection rates were similar between treatment and placebo
Golimumab [110]	2013	PURSUIT-SC	761	100, 200, 400 mg	Clinical response: decrease in Mayo score by 3 or 30%	Week 6 51.4% (200 mg), 54.9% (400 mg) and 30.3% placebo	Serious events and infection rates were similar between treatment and placebo
Vedolizumab [55]	2013	GEMINI	374 randomized; 521 open label	300 mg every 4 or 8 weeks	Clinical response: decrease in Mayo score by 3 or 30%	Week 6 47.1% in vedo vs 25.5%in placebo	Serious events and infection rates were similar between treatment and placebo
Ustekinumab [56]	2019	UNIFI	968	130 mg or weight adjusted dose or 6 mg/kg	Clinical remission: Mayo score ≤ 2 and no subscore >1 and bleeding subscore of 0	8 weeks 16% versus 16% versus versus 5%	Serious events and infection rates were similar between treatment and placebo
Tofacitinib [54]	2019	OCTAVE 1 and 2	598; 541	10 mg po BID	Clinical remission: Mayo score ≤ 2 and no subscore >1 and bleeding subscore of 0	8 weeks OCTAVE 1: 18% vs 8% OCTAVE 2: 17% vs 4%	Increased zoster; increased overall infection and serious infection

by some because it is an oral agent. Tofacitinib was studied in the OCTAVE 1 and OCTAVE 2 induction and maintenance trials. Both trials, each with over 500 patients, reported significantly increased clinical remission at 8 weeks with 10 mg daily of tofacitinib compared to placebo (18.5% versus 8.2%; $p = 0.007$) and significantly increased maintenance of remission at 52 weeks with 5 or 10 mg compared to placebo (34.3% versus 40.6% versus 11.1%; $p < 0.001$); there was a significantly increased rate of infectious complications, particularly herpes zoster in the tofacitinib cohort (Table 45.4) [54].

Biologic Agents/Biosimilars

Three anti-TNFα agents (infliximab, adalimumab, golimumab), an $\alpha_4\beta_7$ anti-integrin (vedolizumab), an anti-IL-12/23 (ustekinumab), and a small molecule JAK inhibitor (tofacitinib) are all effective for the induction of remission in moderate-to-severe ulcerative colitis as compared to placebo. A total of 16 RCTs have compared all these agents individually to placebo; each trial looked at induction of remission at the 6- to 8-week timepoint and maintenance of remission at 30–54 weeks. All agents were superior to placebo with regard to both induction and remission. The potential benefit of vedolizumab is its gut selectivity offering a theoretically improved safety profile. The induction trial, GEMINI 1, randomized 374 patients to vedolizumab versus placebo and found that 16.9% and 40.9% had achieved clinical remission and mucosal healing, respectively, at 6 weeks as compared to 5.4% and 24.8% in the placebo arm [55].

Ustekinumab, the most recently approved biologic agent for ulcerative colitis, also should have good safety profile and low rate of alloimmunity. One trial randomized patients to treatment or control and found significantly improved rates of 8-week clinical remission among both doses of ustekinumab compared to placebo (15.6% versus 15.5% versus 5.3%; $p < 0.001$) [56].

Until the recent VARSITY trial, no clinical trials have compared each of the anti-TNFs to one another [57–59]. Observational trials that have compared infliximab to adalimumab in biologic-naïve patients suggest that the rates of glucocorticoid usage and hospitalization were lower in infliximab-treated patients [60, 61]. In addition, a network meta-analysis recently compared infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, and tofacitinib and found superiority of infliximab to adalimumab (Table 45.4) [62].

The VARSITY trial compared vedolizumab to adalimumab in moderate-to-severe ulcerative colitis and found the rate of clinical remission at week 52 was significantly higher in vedolizumab- versus adalimumab-treated patients (31.3% versus 22.5%; $p = 0.006$) as well as endoscopic improvement (39.7% versus 27.7%; $p < 0.001$). Based on all this data, the AGA now recommends the use of infliximab or vedolizumab for induction of remission in biologic-naïve patients rather than adalimumab. The AGA also recommends that in those patients who are biologic-naïve, tofacitinib only be used in the context of a clinical trial or registry study [25, 47].

In patients naïve to both immunomodulators and anti-TNF agents who also have a normal thiopurine methyltransferase activity, the UC-SUCCESS clinical trial reported that combination therapy of infliximab and azathioprine had superior rates of 16-week remission compared to monotherapy [63]. Therefore, the ACG recommends combining monoclonal antibodies with a thiopurine or methotrexate rather than monoclonal antibody or thiopurine monotherapy, despite a lack of evaluation of thiopurines with other monoclonal antibodies that likely have a lower immunogenicity profile [64].

The first biosimilar to infliximab, CT-P13, was approved by the European Medicines Agency in 2013 and the US Food and Drug Administration in 2016 [65, 66]. In 2015, the first prospective observational study of CT-P13 was published, reporting that 56% of ulcerative colitis patients achieved remission at week 14 [67]. A later study of 144 patients with ulcerative colitis found that 56% achieved remission at week 14 [68]. The efficacy of CT-P13 for induction therapy on mucosal healing was evaluated in a prospective multicenter study of 63 consecutive ulcerative colitis patients. Mucosal healing was detected in 48% and clinical response in 83% at 14 weeks, both of which are higher than the results reported in the original infliximab trials [69]. This suggests biosimilars may be quite effective for induction, although not mentioned in either the ACG and AGA guidelines.

Severe/Fulminant Disease

As previously stated, acute severe ulcerative colitis (ASUC) is defined as 6 or more bowel movements per day plus at least one sign of systemic toxicity including tachycardia, fever, anemia (hemoglobin <10.5 g/dL), or elevated inflammatory markers (ESR > 30 mm/hour) [18]. Patients with ASUC should be admitted to the hospital for inpatient management, disease evaluation, intravenous medication delivery when needed, and surgical consultation. Up to 25% of patients with ulcerative colitis may develop ASUC [70], and those who require a colectomy (40%) represent a higher risk cohort [70]. At the time of hospitalization, patients should be tested for *Clostridium difficile* toxin and have a flexible sigmoidoscopy to assess disease severity and assay for cytomegalovirus (CMV) infection. Patients should be started on venous thromboembolism prophylaxis, and pain should be managed without opioids or nonsteroidal anti-inflammatory medications when possible.

Glucocorticoids

Intravenous systemic glucocorticoids are the mainstay of treatment of ASUC. If a patient fails to respond after 3–5 days, then medical therapy with either infliximab or cyclosporine should be introduced. If a patient achieves remission with infliximab, then he/she should continue with the same therapy for maintenance. If a patient reaches remission with cyclosporine treatment, then the ACG and AGA guidelines recommend transitioning to thiopurines or vedolizumab for the maintenance of remission [24, 47].

The efficacy of glucocorticoids for ASUC was first established in an open-label series of 49 patients given 60 mg of daily prednisolone along with topical hydrocortisone enemas that found 73% of patients were in remission at day 5. Of the patients in remission, 47% maintained their remission, and 18% required surgery [71]. In a larger systematic review of 32 studies including 1948 adult patients, the mean response rate to intravenous glucocorticoids was 67% with only 27% requiring colectomy during the index hospitalization [72]. Further analysis revealed no benefit to a daily dose greater than 60 mg and that the dose could be given in one or more infusions without any change in efficacy. Due to these studies, the AGA recommends using methylprednisolone (60 mg/day) or hydrocortisone (100 mg 3–4 times/day) to induce remission in patients with ASUC [47].

If a patient fails to respond after 3–5 days, then he/she is unlikely to respond to further glucocorticoids alone, and salvage medical therapy with either cyclosporine or infliximab and surgery should be considered. The exception to this recommendation is if the patient is infected with *Clostridium difficile* or CMV. In this case, it is most important that the infectious etiology is evaluated and treated prior to induction with cyclosporine or infliximab.

Immunomodulators (Calcineurin Inhibitors)

The first study investigating cyclosporine for ASUC was a randomized trial of 20 patients relegated to cyclosporine

4 mg/kg/day versus placebo. At 7 days, 9 of 11 patients treated with cyclosporine demonstrated a clinical response versus none in the placebo arm [73]. In other studies, short-term efficacy has been reported [74], but long-term follow-up suggested 80% ultimately required a colectomy [74, 75]. Interestingly, these colectomy rates were lower in thiopurine-naïve patients who were prescribed thiopurines as maintenance at the same time as cyclosporine [75–77]. One study aiming to understand the variable efficacy with different dosages found that clinical response and colectomy rates were similar with 2 mg/kg/day of cyclosporine as compared to 4 mg/kg/day. Thus 2 mg/kg/day is the recommended dose for the treatment of ASUC.

A RCT comparing cyclosporine versus infliximab in patients with ASUC randomized 115 patients across 27 institutions to cyclosporine (2 mg/kg/day for 1 week followed by oral cyclosporine) or infliximab (5 mg/kg at weeks 0, 2, and 6) [78]. In the short-term follow-up, treatment failure, defined as absence of day 7 clinical response, relapse between day 7 and day 98, or absence of steroid-free remission at day 98, was similar in both groups (60% versus 54%). During the long-term follow-up, there was no difference in colectomy-free survival at 1 and 5 years between the treatment arms (70.9% and 61.5%, respectively, in patients who received cyclosporine and 69.1% and 65.1%, respectively, in those who received infliximab) [78]. Another RCT, the CONSTRUCT trial, compared differences in quality of life and healthcare costs. No differences were reported between cyclosporine and infliximab with regard to quality-adjusted survival, frequency of colectomy, time to colectomy, or adverse events (including mortality) [79]. Another multicenter study using registry data from 740 patients treated with cyclosporine or infliximab reported similar colectomy and mortality rates [80].

Biologic Agents/Biosimilars

A key RCT of infliximab for ASUC included 45 patients not responding to 4 days of glucocorticoid therapy. These patients were randomized to a single infusion of infliximab 5 mg/kg versus placebo. Among the 24 randomized to infliximab, only 7 patients required a colectomy at month 3, which was significantly less compared to the 14 of 21 in the placebo group [81]. Many studies have since followed and confirmed the short-term efficacy of infliximab in ASUC with long-term colectomy-free survival of 71%, 64%, 59%, and 53% at 3, 12, 36, and 60 months, respectively [82–84]. Due to the apparent efficacy of infliximab, additional trials have been focused on how to optimize infliximab dosing, owing to the significant fecal drug loss during a colitis flare [85]. It is possible to significantly decrease colectomy rates with three induction doses within 24 days as compared to standard dosing in the first month (7% versus 40% colectomy rates). However, by 3 months no differences were seen in colectomy rates [86].

No safety or efficacy data exist regarding the use of adalimumab, golimumab, vedolizumab, and ustekinumab as rescue therapy in ASUC. Therefore, formal societal recommendations do not support their use in this setting, and medical salvage therapy remains confined to cyclosporine or infliximab. The decision to choose one over the other is related to physician preference and overall familiarity with the drug. This likely explains why infliximab is more often used, as providers are typically more familiar with prescribing, dosing, and managing adverse events associated with infliximab contrasted to cyclosporine.

The ability to use either infliximab or cyclosporine after the other in the setting of failed salvage therapy is not well supported. A small retrospective review of 10 patients receiving infliximab after failing cyclosporine and 9 patients receiving cyclosporine after infliximab had remission in the 30–40% range and severe adverse outcomes in 16% including 1 death [87]. However, other studies have shown that cyclosporine induction can be safely used after infliximab failure, but colectomy rates are as high as 60% at 1 year in this setting [88]. Overall, systematic reviews of this approach suggest an increased risk of adverse events and a significant colectomy rate [89]. Thus, an attempt at salvage therapy with multiple agents is not generally recommended.

Limited studies on the safety and efficacy of CT-P13, the first biosimilar to infliximab, show that CT-P13 is safe in the setting of ASUC with similar efficacy to infliximab. The first study included 63 patients of which 24 were in an acute flare. Mucosal healing was achieved in two-thirds of patients by the end of induction therapy [69]. The second study investigated infliximab versus an infliximab biosimilar among 83 patients and found the biosimilar to be just as effective as infliximab for rescue therapy; clinical response following three induction doses was 81% and 77% in the infliximab and biosimilar groups, respectively, with endoscopic remission rates of 42% with infliximab and 32% with the biosimilar. The authors concluded that either could be used with comparable efficacy for rescue therapy, but maintenance should be continued following induction [90].

Maintenance of Remission

Once clinical remission has been achieved from the aforementioned treatment options, the management goal changes to maintenance of remission or preventing clinical and endoscopic relapse. Some patients, with ulcerative proctitis and less than one flare per year responsive to topical mesalamine, do not require ongoing maintenance therapy. These patients typically enjoy long-term remission without relapse, and their disease generally responds to topical mesalamine if it does. In contrast, the patients that most often require maintenance therapy are those with ulcerative proctitis and more

than one disease flare per year, all patients with ulcerative proctosigmoiditis, and all patients with ulcerative colitis proximal to the sigmoid colon which includes left-sided colitis and extensive colitis [91]. The choice of maintenance therapy depends on the specific agent used to induce remission, anatomical distribution of disease, patient preferences, clinician preferences, and insurance coverage and cost.

5-ASA Compounds (Topical, Oral)

In patients with previous moderate-to-severe disease, 5-ASA therapy is not recommended as it is unlikely to be effective. Similarly, in patients with mild-to-moderate disease who have achieved remission with immunomodulators, monoclonal antibodies, or tofacitinib, there is no utility in continuing 5-ASA agents for the maintenance of remission. However, in patients with mildly active proctitis, rectal 5-ASA (1 gram/day) can be used for maintenance of remission. A meta-analysis of seven trials reported improved remission in patients treated with 5-ASA as compared to placebo [92]. In addition, time to relapse was longer in those treated with 5-ASA agents as compared to placebo.

If the patient has mildly active left-sided or extensive ulcerative colitis, then oral 5-ASA derivative therapy (at least 2 grams/day) can be used as maintenance therapy. A meta-analysis of 11 trails demonstrated superior efficacy of oral 5-ASA-containing compounds compared to placebo for the maintenance of remission [92]. While standard- to high-dose approaches were significantly better than a low-dose prescription, the type of 5-ASA compound was not predictive of relapse.

Glucocorticoids

Budesonide MMX® has not been studied for the maintenance of remission of previously mild-to-moderate or moderate-to-severe ulcerative colitis. Both the ACG and AGA recommend that systemic glucocorticoids not be used for maintenance of remission but rather tapered over the course of 8–12 weeks due to their side effect profile and potential complications [38, 93–95].

Immunomodulators

Four trials have compared thiopurines versus placebo, and three trials have compared thiopurines to 5-ASA-containing compounds for the maintenance of remission [49, 52, 96–100]. Remission was defined either as prevention of relapse or ability to maintain glucocorticoid-free remission. On meta-analysis, thiopurines were more effective than placebo and 5-ASA. Thiopurine therapy also provided clinical benefit when treating patients who had failed or could not tolerate sulfasalazine or mesalamine [101]. Thus, the ACG and AGA recommend thiopurines can be used for maintenance of remission.

In contrast, methotrexate was not found to be superior to placebo in the maintenance of remission in two separate RCTs [102, 103]. In one of the studies, the US-based Methotrexate Response in Treatment of Ulcerative Colitis (MERIT-UC) trial, 66% of methotrexate-treated patients experienced relapse as compared to 63% given placebo [102, 103]. Therefore, the AGA does not recommend using methotrexate as monotherapy for the maintenance of remission.

Tofacitinib has shown efficacy in maintenance after control of moderate-to-severe ulcerative colitis. The maintenance tofacitinib trial compared 52-week remission rates among tofacitinib at 5 mg twice daily and 10 mg twice daily versus placebo and found remission rates were 34.3%, 40.6%, and 11%, respectively. Of note, there were no increased adverse events (e.g., venous thromboembolism) except for increased rates of herpes zoster infection in the tofacitinib group (Table 45.5) [54].

Biologic Agents/Biosimilars

In moderate-to-severe colitis, the ACG recommends using infliximab, adalimumab, golimumab, or vedolizumab for maintenance of remission in patients who have previously achieved successful induction with each of these agents. However, the AGA does not support or refute the use of infliximab, adalimumab, golimumab, or vedolizumab for maintenance of remission [47].

In patients who had an initial response to anti-TNF agent therapy during their induction dosing, anti-TNF agents are significantly better compared to placebo for maintaining remission [57]. A systematic review and meta-analysis of six placebo-controlled double-blinded RCTs demonstrated that infliximab, adalimumab, and golimumab were all superior to placebo in the maintenance of remission [58]. In addition, the study also reported no one particular agent was superior to another in the maintenance of remission.

Similar to the anti-TNF agents, vedolizumab is more effective in maintenance of remission as compared to placebo [58, 104]. A systematic review of 4 studies of 606 vedolizumab-treated patients found that vedolizumab was significantly superior to placebo without differences in adverse events. In addition, a trial of maintenance therapy of those that responded to induction found that 40% of vedolizumab patients maintained remission at week 52 compared to 16% who received placebo [55]. Similarly, a maintenance trial using ustekinumab reported significantly improved maintenance of clinical remission at week 44 compared to

Table 45.5 Pivotal trials for maintenance of UC

Drug	Approval by the FDA for UC	Pivotal studies	Number of patients randomized	Dosage	Measure of remission/ clinical response	Rate of Induction	Side effects
Infliximab [108]	2005	ACT 1 and 2	364; 364	5 mg/kg and 10 mg/kg	Clinical response = decrease in Mayo score by 3 or 30% at week 30 and 54	More likely to have clinical response at week 30 and 54	Serious events and infection rates were similar between treatment and placebo
Adalimumab [100]	2012	ULTRA 1 and 2	576; 494	160, 80, 40, 40 mg SC	Clinical remission: Mayo score ≤ 2 and no subscore >1 and bleeding subscore of 0	Week 52 17.3% vs 8.5%	Serious events and infection rates were similar between treatment and placebo
Golimumab [110]	2013	PURSUIT	144	100, 200, 400 mg	Clinical remission: Mayo score ≤ 2 and no subscore >1 and bleeding subscore of 0	Week 54 47% (50 mg), 49.7% (100 mg) and 31.2% (placebo)	Serious events and infection rates were similar between treatment and placebo
Vedolizumab [55]	2013	GEMINI	374 randomized; 521 open labels	300 mg every 4 or 8 weeks	Clinical remission = decrease in Mayo score by 3 or 30% at week 52	Week 52 41.8% vedo Q 8 weeks and 44.8% of vedo Q 4 weeks versus 15.9% placebo	Serious events and infection rates were similar between treatment and placebo
Ustekinumab [56]	2019	UNIFI	968	130 mg or 6 mg/ kg	Clinical remission: Mayo score ≤ 2 and no subscore >1 and bleeding subscore of 0subscore of 0	Week 44 38.4% (Q 12-week dose) vs 43.8% (Q 8-week dose) and 24% placebo	Serious events and infection rates were similar between treatment and placebo
Tofacitinib [54]	2019	OCTAVE 1 and 2	598; 541	10 mg po BID	Clinical remission: Mayo score ≤ 2 and no subscore >1 and bleeding subscore of 0subscore of 0	52 weeks 34.3% in 5 mg, 40.6% in 10 mg and 111.1% in placebo	Increased zoster; increased overall infection and serious infection

placebo (18.4% with 12-week dosing versus 43.8% with 8-week dosing versus 24% with placebo) (Table 45.5).

With regard to biosimilars, a recent study looking at the switch from infliximab to CT-P13 reported the move was safe and found no changes in 6-month disease activity scores, CRP, hemoglobin, fecal calprotectin, or drug antibody levels [105]. A later meta-analysis of 8 studies comprised of 594 inflammatory bowel disease patients found that switching patients from infliximab to CT-P13 is an effective and cost-effective strategy [106]. In addition to the ability to switch from infliximab for maintenance therapy, a multicenter observational cohort study also found that CT-P13 achieved long-term mucosal healing at week 54, again underscoring its success for maintenance of remission [107].

Conclusion

The expanding plethora of medications used to treat ulcerative colitis challenges a thorough understanding of the optimal timing and use of each agent. Appropriate triaging of medications to optimize clinical and endoscopic outcomes is based upon numerous patient and disease-specific factors including patient age, extent of inflammation, symptom severity, treatment response, and risk for adverse effects. It is important for surgeons to understand the indications, dosing, benefits, and risks of the various types of medications in order to participate in multidisciplinary care discussions and ensure optimal perioperative care following preoperative exposure to various medications. National guidelines by gastroenterologists provide a useful tool to help guide clinical practice and offer a starting point to facilitate discussions between gastroenterologists, surgeons, and patients concerned with optimizing and individualizing treatment pathways.

References

1. Byrne CM, Tan KK, Young JM, Selby W, Solomon MJ. Patient and clinician preferences for surgical and medical treatment options in ulcerative colitis. Colorectal Dis. 2014;16:285–92.
2. Goel A, Aggarwal BB. Curcumin, the golden spice from Indian saffron, is a chemosensitizer and radiosensitizer for tumors and chemoprotector and radioprotector for normal organs. Nutr Cancer. 2010;62:919–30.
3. Chandan S, Mohan BP, Chandan OC, et al. Curcumin use in ulcerative colitis: is it ready for prime time? A systematic review and meta-analysis of clinical trials. Ann Gastroenterol. 2020;33:53–8.

4. Asto E, Mendez I, Audivert S, Farran-Codina A, Espadaler J. The efficacy of probiotics, prebiotic inulin-type fructans, and synbiotics in human ulcerative colitis: a systematic review and meta-analysis. Nutrients. 2019;11:293.
5. Ford AC, Achkar JP, Khan KJ, et al. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. Am J Gastroenterol. 2011;106:601–16.
6. Tripathi K, Dunzendorfer T. Budesonide-related iatrogenic Cushing's syndrome in microscopic colitis. ACG Case Rep J. 2017;4:e5.
7. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet (London, England). 2009;374:1617–25.
8. Chaparro M, Ordas I, Cabre E, et al. Safety of thiopurine therapy in inflammatory bowel disease: long-term follow-up study of 3931 patients. Inflamm Bowel Dis. 2013;19:1404–10.
9. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT registry. Am J Gastroenterol. 2012;107:1409–22.
10. Schreiber SL, Crabtree GR. The mechanism of action of cyclosporin A and FK506. Immunol Today. 1992;13:136–42.
11. Garcia-Lopez S, Gomollon-Garcia F, Perez-Gisbert J. Cyclosporine in the treatment of severe attack of ulcerative colitis: a systematic review. Gastroenterol Hepatol. 2005;28:607–14.
12. Godat S, Fournier N, Safroneeva E, et al. Frequency and type of drug-related side effects necessitating treatment discontinuation in the Swiss Inflammatory Bowel Disease Cohort. Eur J Gastroenterol Hepatol. 2018;30:612–20.
13. Danese S, Argollo M, Le Berre C, Peyrin-Biroulet L. JAK selectivity for inflammatory bowel disease treatment: does it clinically matter? Gut. 2019;68:1893–9.
14. Agrawal M, Kim ES, Colombel JF. JAK inhibitors safety in ulcerative colitis: practical implications. J Crohns Colitis. 2020;14:S755–60.
15. Papamichael K, Vogelzang EH, Lambert J, Wolbink G, Cheifetz AS. Therapeutic drug monitoring with biologic agents in immune mediated inflammatory diseases. Expert Rev Clin Immunol. 2019;15:837–48.
16. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369:711–21.
17. Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. Gut. 2017;66:839–51.
18. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J. 1955;2:1041–8.
19. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317:1625–9.
20. Dias CC, Rodrigues PP, da Costa-Pereira A, Magro F. Clinical predictors of colectomy in patients with ulcerative colitis: systematic review and meta-analysis of cohort studies. J Crohns Colitis. 2015;9:156–63.
21. Dassopoulos T, Cohen RD, Scherl EJ, Schwartz RM, Kosinski L, Regueiro MD. Ulcerative colitis care pathway. Gastroenterology. 2015;149:238–45.
22. Fumery M, Singh S, Dulai PS, Gower-Rousseau C, Peyrin-Biroulet L, Sandborn WJ. Natural history of adult ulcerative colitis in population-based cohorts: a systematic review. Clin Gastroenterol Hepatol. 2018;16:343–56.e3.
23. Narula N, Marshall JK, Colombel JF, et al. Systematic review and meta-analysis: infliximab or cyclosporine as rescue therapy in patients with severe ulcerative colitis refractory to steroids. Am J Gastroenterol. 2016;111:477–91.
24. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. Am J Gastroenterol. 2019;114:384–413.
25. Singh S, Feuerstein JD, Binion DG, Tremaine WJ. AGA technical review on the management of mild-to-moderate ulcerative colitis. Gastroenterology. 2019;156:769–808.e29.
26. Feagan BG, Chande N, MacDonald JK. Are there any differences in the efficacy and safety of different formulations of Oral 5-ASA used for induction and maintenance of remission in ulcerative colitis? evidence from cochrane reviews. Inflamm Bowel Dis. 2013;19:2031–40.
27. Sandborn WJ, Hanauer SB. Systematic review: the pharmacokinetic profiles of oral mesalazine formulations and mesalazine pro-drugs used in the management of ulcerative colitis. Aliment Pharmacol Ther. 2003;17:29–42.
28. Ko CW, Singh S, Feuerstein JD, Falck-Ytter C, Falck-Ytter Y, Cross RK. AGA clinical practice guidelines on the management of mild-to-moderate ulcerative colitis. Gastroenterology. 2019;156:748–64.
29. d'Albasio G, Pacini F, Camarri E, et al. Combined therapy with 5-aminosalicylic acid tablets and enemas for maintaining remission in ulcerative colitis: a randomized double-blind study. Am J Gastroenterol. 1997;92:1143–7.
30. Safdi M, DeMicco M, Sninsky C, et al. A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. Am J Gastroenterol. 1997;92:1867–71.
31. Marshall JK, Thabane M, Steinhart AH, Newman JR, Anand A, Irvine EJ. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2010:Cd004115.
32. Hengge UR, Ruzicka T, Schwartz RA, Cork MJ. Adverse effects of topical glucocorticosteroids. J Am Acad Dermatol. 2006;54:1–15; quiz 6–8.
33. Lamet M, Ptak T, Dallaire C, et al. Efficacy and safety of mesalamine 1 g HS versus 500 mg BID suppositories in mild to moderate ulcerative proctitis: a multicenter randomized study. Inflamm Bowel Dis. 2005;11:625–30.
34. Hanauer S, Schwartz J, Robinson M, et al. Mesalamine capsules for treatment of active ulcerative colitis: results of a controlled trial. Pentasa Study Group. Am J Gastroenterol. 1993;88:1188–97.
35. Ito H, Iida M, Matsumoto T, et al. Direct comparison of two different mesalamine formulations for the maintenance of remission in patients with ulcerative colitis: a double-blind, randomized study. Inflamm Bowel Dis. 2010;16:1575–82.
36. Sninsky CA, Cort DH, Shanahan F, et al. Oral mesalamine (Asacol) for mildly to moderately active ulcerative colitis. A multicenter study. Ann Intern Med. 1991;115:350–5.
37. Kamm MA, Sandborn WJ, Gassull M, et al. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. Gastroenterology. 2007;132:66–75; quiz 432–3.
38. Lichtenstein GR, Kamm MA, Boddu P, et al. Effect of once- or twice-daily MMX mesalamine (SPD476) for the induction of remission of mild to moderately active ulcerative colitis. Clin Gastroenterol Hepatol. 2007;5:95–102.
39. Pontes C, Vives R, Torres F, Panes J. Safety and activity of dersalazine sodium in patients with mild-to-moderate active colitis: double-blind randomized proof of concept study. Inflamm Bowel Dis. 2014;20:2004–12.
40. Sandborn WJ, Travis S, Moro L, et al. Once-daily budesonide MMX(R) extended-release tablets induce remission in patients with mild to moderate ulcerative colitis: results from the CORE I study. Gastroenterology. 2012;143:1218–26.e2.
41. Sutherland LR, Robinson M, Onstad G, et al. A double-blind, placebo controlled, multicentre study of the efficacy and safety of

5-aminosalicylic acid tablets in the treatment of ulcerative colitis. Can J Gastroenterol. 1990;4:921345.
42. Ford AC, Khan KJ, Achkar JP, Moayyedi P. Efficacy of oral vs. topical, or combined oral and topical 5-aminosalicylates, in Ulcerative Colitis: systematic review and meta-analysis. Am J Gastroenterol. 2012;107:167–76; author reply 77.
43. Wang Y, Parker CE, Bhanji T, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2016;4:Cd000543.
44. Rubin DT, Cohen RD, Sandborn WJ, et al. Budesonide multimatrix is efficacious for mesalamine-refractory, mild to moderate ulcerative colitis: a randomised, placebo-controlled trial. J Crohns Colitis. 2017;11:785–91.
45. Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2011;106:590–9; quiz 600.
46. Bhat S, Zahorian T, Robert R, Farraye FA. Advocating for patients with inflammatory bowel disease: how to navigate the prior authorization process. Inflamm Bowel Dis. 2019;25:1621–8.
47. Feuerstein JD, Isaacs KL, Schneider Y, Siddique SM, Falck-Ytter Y, Singh S. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. Gastroenterology. 2020;158:1450–61.
48. Feagan BG, Macdonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2012;10:Cd000544.
49. Jewell DP, Truelove SC. Azathioprine in ulcerative colitis: final report on controlled therapeutic trial. Br Med J. 1974;4:627–30.
50. Chande N, Wang Y, MacDonald JK, McDonald JW. Methotrexate for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2014:CD006618.
51. Khan KJ, Dubinsky MC, Ford AC, Ullman TA, Talley NJ, Moayyedi P. Efficacy of immunosuppressive therapy for inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol. 2011;106:630–42.
52. Sood A, Midha V, Sood N, Kaushal V. Role of azathioprine in severe ulcerative colitis: one-year, placebo-controlled, randomized trial. Indian J Gastroenterol. 2000;19:14–6.
53. Carbonnel F, Colombel JF, Filippi J, et al. Methotrexate is not superior to placebo for inducing steroid-free remission, but induces steroid-free clinical remission in a larger proportion of patients with ulcerative colitis. Gastroenterology. 2016;150:380–8.e4.
54. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2017;376:1723–36.
55. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369:699–710.
56. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2019;381:1201–14.
57. Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2011;106:644–59, quiz 60.
58. Danese S, Fiorino G, Peyrin-Biroulet L, et al. Biological agents for moderately to severely active ulcerative colitis: a systematic review and network meta-analysis. Ann Intern Med. 2014;160:704–11.
59. Stidham RW, Lee TC, Higgins PD, et al. Systematic review with network meta-analysis: the efficacy of anti-tumour necrosis factor-alpha agents for the treatment of ulcerative colitis. Aliment Pharmacol Ther. 2014;39:660–71.
60. Singh S, Andersen NN, Andersson M, Loftus EV Jr, Jess T. Comparison of infliximab and adalimumab in biologic-naive patients with ulcerative colitis: a nationwide danish cohort study. Clin Gastroenterol Hepatol. 2017;15:1218–25.e7.
61. Singh S, Heien HC, Sangaralingham LR, et al. Comparative effectiveness and safety of infliximab and adalimumab in patients with ulcerative colitis. Aliment Pharmacol Ther. 2016;43:994–1003.
62. Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. Ann Intern Med. 2013;159:130–7.
63. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology. 2014;146:392–400.e3.
64. Vermeire S, Gils A, Accossato P, Lula S, Marren A. Immunogenicity of biologics in inflammatory bowel disease. Therap Adv Gastroenterol. 2018;11:1756283x17750355.
65. Beck A, Reichert JM. Approval of the first biosimilar antibodies in Europe: a major landmark for the biopharmaceutical industry. MAbs. 2013;5:621–3.
66. FDA approves Inflectra, a biosimilar to Remicade | FDA. 2016. Accessed 12 Jan 2020, at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm494227.htm.
67. Jahnsen J, Detlie TE, Vatn S, Ricanek P. Biosimilar infliximab (CT-P13) in the treatment of inflammatory bowel disease: a Norwegian observational study. Expert Rev Gastroenterol Hepatol. 2015;9:45–52.
68. Gecse KB, Vegh Z, Kurti Z, et al. Final results on efficacy and safety of biosimilar infliximab after one-year: results from a prospective nationwide cohort. J Crohns Colitis. 2017;11(Supplement 1):S246.
69. Farkas K, Rutka M, Golovics PA, et al. Efficacy of infliximab biosimilar CT-P13 induction therapy on mucosal healing in ulcerative colitis. J Crohns Colitis. 2016;10:1273–8.
70. Dinesen LC, Walsh AJ, Protic MN, et al. The pattern and outcome of acute severe colitis. J Crohns Colitis. 2010;4:431–7.
71. Truelove SC, Jewell DP. Intensive intravenous regimen for severe attacks of ulcerative colitis. Lancet (London, England). 1974;1:1067–70.
72. Turner D, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. Clin Gastroenterol Hepatol. 2007;5:103–10.
73. Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med. 1994;330:1841–5.
74. Campbell S, Travis S, Jewell D. Ciclosporin use in acute ulcerative colitis: a long-term experience. Eur J Gastroenterol Hepatol. 2005;17:79–84.
75. Moskovitz DN, Van Assche G, Maenhout B, et al. Incidence of colectomy during long-term follow-up after cyclosporine-induced remission of severe ulcerative colitis. Clin Gastroenterol Hepatol. 2006;4:760–5.
76. Cheifetz AS, Stern J, Garud S, et al. Cyclosporine is safe and effective in patients with severe ulcerative colitis. J Clin Gastroenterol. 2011;45:107–12.
77. Walch A, Meshkat M, Vogelsang H, et al. Long-term outcome in patients with ulcerative colitis treated with intravenous cyclosporine A is determined by previous exposure to thiopurines. J Crohns Colitis. 2010;4:398–404.
78. Laharie D, Bourreille A, Branche J, et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. Lancet (London, England). 2012;380:1909–15.
79. Williams JG, Alam MF, Alrubaiy L, et al. Infliximab versus ciclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomised trial. Lancet Gastroenterol Hepatol. 2016;1:15–24.
80. Ordas I, Domenech E, Manosa M, et al. Long-term efficacy and safety of cyclosporine in a cohort of steroid-refractory acute

severe ulcerative colitis patients from the ENEIDA registry (1989–2013): a nationwide multicenter study. Am J Gastroenterol. 2017;112:1709–18.
81. Jarnerot G, Hertervig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology. 2005;128:1805–11.
82. Bressler B, Law JK, Al Nahdi Sheraisher N, et al. The use of infliximab for treatment of hospitalized patients with acute severe ulcerative colitis. Can J Gastroenterol/Journal canadien de gastroenterologie. 2008;22:937–40.
83. Halpin SJ, Hamlin PJ, Greer DP, Warren L, Ford AC. Efficacy of infliximab in acute severe ulcerative colitis: a single-centre experience. World J Gastroenterol. 2013;19:1091–7.
84. Sjoberg M, Magnuson A, Bjork J, et al. Infliximab as rescue therapy in hospitalised patients with steroid-refractory acute ulcerative colitis: a long-term follow-up of 211 Swedish patients. Aliment Pharmacol Ther. 2013;38:377–87.
85. Brandse JF, van den Brink GR, Wildenberg ME, et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. Gastroenterology. 2015;149:350–5.e2.
86. Choi CH, Rutter MD, Askari A, et al. Forty-year analysis of colonoscopic surveillance program for neoplasia in ulcerative colitis: an updated overview. Am J Gastroenterol. 2015;110:1022–34.
87. Maser EA, Deconda D, Lichtiger S, Ullman T, Present DH, Kornbluth A. Cyclosporine and infliximab as rescue therapy for each other in patients with steroid-refractory ulcerative colitis. Clin Gastroenterol Hepatol. 2008;6:1112–6.
88. Weisshof R, Ollech JE, El Jurdi K, et al. Ciclosporin therapy after infliximab failure in hospitalized patients with acute severe colitis is effective and safe. J Crohns Colitis. 2019;13:1105–10.
89. Feuerstein JD, Akbari M, Tapper EB, Cheifetz AS. Systematic review and meta-analysis of third-line salvage therapy with infliximab or cyclosporine in severe ulcerative colitis. Ann Gastroenterol. 2016;29:341–7.
90. Kaniewska M, Moniuszko A, Rydzewska G. The efficacy and safety of the biosimilar product (Inflectra((R))) compared to the reference drug (Remicade((R))) in rescue therapy in adult patients with ulcerative colitis. Prz Gastroenterol. 2017;12:169–74.
91. Carter MJ, Lobo AJ, Travis SPL. Guidelines for the management of inflammatory bowel disease in adults. Gut. 2004;53:v1–v16.
92. Ford AC, Khan KJ, Sandborn WJ, Hanauer SB, Moayyedi P. Efficacy of topical 5-aminosalicylates in preventing relapse of quiescent ulcerative colitis: a meta-analysis. Clin Gastroenterol Hepatol. 2012;10:513–9.
93. Lennard-Jones JE, Misiewicz JJ, Connell AM, Baron JH, Jones FA. Prednisone as maintenance treatment for ulcerative colitis in remission. Lancet (London, England). 1965;1:188–9.
94. Taylor K, Gibson PR. Conventional therapy of ulcerative colitis: corticosteroids. Springer International Publishing: New York NY USA; 2017. p. 399–412.
95. Truelove SC, Witts LJ. Cortisone and corticotrophin in ulcerative colitis. Br Med J. 1959;1:387–94.
96. Ardizzone S, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi Porro G. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. Gut. 2006;55:47–53.
97. Hawthorne AB, Logan RF, Hawkey CJ, et al. Randomised controlled trial of azathioprine withdrawal in ulcerative colitis. BMJ (Clinical Research ed). 1992;305:20–2.
98. Mate-Jimenez J, Hermida C, Cantero-Perona J, Moreno-Otero R. 6-mercaptopurine or methotrexate added to prednisone induces and maintains remission in steroid-dependent inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2000;12:1227–33.
99. Sood A, Kaushal V, Midha V, Bhatia KL, Sood N, Malhotra V. The beneficial effect of azathioprine on maintenance of remission in severe ulcerative colitis. J Gastroenterol. 2002;37:270–4.
100. Sood A, Midha V, Sood N, Avasthi G. Azathioprine versus sulfasalazine in maintenance of remission in severe ulcerative colitis. Indian J Gastroenterol. 2003;22:79–81.
101. Timmer A, McDonald JW, Tsoulis DJ, Macdonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2012:Cd000478.
102. Herfarth H, Barnes EL, Valentine JF, et al. Methotrexate is not superior to placebo in maintaining steroid-free response or remission in ulcerative colitis. Gastroenterology. 2018;155:1098–108.e9.
103. Wang Y, MacDonald JK, Vandermeer B, Griffiths AM, El-Matary W. Methotrexate for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2015:Cd007560.
104. Christensen B, Colman RJ, Micic D, et al. Vedolizumab as induction and maintenance for inflammatory bowel disease: 12-month effectiveness and safety. Inflamm Bowel Dis. 2018;24:849–60.
105. Buer LC, Moum BA, Cvancarova M, Warren DJ, Medhus AW, Hoivik ML. Switching from Remicade(R) to Remsima(R) is well tolerated and feasible: a prospective, open-label study. J Crohns Colitis. 2017;11:297–304.
106. Kashani AMD, Syal GMD, Bonthala NMD, McGovern DPB, David SMD. Efficacy of infliximab biosimilar for induction and maintenance therapy in inflammatory bowel disease after switch from drug originator: a meta-analysis: 705. Am J Gastroenterol. 2017;112 Supplement 2017 ACG annual meeting:S390–S1.
107. Balint A, Rutka M, Kolar M, et al. Infliximab biosimilar CT-P13 therapy is effective in maintaining endoscopic remission in ulcerative colitis - results from multicenter observational cohort. Expert Opin Biol Ther. 2018;18:1181–7.
108. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353:2462–76.
109. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142:257–65.e1–3.
110. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146:85–95; quiz e14–5.

Medical Therapy for Crohn's Disease

46

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Key Concepts

- Antibiotics, probiotics, diets, and fecal transplant do not appear offer clinically significant benefit for treatment of Crohn's disease.
- Exclusive enteral nutrition is beneficial in children but has not yet be shown to be of benefit in adults.
- 5-Aminosalicylates are widely recognized to have role in treatement of mucosal ulcerative colitis, but have a very limited role in the treatment of CD.
- Budesonide is efficacious for induction of clinical remission for CD patients when compared with placebo.
- Systemic steroids are indicated for induction of remission, but not for maintenance of remission due to its side effects; steroid dependency is an indication for surgery.
- Thiopurine and methotrexate monotherapy is not efficacious for induction of remission, but for maintenance of remission as a steroid-sparing agent; these medications are most commonly used in combination with biologics to decrease immunogenicity to the biologic agent.
- Biologic agents are indicated for induction and maintenance of remission in patients with moderate-to-severe Crohn's disease.
- Biosimilars present no differences in efficacy or safety compared to their originator compounds and have the advantage of lower cost.
- Therapeutic drug monitoring (TDM) of drug levels and anti-drug antibodies (ADA) allows more precise management of patients with Crohn's disease.

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History

The first case series describing regional enteritis was published in 1932 by a group of physicians at Mount Sinai Medical Center in New York City [1–3]. A senior surgeon, Dr. A.A. Berg, operated on 12 patients with terminal ileitis, and Drs. Leon Ginzburg and Gordon Oppenheimer wrote the initial manuscript. Of note, after Dr. Berg declined to be involved as a coauthor, Dr. Burrill Crohn was brought in as a third contributing author with two additional patients. At that time, the journal's publication policy was to order the authors alphabetically – thus Dr. Crohn was the first author, and regional enteritis subsequently became known as Crohn's disease, not Berg's disease, nor Ginzburg-Oppenheimer disease [3, 4].

Introduction

As surgeons who care for patients with inflammatory bowel diseases (IBD), just as we expect IBD-gastroenterologists (GI) to be facile with surgical treatment options, it is their expectation that we be facile with the medical therapies to which our patients are exposed. The treating colorectal surgeon should be able to manage these medications in the perioperative period, and may be called upon as part of the multidisciplinary team to provide perspective on initiation, continuation, or escalation of medical therapies as part of surgical decision-making. The types and timing of medical therapy may also have implications for the type and timing of surgical intervention. In this chapter, we will review the profiles of the most commonly prescribed medical therapies for Crohn's disease (CD). We will focus the role of each class of medications has in the induction and maintenance of remission, efficacy, commonly prescribed forms and dosing schedules, side-effect profiles, and perioperative management for these complex patients. Interested readers are referred to the recommendations of the American

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Gastroenterology Association (AGA) 2013 Guideline on Medical Management in Crohn's [5], the American College of Gastroenterology (ACG) 2018 Crohn's Guideline [6, 7], and the European Crohn's and Colitis Organization (ECCO) 2020 Crohn's Guideline [8]. A summary of the treatment recommendations for these guidelines is shown in Table 46.1.

The AGA guideline [5], which is now the oldest and due to be updated, was limited to 9 recommendations on the use of thiopurines, methotrexate (MTX), and TNF inhibitors (TNFi's) for the induction of remission and maintenance of remission, while the ACG guideline is the most comprehensive and made a total of 60 recommendations which were stratified based on the severity of illness; mild-to-moderately severe disease/low-risk disease vs. moderate-to-severe disease/moderate-to-high-risk disease vs. severe fulminant disease vs. perianal disease. The ACG guideline also made recommendations regarding postoperative prophylaxis including smoking cessation and that intra-abdominal abscesses should be treated with antibiotics and either radiologic or surgical drainage [2]. Finally, the recently updated ECCO guideline recommendations were stratified in a manner similar to the AGA's based on induction (10 recommendations) and maintenance (13 recommendations) of remission, plus perianal disease (7 recommendations) for a total of 30 recommendations.

In contrast to ulcerative colitis (UC), for which surgery is curative for the colonic and rectal manifestations of disease, patients with CD have a life-long disease for which surgery only manages the complications of the inflammatory, fibrostenotic, penetrating, and neoplastic manifestations of disease. Surgery will often "reset the clock," and many patients will be able to be managed expectantly without ongoing medical therapy and a colonosocpy 6 months after ileocolic resection to assess disease activity. However, those with high-risk phenotypes (Table 46.2) will require active postoperative medical therapy to prevent or delay post-operative recurrence (POR).

Table 46.2 Example of high-risk features as indications for more aggressive medical therapy in luminal CD

Male sex	Short-interval recurrence(s)
Young onset of disease	Multifocal disease (*i.e.*, diffuse jejunoileitis)
Active smokers	Granulomas
Penetrating phenotype	Perianal disease

Table 46.1 Summary of medication treatment recommendations by the various society guidelines. Note AGA and ECCO recommendations based on induction vs. maintenance, ACG based on severity.

	Induction of remission in CD			Maintenance of remission in CD			
Medication	AGA[5]	ACG[6]	ECCO[8]	AGA[5]	ACG[6]	ECCO[8]	Notes
Antibiotics	--	No*	No	--	--	No	* Role limited to treatment of intra-abdominal abscesses, perianal cellulitis, or to decrease perianal fistula drainage amount
Oral 5-ASA	--	No*	No	--	No	No	*For mild colonic symptoms
Rectal 5-ASA	--	--	No	--	--	No	--
Antimotility, diet, etc.	--	Yes	--	--	--	--	--
Topical steroids (budesonide)	--	Yes	Yes	--	No (>4 mo.)	Yes	Ileal or right colonic disease
Systemic steroids	--	Yes	Yes	--	No	No	Short-term only
TPMT testing	--	Yes	--	--	--	--	Before TP initiation
TP monotherapy	No	No	No	Yes	Yes +/−TNFi	Yes*	*For steroid sparing/fistulae otherwise recommend *against* early introduction in new patients; recommend continuation in those already on TP in remission due to risk of relapse
MTX monotherapy	No	Yes	--	Yes	Yes +/−TNFi	Yes*	*Steroid sparing; parenteral recommended
TNFi monotherapy	Yes	Yes	Yes	Yes	Yes	Yes	Steroid and IMM resistance; severe disease; fistulae; perianal disease
TNFi combo-therapy	Yes	Yes, if naïve to both	Yes	Yes	Yes, over monotherapy	Yes	TPs or MTX; see SONIC trial [70]
Vedolizumab	--	Yes	Yes	--	Yes	Yes	+/− IMM
Ustekinumab	--	Yes*	Yes	--	Yes	Yes	*In TNFi exposed or naïve
Cyclosporine	--	No	--	--	--	--	--
Tofacitinib	--	--	No	--	--	No	Not yet FDA-approved for CD

Microbiome Therapies

Antibiotics

Overall, antibiotics are probably not efficacious for induction or maintenance of remission in CD [9–11]. A systematic review with meta-analysis from 2011 found that in active CD, compared to placebo, antibiotics may be efficacious (RR 0.85, 95% CI 0.73–0.99, $p = 0.03$); however this pooled analysis combined a number of different antibiotics, and the excessive heterogeneity precluded definitive conclusions. The Cochrane collaboration updated their review in 2019 and found 13 randomized controlled trials (RCT) examining the role of antibiotics for the induction and maintenance of remission [12]. They concluded that although antibiotics may be modestly beneficial, this may not be clinically significant based on moderate- to high-quality evidence. Although there was high-quality evidence that antibiotics are safe, efficacy for maintenance of remission was not demonstrated and remains uncertain. Therefore, the ACG and ECCO guidelines do not recommend them for induction or maintenance of remission, nor for maintenance of remission, consistent with North American practice [11].

Although antibiotics likely do not have a definitive role in the induction or maintenance of remission for luminal or perianal CD, they obviously have a role in the management of septic complications of penetrating CD; aspirates from percutaneously or intraoperatively drained abdominopelvic abscesses should be sent for aerobic, anaerobic, and fungal cultures with sensitivities to guide optimal management [6, 13]. The Toronto Consensus statement concluded that antibiotics only have a role in initial symptomatic control of perianal disease [14]. Of note, ciprofloxacin has recently had a black box warning for tendinopathy, especially in older patients also receiving corticosteroids [15]. Low-dose metronidazole may be used to decrease drainage. The principles of management of perianal CD are covered in another chapter.

Probiotics

Probiotics are beneficial microorganisms that can alter the gut's microbiota, metabolic activity, and immunomodulation to confer patient benefit. These bacteria and fungi alter microbial diversity through competitive inhibition of other microbes, enhance mucosal barrier function via the production of short-chain fatty acids, and interact with intestinal dendritic cells to instigate an anti-inflammatory response. The microorganisms must be of human origin, nonpathogenic, and able to survive the gastrointestinal transit in order to be beneficial. Unfortunately, multiple meta-analyses suggest that probiotics are ineffective for induction and maintenance of remission in patients with CD and may not be without risks [16–18].

Dietary Interventions

Similarly, dietary interventions have failed to demonstrate efficacy for the induction and maintenance of remission [19]. The Cochrane group performed a meta-analysis of 18 RCTs including 1,878 patients who received dietary intervention. Interventions included high-fiber, low-refined carbohydrate diets, low-microparticle diets, low-calcium diets, symptom-guided diets, and highly restricted organic diets. In general, efficacy was suggested by several of the diets, particularly the symptom-based and several restrictive diets; but overall the studies were heterogenous, prone to bias, and of low- or very-low quality of evidence. The authors made no firm conclusions but did note that there are several well-designed ongoing RCTs in over 500 patients examining this topic, and that the meta-analysis would be updated subsequently.

Fecal Transplant

The other manner in which a patient's microbiota can be altered is via fecal microbiota transplant (FMT). This management has proven useful in treating recurrent *Clostridium difficile* infections (CDI), but has not been adequately studied nor shown efficacy in CD. A recent small pilot RCT of 17 patients with CD who achieved remission with steroids and underwent FMT did not demonstrate the primary efficacy endpoint, although endoscopic scores and C-reactive protein (CRP) levels were significantly better in the FMT-treated patients [20]. A meta-analysis suggested FMT may have efficacy in UC but not Crohn's; no safety concerns were raised by this study [21]. The Cochrane groups meta-analysis on this topic suggested a lack of available studies of FMT for CD, with no studies examining the role of FMT for induction of remission in CD [22]. Interestingly, a separate meta-analysis of FMT for CDI in IBD patients demonstrated efficacy, just as in the non-IBD population [23]. Of note, on March 12, 2020 the Food & Drug Administration (FDA) released a Safety Alert after 2 patients with chornic medical conditions who received FMT for CDI died of complications related to FMT-related transmission of enteropathogenic and/or shigatoxin-releasing *E. coli*.

Exclusive Enteral Nutrition

A promising form of nutritional intervention specific to CD is exclusive enteral nutrition (EEN). EEN is a nutritional intervention where patients are placed on a full-liquid monodiet with a commercially available nutritional supplementation [24]. In pediatric CD patients, EEN has been shown to

be more effective than steroids for induction of remission, but this has not yet been replicated in adult CD patients [25]. Presently, some centers use EEN in adults while they are tapered off steroids as they await elective surgery [26].

5-ASA Therapy

5-Aminosalicylate (5-ASA) moieties, which have a large role in the medical treatment of UC, are widely recognized to have a limited role in the treatment of CD. The indication for this class of medications is for the induction and maintenance of remission in mild-to-moderate UC. These medications are covered more fully in the Medical Therapy of UC chapter. The mechanism of action of 5-ASAs is as topical anti-inflammatory agents, which explains their efficacy in mucosal UC as opposed to CD, which is a full-thickness bowel disease.

Multiple well-designed double-blinded placebo-controlled RCTs of oral formations with varying dosages and meta-analyses have concluded that oral 5-ASAs lack efficacy for the induction of clinical remission for ileal, ileocolic, or colonic CD. In addition, as noted in the meta-analysis within the ECCO CD guidelines, oral 5-ASAs also lack efficacy for the maintenance of remission (RR 1.03, 95% CO 0.92. 1.16) [8].

Isolated Colonic Crohn's

Nonetheless, the question remains if there is a role for 5-ASAs in isolated colonic CD. The largest trials of 5-ASAs for colonic disease were the National Cooperative Crohn's Disease Study (NCCDS) and the European Cooperative Crohn's Disease Study (ECCDS) [27, 28]. There were mixed results in the early clinical trials with mild-to-moderate disease, but these studies also lacked endoscopic or biochemical data [29]. Thus, a need exists to replace this older data with new studies which include modern assessments tools [30]. Some providers will use 5-ASAs in patients with mild colonic CD and assess response, in a treat-to-target manner with mucosal healing as the endpoint. 5-ASAs are not approved for CD in the USA but are approved in Europe, Canada, Australia, and Japan. Of note, the ACG and ECCO treatment guidelines also concluded that 5-ASAs lack efficacy for induction of remission in CD [6, 8].

Crohn's Proctitis

Despite the overall lack of efficacy for the induction or maintenance of remission of CD, there may be a role for 5-ASA rectal formulations for patients with proctitis [31]. Proctitis may result in disabling fecal urgency, tenesmus, and agoraphobia. 5-ASA enemas and suppositories may have a role in palliating these symptoms as adjuncts to primary medical therapy. Mesalamine suppositories are typically prescribed at doses of 500–1000 mg per rectum at bedtime, with mesalamine enemas at 4 grams/60 cc enemas 1–2 times per day. These formulations are typically well-tolerated but often require prior authorization and/or may be non-formulary for many commercial insurance plans.

Side-Effects and Perioperative Management

5-ASA medications have an excellent safety profile and may be resumed postoperatively. The most common side-effects of these medications include gastrointestinal (GI) upset, headaches, and skin hypersensitivity to sun [29]. Rare side-effects include bone marrow suppression, fever, hemolytic anemia, hepatitis, hypersensitivity reactions, pancreatitis, pneumonitis, and rash. Patients who take sulfasalazine must also take folic acid (1 mg daily) because the medication depletes folic acid stores [29, 31].

Corticosteroids

Topical Corticosteroids

Budesonide is a synthetic glucocorticoid which is administered as an oral enteric-coated capsule which resists gastric degradation. Budesonide has high first-pass metabolism and very limited systemic absorption and is generally well-tolerated [32]. It comes in 3 mg capsule and is dosed up to 9 mg per day. Of note, budesonide is the mainstay of therapy for induction of remission in microscopic and collagenous colitis. In order to target small bowel proximal to the terminal ileum, the "open-capsule technique" may be chosen for administration; half of the daily dose (one full 3 mg capsule and half of one 3 mg capsule) is opened and sprinkled on food. The Multimatrix® (MMX®) formulation allows for controlled release for use in the colon [33].

A Cochrane meta-analysis found that budesonide was efficacious in the induction of clinical remission for CD patients, when compared with placebo [34]. This meta-analysis also stated that budesonide was not as effective as conventional steroids but was significantly safer. They also found a lack of efficacy for maintenance of remission. The ACG and ECCO guidelines recommend budesonide for the induction of remission in mild-to-moderate ileal or right-sided colonic disease [6, 8]. For maintenance of remission, the ACG guidelines suggest it not be used for more than 4 months, but the ECCO guidelines allow for maintenance therapy with budesonide [6, 8].

Table 46.3 Side-effects of budesonide with long-term use

Frequency	Organ system	Effect
Common	Endocrine	Cushingoid features, hypokalemia
	Psychiatric	Mood changes
	Optic	Blurry vision
	Cardiac	Palpitations
	GI	Dyspepsia
	Skin	Skin reactions
	Reproductive	Altered menses
Uncommon	Nervous system	Tremor
Rare	Musculoskeletal	Reduced growth velocity
	Systemic	Anaphylaxis

Adapted with permission from: O'Donnell and O'Morain [32]. Copyright © 2010 Sage Publications

Table 46.4 Glucocorticoid conversion table

Class (T ½ in hours)	Corticosteroid	Equivalent dose in mg	Potency relative to hydrocortisone (anti-inflammatory/ mineralocorticoid)
Short-acting (8–12)	Cortisone	25	1/1
	Hydrocortisone	20	0.8/0.8
Intermediate-acting (18–36)	Prednisone	5	4/0.8
	Prednisolone	5	4/0.8
	Methylprednisolone	4	5/0.5
	Triamcinolone	4	5/0
Long-acting (36–54)	Betamethasone	0.6	30/0
	Dexamethasone	0.75	30/0

Modified from: Nicolaides *et al*. [37]

Side-Effects and Perioperative Management

Although well-tolerated and safer than traditional steroids, budesonide may have side effects (Table 46.3), especially when used for prolonged periods of time. When used for less than 1 year, the side-effect profile is similar to that of placebo with rare occurrences of the clinically important side effects typically associated with traditional glucocorticoids [35]. Given the excellent safety profile of budesonide with its limited systemic absorption, budesonide may be safely held immediately before and after surgery, stress-dose steroids are *not* needed, and resumption postoperatively may not be necessary.

Systemic Corticosteroids

Traditional corticosteroids are powerful systemic anti-inflammatory drugs which were first used by Truelove and Witt for the treatment of IBD in 1955 [36, 37]. Although they are extremely efficacious as anti-inflammatories, they have an unfavorable side-effect profile which limits their clinical utility to induction of remission in otherwise medically refractory disease. A meta-analysis limited to randomized controlled trials identified 2 trials including 267 patients using standard oral glucocorticoids to induce remission in active Crohn's disease [38]. Overall, 79 of 132 patients (60%) assigned to oral glucocorticoids achieved remission compared with 42 of 135 (31%) prescribed placebo. Moreover, the number needed to treat to achieve remission in one patient with standard glucocorticoids was 3 (95% CI, 2–11), which is very low and associated with high efficacy. Both the ACG and ECCO guidelines recommend systemic steroids for induction of remission, but not for maintenance of remission [6, 8]. Steroids should not be used chronically as long-term use carries have a high risk of serious adverse events. The need for systemic steroids represents a "bad omen" or "tipping point" for patients with CD, as it is associated with a more complicated disease course. Steroid dependency is an indication for surgery.

For outpatient induction of remission, prednisone is typically prescribed at 40 mg by mouth daily and tapered by 5–10 mg per week; but this depends on what other medical or surgical options the patient, gastroenterologist, and colorectal surgeon are contemplating. Steroid conversion calculators and tables (Table 46.4) [37], widely available on the Internet, allow for conversion between enteral, parenteral, and various formulations.

Safety

Despite the substantial efficacy for induction of remission in CD, chronic corticosteroid treatment is among the most significant risk factors for postoperative infectious and/or wound complications. A summary of the toxicity of corticosteroid therapy is shown in Table 46.5 [37]. The side effects are organ-based and wide-ranging and for the most part dose- and duration-dependent. Cessation of steroid therapy will ameliorate some, but not all, of the risks of exposure to these medications. The side effects would not likely be considered acceptable, if not for the wide therapeutic effect across a wide range of human auto-inflammatory and autoimmune diseases. Many of these diseases lacked any efficacious therapy other than corticosteroids until recently. Chronic steroid use, loosely defined as more than several months, has largely fallen by the wayside as new biologic treatments with better short- and long-term safety profiles continue to be developed and marketed.

Stress-Dose Steroids and Tapering

Of note, several publications have examined the role of stress-dose steroids in the perioperative period for IBD [39–42]. In a series of steroid-dependent UC patients, only one patient developed postoperative adrenal insufficiency [39]. The authors concluded that stress-dosing was not beneficial, but all steroid-dependent patients should be monitored after surgery for symptoms of adrenal insufficiency. Two studies from Cedars Sinai had similarly questioned the utility of stress-dose steroids at the time of surgery for IBD [41, 42]. In the era of enhanced recovery, many patients receive 8 mg of intraoperative dexamethasone for postoperative nausea and vomiting prophylaxis which effectively replaces the

Table 46.5 Toxicity of chronic corticosteroid treatment

Organ system	Unwanted Effect	Notes
Systemic	Cushingoid appearance, weight gain	Occurs in >70%, 4–8% mean increase in body weight Adipose redistribution: truncal, facial, dorsocervical; occurs in ~25% >= 7.5 mg prednisone/day
	Immunosuppression	Mainly by sequestration of CD4+ T-lymphocytes in the reticuloendothelial system, and by inhibiting the transcription of cytokines; profoundly inhibits lymphocyte migration into lymph nodes
	Impaired wound healing	Decreased collagen synthesis and maturation, inhibited leukocyte/macrophage infiltration Potentially maybe overcome by epidermal-derived growth factor, TGF-beta, platelet-derived growth factor, tetrachlorodecaoxygen, and retinoic acid (vitamin A)
Endocrine	HPA-axis suppression	Wide-ranging, non-specific, symptoms may overlap with Crohn's (see Table 46.6). ***Avoid abrupt cessation of therapy***
	Hyperglycemia/diabetes	Increased insulin resistance; +risk of persistent diabetes
Musculoskeletal	Osteoporosis, avascular necrosis, fractures	Osteoblast and osteocyte suppression and apoptosis Reduced bone mineral density Osteonecrosis develops in 9–40% of adults, often misdiagnosed as lumbar symptoms
	Myopathy	Catabolic effect on skeletal muscle
Optic	Cataracts, glaucoma	Cataracts (reduced acuity) which require earlier surgical treatment -Painless glaucoma (decreased visual field) can cause permanent optic nerve damage
Cardiovascular	Hypertension, obesity, dyslipidemia, arrythmias	Higher CV event risk with >= 7.5 mg prednisone/day Risk of sudden death even with pulse therapy if pre-existing kidney/heart disease
GI	Gastroesophageal ulceration, acute pancreatitis	Ulcer/hemorrhage risk increased if concurrent NSAID use pancreatitis may be secondary to systemic lupus erythematosus (SLE), or TP treatment, rather than drug effect
Psychiatric/ Cognitive	Various	Wide range: memory impairment, agitation, anxiety, fear, hypomania, insomnia, irritability, lethargy, mood lability, frank psychosis Heightened if concomitant pre-existing conditions
Skin	Various	Atrophic skin changes, thin fragile skin; purpura; red striae

Modified from: Nicolaides et al. [37]

Table 46.6 Signs and symptoms of adrenal suppression and Addisonian crisis

Adrenal suppression	Addisonian crisis
Malaise/weakness/fatigue	Hypotension, fluid-refractory and otherwise un-explained
Nausea/vomiting/diarrhea	Hyponatremia
Abdominal pain	Unexplained hypoglycemia
Morning headache	Lethargy
Fever	Decreased consciousness/seizure/ coma
Anorexia/weight loss	
Myalgia/arthralgia	
Psychiatric symptoms	
Growth suppression (in children)	

Modified from: Nicolaides et al. [37]

need for stress-dose steroids [26]. For patients who received a short-term (1-2 weeks) of steroids preoperatively, it is our practice to simply stop them postoperatively, and for those on chronic steroids to continue post-operative corticosteroids at the same dose, or dose-equivalent, the patient was receiving preoperatively [43–45].

Chronic steroid therapy must not be stopped abruptly lest patients develop severe Addisonian crisis with circulatory collapse (Table 46.6). On the other hand, no evidence-based guidelines for steroid tapering exist [46]. When patients do present to surgery receiving corticosteroids, the rapidity with which they may be tapered depends on the chronicity of treatment. We typically reduce the dose by 50% every 5–7 days. Sometimes a slow taper with several additional weeks is required if the patient has been on steroids for a prolonged period to avoid withdrawal symptoms such as fatigue, lethargy, and depression. Testing for adrenal suppression in such cases is typically not needed; the patients can either be counseled that these uncomfortable symptoms will eventually pass, or their corticosteroid dose can be increased with a more prolonged tapering schedule. Readers are referred to the an excellent resource Glucocorticoid Therapy and Adrenal Suppression in the Internet book *Endotext* for further reading at www.endotext.org.

Immunomodulators

Thiopurines

Thiopurines (TPs), namely 6-mercaptopurine (6MP) and azathioprine (AZA), along with methotrexate (MTX), are known as immunomodulators (IMM) [5, 6, 9]. TPs are purine analogs and thus antimetabolites, which inhibit DNA and

have antiproliferative properties and proapoptotic action on activated T-lymphocytes [31]. The typical dose of AZA is 2 mg/kg daily, while 6MP is typically 1 mg/kg daily. AZA and 6MP are typically started at low doses (50 mg and 10 mg, respectively) with biweekly complete blood counts and liver function testing and given normal labs dose escalation every 2 weeks to the desired dose. Of note, the clinical effect of TP therapy takes several months, so patients are typically re-evaluated after 3 months of therapy [31].

TP Pharmacokinetics

AZA is a prodrug of 6MP, and both AZA and 6MP are prodrugs of 6-thioguanine (6TG). AZA and 6MP are converted by intracellular thiopurine methyltransferase (TPMT) to 6TG (Fig. 46.1) [47]. Clinical TPMT activity testing is critically important for patients prior to being placed on TG treatment [48]. While 80% of the population has normal TPMT metabolism, ~10% have hyperactive TPMT metabolic activity ("shunters") which leads to the accumulation of toxic secondary metabolite, increasing the likelihood of drug side-effects such as hepatotoxicity [49]. Shunters, as the name implies, also shunt drug away from the normal metabolic pathway, resulting in less clinical activity. The shunting can be overcome by using allopurinol, which inhibits secondary metabolite production, and prescribing 25% of the usual TG dose [49].

In addition to the shunters, 10% of the population are heterozygous for TPMT and have intermediate (lower than average) metabolic activity, and 0.3% of the population are TPMT deficient (homozygous). The intermediate activity patients require a higher than average dose to acquire the desirous effect, while the deficient population will not be clinically responsive to TP treatment [48, 49].

Monotherapy

Current guidelines agree that TP are efficacious at the maintenance of remission of luminal CD obtained by other means and that they are *not* efficacious for the *induction* of remission in mild-to-moderate luminal CD [5, 6, 9]. This is mainly due to their onset of action; thus they may be started concomitantly with other medications for the induction of remission, which can then be weaned (in the case of steroids) while the TPs take effect. Thus, TPs have traditionally served a role as monotherapy for the maintenance of remission in CD as a steroid-sparing agent.

Specifically, when patients were unable to be weaned off steroids, TP therapy would provide an exit strategy from the steroid dependency in patients who were able to achieve but not maintain remission without continued steroids. In a meta-analysis of placebo-controlled randomized trial in steroid-dependent patients, AZA was shown to be superior to placebo (RR 1.19, 95% CI 1.05–1.34) for maintenance of remission as a steroid-sparing agent [5]. Combination therapy will be covered below in the section on biologics.

Relative contraindications include patients with neoplasia or hematologic comorbidities [49]. MTX is a relatively safe and more widely acceptable alternative in older patients and especially in young men. The EBV status in young males is important, as young men with +EBV status are at a very small but demonstrable risk of developing hepatocellular T-cell lymphoma, a universally-fatal condition, thus TGs are avoided in these at-risk patients. In addition, EBV naïve patients are at risks of developing hemaphagocystosis.

Side Effects and Perioperative Management

The side effects of TG therapy can be significant and are shown in Table 46.7. Idiosyncratic pancreatitis is the most common dose-independent side effect; hepatitis, which is

Table 46.7 Side effects of TG therapy

Type	Toxicity	Frequency	Testing
Dose-independent	Pancreatitis	<15%	Lipase
	Flu-like symptoms	5%	Patient-reported
	Rash	4%	Patient-reported
Dose-dependent	Hepatitis	<30%	LFTs, TPMT testing
	GI intolerance	<20%	Patient-reported
	Leukopenia	10%	CBC, TPMT testing
	Agranulocytosis	0.3%	CBC, TPMT testing

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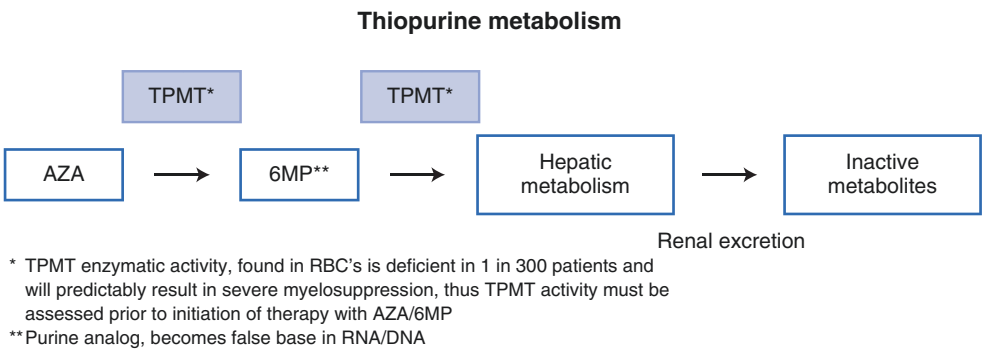

Fig. 46.1 Thiopurine metabolism

dose-dependent and whose risk increases with ongoing therapy, is the most common overall. Many patients have GI side-effects from TG therapy; CBCs are used to assess for hematologic consequences. It is controversial whether long-term use has been associated with malignancy. The best available population-based cohort data comes from the CESAME – Cancer and Increased Risk Associated with Inflammatory Bowel Disease in France study group. They suggest risk is increased in IBD patients receiving TP therapy for hematologic neoplasia including leukemia and lymphoma, non-melanoma skin cancer, cervical cancer, and urinary tract cancer. The risk of colorectal adenocarcinoma may actually be lower due to control of intestinal inflammation [50–52]. TG therapy also have a number of drug-drug interactions to be aware of including ACE inhibitors, allopurinol, anticoagulants, sulfamethoxazole/trimethoprim, and other immunomodulators including MTX and cyclosporine A [49].

TP may be safely used in the perioperative period. Although therapeutic efficacy takes several months to be observed, the half-live of these medications is very short. In addition, TPs have not been shown to be associated with postoperative complications in IBD patients [53]. Thus, most surgeons hold TP therapy in the immediate postoperative period and allow the referring gastroenterologist to reassess the need for ongoing IMM therapy.

Table 46.8 Side effects of MTX

Organ	Symptoms	Mitigation strategy
Gastrointestinal	Mucositis, diarrhea	5 mg folate weekly, switch from PO to SC/IM route
Bone marrow	Anemia, leukopenia	5 mg folate weekly
Hepatic	Steatosis, fibrosis, cirrhosis	Avoid dose >1 g
Pulmonary	Pneumonitis, PCP pneumonia	Monitor symptoms
Renal	Renal insufficiency (rare)	Monitor GFR/reduce dose
Reproductive	Teratogenic	Abstinence/contraceptive

Adapted from Bedou et al. [56]. No permission required https://www.mdpi.com/openaccess

Table 46.9 Summary of biologic medications for CD

		Dose	
Medication	Route	induction	Maintenance
Infliximab	Intravenous	5 mg/kg at weeks 0, 2, and 6	5–10 mg/kg every 8 weeks
Adalimumab	Subcutaneous	160 mg at week 0, 80 mg at week 0	40 mg every 2 weeks
Certolizumab pegol	Subcutaneous	400 mg at weeks 0, 2, and 4	400 mg every 4 weeks
Natalizumab	Intravenous	None	300 mg every 4 weeks
Vedolizumab	Intravenous	300 mg at weeks 0, 2, and 6	300 mg every 8 weeks

Methotrexate

The other drug in the immunomodulator class is MTX, which is also an antimetabolite, similar to the TGs. The discovery of MTX as a powerful inhibitor of cellular metabolism and mitosis was honored with a Nobel Prize in 1988, and the first trial demonstrating a benefit of MTX in CD was in 1989 [54, 55]. MTX has efficacy in the maintenance of remission of luminal CD obtained by other means and is not recommended for the induction of remission [5, 6, 9]. MTX inhibits TNF, MMPs, JAK 1/2, and IL-23 pathways [56]. It is typically prescribed at a dose of 25 mg subcutaneously (SC) or intramuscular (IM) weekly for active CD, and 15 mg PO/SC weekly for maintenance therapy, both with 5 mg of folic acid PO weekly.

Side-Effects and Perioperative Management

Similar to TPs, MTX may have dose-limiting toxicity (Table 46.8). For fertile young couples, pregnancy must be avoided as MTX is a known teratogenic agent and abortifacient, and abstinence and/or high-quality contraceptives should be used [57–60]. An effect of MTX on sperm counts and quality has also been described.

MTX inhibits dividing cells and thus may interfere with wound healing. However, it has a very short half-life. MTX does not appear to be associated with postoperative complications [61]. Thus, the perioperative management of MTX is the same as for TPs mentioned above; they may be safely discontinued prior to surgery and held in the postoperative period, and their ongoing therapeutics need to be reassessed by the GI team after recovery.

Biologic Therapy

Since the FDA approval of infliximab in 1998, biologic agents (summarized in Table 46.9) have revolutionized the treatment of CD. Rather than indiscriminate immunosuppression, biologic medications are monoclonal antibodies directed at particular proteins that drive the inflammatory cascade of IBD. They are approved to induce and maintain remission in moderate-to-severe CD. This is defined using clinical and endoscopic factors and typically includes a Crohn's disease activity index (CDAI) >220, a Crohn's disease endoscopic index of severity (CDEIS) >8, or a simple endoscopic score (SES-CD) >6. At present, there are three categories of biologic agents with six commonly used medications that are FDA-approved for this indication:

1. *Tumor Necrosis Factor inhibitor (TNFi) agents*
   - Infliximab
   - Adalimumab
   - Certolizumab pegol
2. *Anti-integrin agents*
   - Natalizumab
   - Vedolizumab
3. *Anti-interleukin agents*
   - Ustekinumab

Selection of biologic therapy should be driven by patient and physician preference; but in reality, insurance approval and cost are often factors into which agent is ultimately chosen. A 2017 review of insurance policies regarding biologic use for IBD reported that 90% of policies are inconsistent with AGA guidelines [62].

The positioning of biologic agents in the therapeutic algorithm is a matter of debate. Historically, a "step-up" strategy starting with 5-ASA compounds, IMM, and corticosteroids with escalation to biological therapy after failure to maintain remission has been employed. The top-down approach (early utilization of biologics) has been suggested for patients presenting with poor prognostic factors suggesting a complicated phenotype (Table 46.2). The goal of this approach is to optimally control disease and prevent complications such as fistula or stricture, where medical therapy is less or ineffective. Factors such as early age of diagnosis, stricturing or fistulizing disease, perianal or severe rectal disease, extensive involvement of the GI tract, deep ulcerations, prior surgical resection, or rapid onset should be considered for early biologic therapy. High-risk patients have shown benefit from the early use of TNFi's for an overall risk reduction of surgery, hospitalization, loss of response, and the development of disease-related complications [63].

Before initiation of biologic therapy, routine assessment for tuberculosis (typically using QuantiFERON-TB Gold) and viral hepatitis and selective assessment for histoplasmosis and blastomycosis should be initiated. Patients should be vaccinated against pneumococcus, varicella, human papilloma virus, influenza vaccine, hepatitis A vaccine, and herpes zoster.

Antitumor Necrosis Factor Agents

The TNFi agents are infliximab, adalimumab, and certolizumab pegol. These medications successfully modulate the immune system by binding to tumor necrosis factor alpha (TNF-alpha) and inhibiting signal transduction and limiting inflammation. These agents are proven to induce remission and provide maintenance therapy in patients with moderate-to-severe CD and are supported by the AGA, ACG, and ECCO guidelines [5, 6, 8]. Several meta-analyses of RCTs support their use in those who failed therapy with steroids or other forms of immunosuppression [64–66]. TNFi's- are particularly useful in the management of perianal or rectal disease, fistulizing CD, patients at high-risk for postoperative recurrence, and those with pyoderma. Response may be seen within the first few weeks after starting therapy, but maybe delayed up to 6 weeks after initiation.

Infliximab (IFX) is a chimeric mouse-human immunoglobulin (Ig) monoclonal antibody. This is typically administered with intravenous induction dosing at 5 mg/kg at weeks zero, two, and six followed by maintenance therapy every 8 weeks thereafter. IFX is the only agent with a phase 3 study demonstrating efficacy for the treatment of fistulizing disease, particularly perianal disease [67]. There are some data suggesting that infliximab is also associated with fewer hospitalizations, surgeries, and steroid use when compared with other TNFi agents for CD [68].

Adalimumab (ADA) is a fully human Ig monoclonal antibody given subcutaneously. This is started with induction dosing of 160 mg at week zero, followed by 80 mg at week 2, and then 40 mg every 2 weeks thereafter.

Certolizumab pegol is a PEG-ylated Fab fragment. This medication is self-administered subcutaneously at a dose of 400 mg at weeks 0, 2, and 4, followed by 400 mg every 4 weeks thereafter.

Adverse events with TNFi drugs include psoriasis, arthritis, hepatoxicity, rarely cytopenia, and an increased risk of melanoma and lymphoma formation [69]. Patents on combination therapy with immunomodulators may also have an increased risk of non-melanoma skin cancers and lymphoma [69]. Patients are also at risk for opportunistic infections.

Combination Therapy

The use of combination therapy with immunomodulators has been shown to increase TNFi serum concentrations while minimizing the risk of adverse drug reactions [70]. Unfortunately, combination therapy has also been associated with an increased risk of opportunistic infections [71, 72].

When starting IFX, combination therapy with a TP is generally recommended. The SONIC (Study Of Biologic and Immunomodulator Naïve Patients In Crohn's Disease) trial compared IFX with AZA to each therapy alone in treatment naïve patients [70]. Combination therapy was more likely to result in mucosal healing [RR: 1.82; 95% CI: 1.01–3.26] and clinical remission at 26 weeks. The authors also found significantly lower rates of serious adverse events in those on combination therapy [RR: 0.56; 95% CI: 0.32–0.97]. No controlled trial has addressed whether to continue immunomodulators (IMM) when starting a TNFi after failure of IMM monotherapy. A post hoc subgroup meta-analysis of controlled trials of these types of patients showed no added benefit for the continued use of IMM with TNFi regarding 6 month remission [OR: 1.02; 95% CI: 0.80–1.31], induction

of complete response [OR: 1.08; 95% CI: 0.79–1.4] or partial response [OR, 1.25; 95% CI, 0.84–1.88], maintenance therapy [OR: 1.53; 95% CI, 0.67–3.49], or fistula closure [OR: 1.10; 95% CI, 0.68–1.78] [73]. However, TNFi and other biologic agents are intrinsically antigenic, although the non-TNFi's are less antigenic and combination therapy is most commonly used with the TNFi's. The development of anti-drug antibodies (ADA) leading to loss of response is an important consideration; in the absence of direct evidence, an individualized approach to combination therapy seems appropriate [73].

The REACT [Early Combined Immunosuppression for the Management of Crohn's Disease] trial showed that the early use of biologic therapy combined with IMMs as compared with a more conventional stepwise management was associated with significantly lower rates of complications including need for hospitalization, serious disease-related outcomes, or surgery in patients with early CD [63]. Of note, there was no significant difference between the two groups of patients in steroid-free remission, the trial's primary outcome. The "Enhanced Algorithm for Crohn's Treatment Incorporating Early Combination Therapy [REACT2]" is currently enrolling with a primary endpoint based on mucosal healing.

The DIAMOND [Deep Remission of Immunomodulator and Adalimumab Combination Therapy for Crohn's Disease] trial is the only RCT that studied the use of combination therapy of adalimumab with thiopurines versus monotherapy for inducing remission [74]. Combination therapy was not superior for remission [RR: 0.95; 95% CI: 0.78–1.15]. While combination therapy was associated with endoscopic improvement at week 26 [RR: 1.32; 95% CI: 1.06–1.65], this benefit was lost at 1 year. There was no increase in adverse events associated with combination therapy [RR: 1.03; 95% CI: 0.60–1.78], but the dose of AZA used in this trial was lower than what is typically used in CD. Given the ability of immunomodulators to reduce the rate of ADA formation, long-term combination therapy in ADA may very well have a benefit outside of short-term clinical remission or maintenance.

Leukocyte-Trafficking Agents

Leukocyte-trafficking agents, or integrin receptor antagonists, prevent margination of leukocytes by blocking the surface integrins and preventing adhesion to endothelial cells. Natalizumab inhibits the α4 integrin, while vedolizumab blocks the α4β7 heterodimer and is gut selective.

Natalizumab is an infusional drug dosed at 300 mg every 4 weeks and is effective in the treatment of CD [75]. Because this medication is not specific to the GI tract, there is a rare but increased risk of progressive multifocal leukoencephalopathy (PML) resulting from infection with the John Cunningham (JC) virus [76]. This risk is reported to be as high as 1 in 100 who are antibody positive for JC virus, so patients should be surveilled for infection before starting treatment and at every 6 months after. Fear of this dreaded complication, combined with the demonstrated efficacy of novel biologics, has largely led to the abandonment of this medication for CD.

Vedolizumab is also an intravenous medication, with a 300 mg dose at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter. The onset of action is quite slow, and initial response is typically seen within 12 weeks of starting the drug [77]. Vedolizumab has historically been used in those patients who have had an inadequate response, lost response, or could not tolerate anti-TNF, corticosteroids or IMM therapy. Failure of other therapies is not a requirement, however, and it can be positioned as first-line agent in patients with active disease. Vedolizumab has been shown to achieve clinical response, clinical remission, and steroid-free remission, and use is supported by the ACG and ECCO guidelines [6, 8, 77–79]. Because it is selective to the GI tract, there is no known risk for PML, unlike natalizumab. Patients who have received prior treatment with TNFi agents may require longer treatment to reach efficacy [80]. Those patients appear to have the same efficacy at 10 weeks that TNFi-naïve patients experience at 6 weeks. Prospective clinical trials comparing vedolizumab monotherapy with combination therapy has not been reported.

A recent network meta-analysis suggests that ADA or combination therapy with IFX and AZA is more effective than vedolizumab in inducing and maintaining remission in CD [81].

Interleukin-12 and -23 Antagonist

In 2016, the FDA-approved ustekinumab for use in moderate-to-severe CD. This drug targets the p40 subunit of interleukin-23 and interleukin-12. Induction should be given intravenously usually at 6 mg/kg followed by maintenance dosing of 90 mg subcutaneously every 8 weeks. The onset of action is usually seen within 6 weeks.

Ustekinumab is efficacious in treating patients with moderate-to-severe CD who have failed both conventional non-biologic therapy and TNFi medications but also can be positioned as a first-line agent [82]. Consistent with clinical trials, a large database study of patients undergoing treatment for psoriasis demonstrated an excellent safety profile without a significant increase in infections or malignancies [83]. There have been no trials directly comparing ustekinumab to integrin receptor antagonists or TNFi agents, and the choice of first biologic is at the discretion of the patient and provider. Ustekinumab may be less effective in

patients who have failed TNFi therapy [84]. Both the ACG and ECCO guidelines support its use for both induction and maintenance of remission [6, 8].

Biosimilars

Biosimilar medications are highly structurally and clinically similar to an already FDA-approved originator product, and they undergo an accelerated and abbreviated FDA-approval pathway. These mediations should present no differences in efficacy or safety compared to their originator compounds and have the advantage of lower cost. Biosimilars were approved for the treatment of IBD in September 2013 in Europe and in April 2016 in the USA.

Biosimilar TNFi agents are effective treatments for patients with moderate-to-severe CD and can be used for *de novo* induction and maintenance therapy. The major advantage of biosimilar therapy is cost. Five agents have gained approval for infliximab and adalimumab, with many more expected in coming years:

- Infliximab-abda
- Infliximab-dyyb
- Infliximab-qbtx
- Adalimumab-atto
- Adalimumab-adbm

While other generic small-molecule drugs are exact replicas, the same is not true for TNFi biosimilars. Exact replicas cannot be made of biologics because of their structural complexity and complicated manufacturing process. Their amino acid sequences remain the same, but they may differ in their glycosylation patterns. This influences a molecular solubility, stability, clearance, immunogenicity, and immune effector function [6, 55]. At present, there is not sufficient data to support the safety and efficacy of switching patients with stable disease from one biosimilar to another.

A large randomized, non-inferiority phase 3 clinical trial of patients with CD compared IFX to the biosimilar infliximab-dyyb in biologic naïve patients [85]. Patients were randomly assigned to receive infliximab-dyyb then infliximab-dyyb, infliximab-dyyb then IFX, IFX then IFX, or IFX then infliximab-dyyb; the medication switch occurring at week 30. A total of 220 patients were enrolled, and response rates at week 6 were similar for infliximab-dyyb [69.4%, 95% CI 59.9–77.8] and IFX [74.3%, 95% CI 65.1–82.2], establishing non-inferiority. Adverse events were similar in each group. There is still a significant paucity of data around interchangeability, limiting adoption at this time despite cost savings.

Induction and Maintenance of Remission

Principles of Induction Therapy

Mild Disease

Mild disease limited to the terminal ileum may be managed with symptom control and dietary changes or by using budesonide. Mesalamine and antibiotics have not been associated with significant benefit. For mild disease involving the colon, 5-ASA compounds or steroids can be used. Mild disease with upper gastrointestinal involvement should be treated initially with steroids and immunomodulators; for those with clinical features suggestive of a more aggressive phenotype, consideration should be given for early biologic therapy.

Moderate Disease

Moderate ileal disease should be treated with budesonide or steroids. If indicated for complications of local sepsis, antibiotics can also be added. Alternative strategies can include steroids plus an immunomodulator, early biologic therapy, or surgery. The LIR!C trial demonstrated that early laparoscopic resection may be considered a reasonable, cost-effective alternative to upfront infliximab therapy in patients with limited (< 30 cm), inflammatory (non-stricturing/non-penetrating) ileocecal Crohn's disease [86, 87].

Colonic disease should be treated with steroids or biologic therapy. In the setting of relapse, combination therapy with biologics and an IMM or an IMM with steroids (if relapses are infrequent) may be considered.

Severe Disease

Severe disease of the terminal ileum should be managed with biologic therapy with or without an IMM. Those with infrequent relapse may be treated with an IMM and steroids at the time of disease exacerbation. Early resection should also be considered. Colonic disease may be treated with steroids. Extensive upper gastrointestinal Crohn's disease should be managed with steroids and IMM. For patients who have relapsed, biologic therapy with or without combination therapy is an option.

Principles of Maintenance Therapy

Target to Treat

Recently, there has been a paradigm shift in the medical management of patients with IBD. Classically, treatment has focused on controlling symptoms with escalation of therapy and a "step-up" approach as the disease progresses or therapies fail. This escalation of therapy appears suboptimal with

respect prevention of disease progression. "Target to treat" is a shift toward to a more nuanced strategy, focusing on both control of symptoms and the objective signs of inflammation, that may occur before symptoms or complications develop. Inflammation can be assessed through blood and stool biomarkers such as fecal calprotectin and C-rective protein (CRP), cross-sectional imaging, and endoscopy. Goals of care are built on minimizing disease activity in the early stages of IBD to avoid progressive bowel damage such as fibrostenotic or penetrating disease.

The goals for target to treat are a combination of patient-reported and clinical outcomes as described by the "Selecting Therapeutic Targets in Inflammatory Bowel Disease" [STRIDE] International Organization for the Study of Inflammatory Bowel Diseases. These outcomes are defined as resolution of abdominal pain and diarrhea or altered bowel habit, endoscopic remission defined absent ulceration at endoscopy, or findings of inflammation on magnetic resonance enterography (MRE) or CT-enterography. The patient-reported endpoints should be assessed at a minimum of 3 month intervals during active disease, and the endoscopic endpoints should be assessed at 6–9 month intervals [88]. Other adjunctive measures include histological remission, and biomarker remission defined as a normal CRP and fecal calprotectin; mucosal healing is inversely associated with risk of relapse, surgery, hospitalization, and inability to wean steroids [88–93].

The "Effect of Tight Control Management on Crohn's Disease" [CALM] was a phase 3 multicenter study comparing a "tight control strategy" to symptom-driven care [93]. In the tight control arm, treatment was escalated with a CDAI >150, fecal calprotectin >250, CRP > 5, and prednisone use within the previous week. In the standard care cohort, treatment was escalated if there was not a decrease in the CDAI >70 or 100 (at randomization or post-randomization, respectively), a CDAI >200, or steroid use within the previous week. Tight control was associated with superior endoscopic remission and a lower rate of Crohn's disease-related hospitalizations when compared to symptom-driven care.

General Principles of Maintenance Therapy

If maintenance was initially achieved with steroids that have been successfully weaned, consideration may be given to no therapy with close observation typically by a 6-month follow-up endoscopic reassessment looking for inflammation. Additionally, isolated disease in the appropriate patient can also be managed by surgical resection followed by a surveillance colonoscopy 6 months post-resection.

IMM monotherapy may also be considered, but oral 5-ASA compounds have not been consistently shown to be effective in maintenance of remission. If induction was achieved with biologic agents, maintenance should be offered. However, combination therapy of biologics and IMM tend to have the best results. Annual endoscopy should be considered for those on biologic agents.

If patients experience a flair while taking a TNFi agent, drug concentrations and ADAs may be checked. Those with low drug level and low levels or absent ADAs may require higher dosing; those with high ADAs typically need to be switched to a different TNFi. Those with normal drug levels and no ADAs typically need to change to a new class of biologics for lack of response.

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) is the measurement of circulating levels of medications and ADA to inform therapy. The role of TDM in the management of transplant recipients has been well established; however, its role in patients with CD is emerging. While there is no definitive evidence to support routine TDM, there are clear theoretical advantages. Goals of care are based on maintaining medical remission while avoiding immunogenicity or loss of response. TDM would seemingly help in these endeavors as the trough concentrations of IMM and biologic therapy can vary. Factors effecting drug levels include disease severity, phenotype, degree of inflammation, combination therapy, patient sex, body mass index, and variability in drug clearance.

TDM can be done reactively following clinical evidence of active disease such as symptoms, endoscopic changes, elevation of CRP or fecal calprotectin, or proactively based on routine measurement done at set timepoints.

Patients usually become refractory to medical therapy for one of three reasons: lack of response, low drug concentrations, or development of ADAs. The AGA has clear guidelines for those on TNFi's for maintenance therapy in the setting of disease recurrence (Fig. 46.2). Adequate trough levels are defined as ≥5μg/mL for IFX, ≥7.5μg/mL for ADA, and ≥20μg/mL for certolizumab pegol. However, there is no consensus of optimal trough concentrations, and those with perianal disease may require higher concentrations for efficacy:

- If the drug level is *normal,* then the dose should be increased or the medication changed
- If the drug level is absent or *low,* check ADAs:
  - If ADAs are *absent or low* assure compliance, then consider:
    1. Shorten the dosing interval
    2. Increase the dose
    3. Combination therapy with an immunomodulator
  - If ADAs are *high* then switch medications

High serum trough levels have been shown to be associated with mucosal healing. A retrospective study of 145

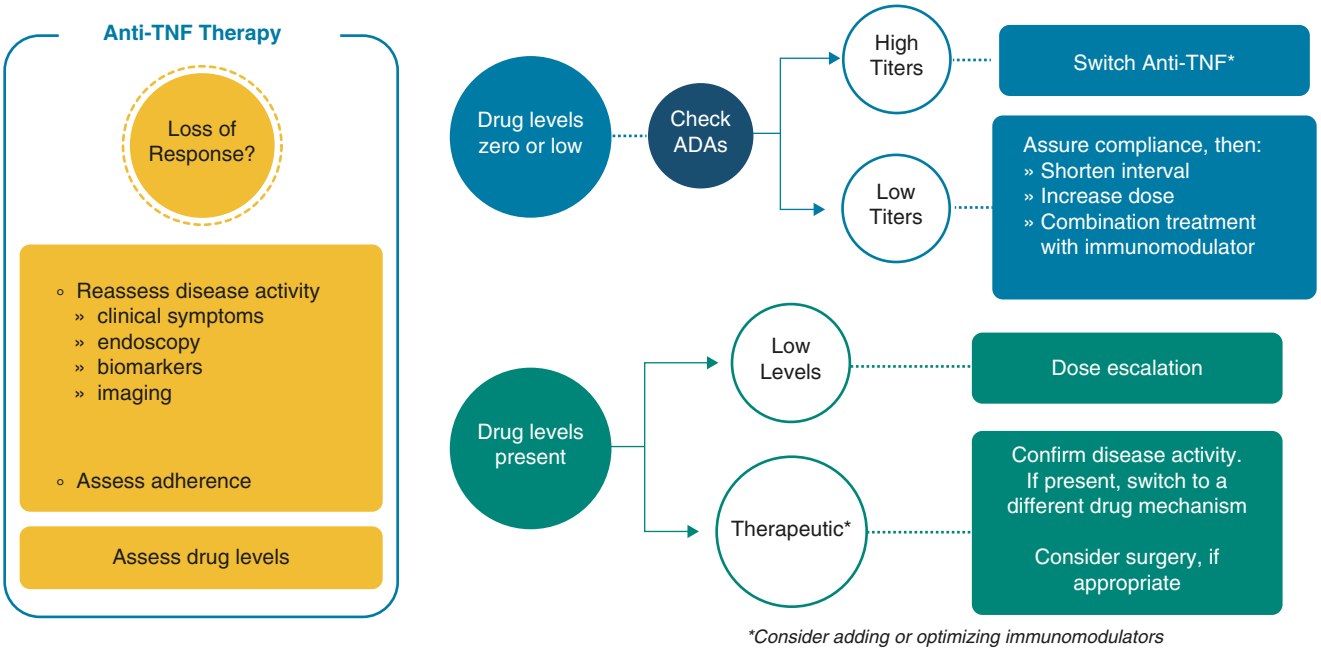

Fig. 46.2 Reactive therapeutic drug monitoring

patients over 5 years examined mucosal healing and associated this with trough levels of IFX and ADA at the same time points [94]. They found IFX levels >5μg/mL and ADA levels >7.1μg/mL identified patients with mucosal healing with 85% specificity. They also noted that higher levels of IFX and ADA beyond 8μg/mL and 12μg/mL, respectively, conferred no significant additional benefit [7].

A post hoc analysis of ACCENT I [A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen I] evaluated the association between IFX trough concentrations and CRP at 14 weeks after induction treatment [95]. Patients with a durable sustained response had higher post-induction trough levels than patients without sustained response. Similarly, a study of 71 patients on ADA correlated high trough serum concentrations with remission [96].

Three large RCTs have been published on the role of TDM. Trough Concentration Adapted Infliximab [TAXIT] randomized 263 IBD patients on maintenance infliximab to dose adjustment for a target concentration of 3–7μg/mL versus empiric dosing [97]. All patients initially had a starting level of 3–7μg/mL and were dose adjusted if appropriate. The study found that those patients who required an increase in dosing to achieve target trough level had a higher rate of remission and a decrease in CRP. They also identified 67 patients who started at drug level >7μg/mL and were able to be dose reduced. This translated to a 28% reduction in cost. TDM did not affect levels of clinical remission at 1 year, but patients did experience fewer flares.

A more recent double-blind RCT known as "Study Investigating Tailored Treatment with Infliximab for Active Crohn's Disease" [TAILORIX] included 122 biologic-naïve patients with active disease [98]. All patients underwent induction with combination therapy (immunomodulator plus IFX). At 14 weeks subjects were randomized to three groups: the control arm (dose increase 10 mg/kg based on clinical symptoms alone) or one of two dose intensification strategies based on clinical symptoms, biomarker analysis, and/or serum infliximab concentrations <3μg/mL. The authors found no benefit of TDM over symptom-guided management in achieving corticosteroid-free remission at 1 year. This study, however, was underpowered, and there was a very low threshold for dose escalation in the control arm.

The Pediatric Crohn's disease Adalimumab-Level-based Optimization Treatment [PAILOT] was a prospective study comparing proactive versus reactive TDM in pediatric patients [99]. The study included 78 biological-naïve children with CD who responded to adalimumab induction therapy and were then randomized to either proactive dose optimization (with a target of 5–10 mg/mL) or reactive testing. They found that clinical improvement was significantly higher in the proactive group versus reactive TDM group.

De-escalation

When contemplating de-escalation of therapy, strong consideration should be given not only to disease control but also to the overall disease characteristics, prior treatment history,

tolerance to medications, and risk for adverse events. Some patients who are at lower risk for serious complications related to CD may benefit from de-escalation of medical therapy. This reduces the risk of immunosuppression and drug toxicity and can improve quality of life and provide for cost savings. De-escalation can mean moving from combination therapy to monotherapy or withdrawing medications completely. However, in the setting of subclinical inflammatory changes, de-escalation can increase the risk of flares, use of steroids, and hospitalizations and can lead to irreversible complications and surgery [100]. Patients discontinuing biologic therapy may develop drug resistance by producing ADAs, limiting future therapeutic options.

De-escalation of combination therapy can be considered in those with well-controlled disease with no prior Crohn's-related resections or significant complications related to their disease course (Fig. 46.3) or after surgical resetting of the clock. Those with upper GI tract CD, repeated penetrating complications, surgeries, or escalated dosing of TNFi's should not be considered for de-escalation. Once selected, patients have to be confirmed to be in deep remission defined by clinical symptoms, normal biomarkers, endoscopy with normal histology, or normal imaging of the small bowel for those with ileal disease. Surveillance after de-escalation includes clinical monitoring of inflammation every 12 weeks for a year with CRP and fecal calprotectin. Prior to de-escalation from biologics, consideration should be given to obtaining drug levels. If low, this suggests the biologic is probably not the source of remission and de-escalation is more likely to be successful.

If biomarkers start to rise, endoscopy or imaging should confirm recurrence, and other sources like infection should be ruled out. If recurrence of active Crohn's is confirmed, the previously successful maintenance medication should be restarted. If needed, budesonide or steroids can be provided as a bridge.

Postoperative Prophylaxis

Off medical therapy, the rate of endoscopic disease approaches 90% at 3 years, while clinical recurrence may reach 60% [101]. The goal of postoperative prophylaxis is medical maintenance of remission, as we know 50% of those who undergoing ileocolic resection will require additional surgery within 10 years [102].

After ileocolic resection, all patients should undergo endoscopic surveillance at 6–12 months [103]. Only one RCT has been performed pertaining to the timing of prophylaxis [104]. The study randomized patients to routine AZA starting early at 8 weeks or to endoscopically guided therapy at 6–12 months. This study found no difference in the two groups; however, potential flaws included mismatched cohorts, high attrition, low accrual, and the use of non-biologic therapy.

Many factors have been associated with the risk of postoperative recurrence, and more aggressive initiation of medication is recommended in these patients. Risk factors for early recurrence include younger patients, male gender, tobacco abuse, penetrating or fistulizing disease, prior operative intervention, and short disease duration. A recent meta-analysis demonstrated a significantly increased risk of postoperative recurrence (OR, 1.7; 95% CI, 1.3–2.1; $p < 0.001$) based on the presence of histopathologically positive margins or presence of plexitis (OR, 2.3; 95% CI, 1.1–4.9; $p = 0.02$) [105].

Numerous RCTs have examined which agent should be utilized for postoperative prophylaxis. Probiotics, 5-ASA, and budesonide show no benefit over placebo [67, 106–108]. Antibiotics may reduce recurrence; but the best evidence to prevent postoperative disease is monotherapy with either biologics or IMM. Early and aggressive prophylaxis is particularly important in patients with risk factors for recurrence. Those patients who are low risk for recurrence (e.g.,

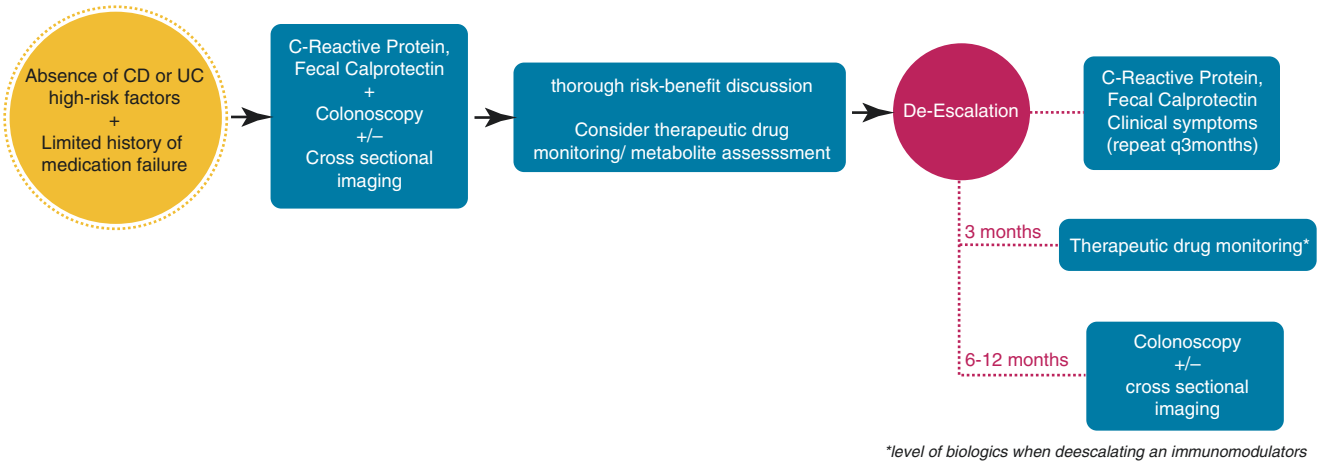

Fig. 46.3 De-escalation of therapy in IBD

isolated short segment ileocolic disease present for a long duration in an elderly non-smoker) can be surveilled 6–12 months after surgery off therapy.

Conclusions

The last two decades have seen unprecedented advances in the medical management of CD. All current strategies for therapy focus on symptom management and control of inflammation to prevent or slow bowel damage. As we improve our understanding of the disease, so too does the capacity to provide new, innovative, safer, and more effective therapies. The approach to medical management over the recent years has shifted to more proactive utilization of medications with targeted assessment to verify efficacy prior to the development of complications. The armamentarium of drug options has expanded considerably. However, the efficacy of these medications remains limited, and surgical intervention is still commonly required to manage complications and to improve or restore patient quality of life.

References

1. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis; a pathologic and clinical entity. Am J Med. 1952;13:583–90.
2. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis: a pathologic and clinical entity. 1932. Mt Sinai J Med. 2000;67:263–8.
3. Mulder DJ, Noble AJ, Justinich CJ, Duffin JM. A tale of two diseases: the history of inflammatory bowel disease. J Crohns Colitis. 2014;8:341–8.
4. Ginzburg L. Regional enteritis: historical perspective (B. Crohn and L. Ginzburg). Gastroenterology. 1986;90:1310–1.
5. Terdiman JP, Gruss CB, Heidelbaugh JJ, Sultan S, Falck-Ytter YT, Practice AGAIC, Quality Management C. American Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF-alpha biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology. 2013;145:1459–63.
6. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults. Am J Gastroenterol. 2018;113:481–517.
7. Lichtenstein GR, Loftus EV Jr, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. Correction: ACG clinical guideline: management of Crohn's disease in adults. Am J Gastroenterol. 2018;113:1101.
8. Torres J, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, Adamina M, Armuzzi A, Bachmann O, Bager P, Biancone L, Bokemeyer B, Bossuyt P, Burisch J, Collins P, El-Hussuna A, Ellul P, Frei-Lanter C, Furfaro F, Gingert C, Gionchetti P, Gomollon F, González-Lorenzo M, Gordon H, Hlavaty T, Juillerat P, Katsanos K, Kopylov U, Krustins E, Lytras T, Maaser C, Magro F, Kenneth Marshall J, Myrelid P, Pellino G, Rosa I, Sabino J, Savarino E, Spinelli A, Stassen L, Uzzan M, Vavricka S, Verstockt B, Warusavitarne J, Zmora O, Fiorino G, European Crohn's and Colitis Organisation. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. J Crohns Colitis. 2019;14:4–22.
9. Gomollon F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, Peyrin-Biroulet L, Cullen GJ, Daperno M, Kucharzik T, Rieder F, Almer S, Armuzzi A, Harbord M, Langhorst J, Sans M, Chowers Y, Fiorino G, Juillerat P, Mantzaris GJ, Rizzello F, Vavricka S, Gionchetti P, ECCO. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. J Crohns Colitis. 2017;11:3–25.
10. Uzzan M, Cosnes J, Amiot A, Gornet JM, Seksik P, Cotte E, Tiret E, Panis Y, Treton X. Long-term follow-up after ileorectal anastomosis for ulcerative colitis: a GETAID/GETAID Chirurgie multicenter retrospective cohort of 343 patients. Ann Surg. 2017;266:1029–34.
11. Khan KJ, Ullman TA, Ford AC, Abreu MT, Abadir A, Marshall JK, Talley NJ, Moayyedi P. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol. 2011;106:661–73.
12. Townsend CM, Parker CE, MacDonald JK, Nguyen TM, Jairath V, Feagan BG, Khanna R. Antibiotics for induction and maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2019;2:CD012730.
13. Feagins LA, Holubar SD, Kane SV, Spechler SJ. Current strategies in the management of intra-abdominal abscesses in Crohn's disease. Clin Gastroenterol Hepatol. 2011;9:842–50.
14. Steinhart AH, Panaccione R, Targownik L, Bressler B, Khanna R, Marshall JK, Afif W, Bernstein CN, Bitton A, Borgaonkar M, Chauhan U, Halloran B, Jones J, Kennedy E, Leontiadis GI, Loftus EV Jr, Meddings J, Moayyedi P, Murthy S, Plamondon S, Rosenfeld G, Schwartz D, Seow CH, Williams C. Clinical practice guideline for the medical management of perianal fistulizing Crohn's disease: the Toronto consensus. Inflamm Bowel Dis. 2019;25:1–13.
15. Alves C, Mendes D, Marques FB. Fluoroquinolones and the risk of tendon injury: a systematic review and meta-analysis. Eur J Clin Pharmacol. 2019;75:1431–43.
16. Butterworth AD, Thomas AG, Akobeng AK. Probiotics for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2008:CD006634.
17. Jonkers D, Penders J, Masclee A, Pierik M. Probiotics in the management of inflammatory bowel disease: a systematic review of intervention studies in adult patients. Drugs. 2012;72:803–23.
18. Derwa Y, Gracie DJ, Hamlin PJ, Ford AC. Systematic review with meta-analysis: the efficacy of probiotics in inflammatory bowel disease. Aliment Pharmacol Ther. 2017;46:389–400.
19. Limketkai BN, Iheozor-Ejiofor Z, Gjuladin-Hellon T, Parian A, Matarese LE, Bracewell K, MacDonald JK, Gordon M, Mullin GE. Dietary interventions for induction and maintenance of remission in inflammatory bowel disease. Cochrane Database Syst Rev. 2019;2:CD012839.
20. Sokol H, Landman C, Seksik P, Berard L, Montil M, Nion-Larmurier I, Bourrier A, Le Gall G, Lalande V, De Rougemont A, Kirchgesner J, Daguenel A, Cachanado M, Rousseau A, Drouet E, Rosenzwajg M, Hagege H, Dray X, Klatzman D, Marteau P, Saint-Antoine IBDN, Beaugerie L, Simon T. Fecal microbiota transplantation to maintain remission in Crohn's disease: a pilot randomized controlled study. Microbiome. 2020;8:12.
21. Paramsothy S, Paramsothy R, Rubin DT, Kamm MA, Kaakoush NO, Mitchell HM, Castano-Rodriguez N. Faecal microbiota transplantation for inflammatory bowel disease: a systematic review and meta-analysis. J Crohns Colitis. 2017;11:1180–99.
22. Imdad A, Nicholson MR, Tanner-Smith EE, Zackular JP, Gomez-Duarte OG, Beaulieu DB, Acra S. Fecal transplantation for treatment of inflammatory bowel disease. Cochrane Database Syst Rev. 2018;11:CD012774.
23. Chen T, Zhou Q, Zhang D, Jiang F, Wu J, Zhou JY, Zheng X, Chen YG. Effect of faecal microbiota transplantation for treatment of Clostridium difficile infection in patients with inflammatory bowel disease: a systematic review and meta-analysis of cohort studies. J Crohns Colitis. 2018;12:710–7.

24. Swaminath A, Feathers A, Ananthakrishnan AN, Falzon L, Li FS. Systematic review with meta-analysis: enteral nutrition therapy for the induction of remission in paediatric Crohn's disease. Aliment Pharmacol Ther. 2017;46:645–56.
25. Narula N, Dhillon A, Zhang D, Sherlock ME, Tondeur M, Zachos M. Enteral nutritional therapy for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2018;4:CD000542.
26. Liska D, Bora Cengiz T, Novello M, Aiello A, Stocchi L, Hull TL, Steele SR, Delaney CP, Holubar SD. Do patients with inflammatory bowel disease benefit from an enhanced recovery pathway? Inflamm Bowel Dis. 2020;26:476–83.
27. Summers RW, Switz DM, Sessions JT Jr, Becktel JM, Best WR, Kern F Jr, Singleton JW. National Cooperative Crohn's Disease Study: results of drug treatment. Gastroenterology. 1979;77:847–69.
28. Malchow H, Ewe K, Brandes JW, Goebell H, Ehms H, Sommer H, Jesdinsky H. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. Gastroenterology. 1984;86:249–66.
29. Ma C, Dutton SJ, Cipriano LE, Singh S, Parker CE, Nguyen TM, Guizzetti L, Gregor JC, Chande N, Hindryckx P, Feagan BG, Jairath V. Systematic review with meta-analysis: prevalence, risk factors and costs of aminosalicylate use in Crohn's disease. Aliment Pharmacol Ther. 2018;48:114–26.
30. Mansfield J, MacDougall L. Editorial: aminosalicylates in Crohn's disease-prevalence, risks, costs and time to re-assess? Aliment Pharmacol Ther. 2018;48:487–8.
31. Girardin M, Manz M, Manser C, Biedermann L, Wanner R, Frei P, Safroneeva E, Mottet C, Rogler G, Schoepfer AM. First-line therapies in inflammatory bowel disease. Digestion. 2012;86 Suppl 1:6–10.
32. O'Donnell S, O'Morain CA. Therapeutic benefits of budesonide in gastroenterology. Ther Adv Chronic Dis. 2010;1(4):177–86.
33. Nardelli S, Pisani LF, Tontini GE, Vecchi M, Pastorelli L. MMX((R)) technology and its applications in gastrointestinal diseases. Therap Adv Gastroenterol. 2017;10:545–52.
34. Kuenzig ME, Rezaie A, Kaplan GG, Otley AR, Steinhart AH, Griffiths AM, Benchimol EI, Seow CH. Budesonide for the induction and maintenance of remission in Crohn's disease: systematic review and meta-analysis for the Cochrane collaboration. J Can Assoc Gastroenterol. 2018;1:159–73.
35. Lichtenstein GR, Bengtsson B, Hapten-White L, Rutgeerts P. Oral budesonide for maintenance of remission of Crohn's disease: a pooled safety analysis. Aliment Pharmacol Ther. 2009;29:643–53.
36. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J. 1955;2:1041–8.
37. Nicolaides NC, Pavlaki AN, Maria Alexandra MA, Chrousos GP. Glucocorticoid therapy and adrenal suppression. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, Hershman JM, Kaltsas G, Koch C, Kopp P, Korbonits M, McLachlan R, Morley JE, New M, Perreault L, Purnell J, Rebar R, Singer F, Trence DL, Vinik A, Wilson DP, editors. Endotext. South Dartmouth: MDText.com, Inc; 2000.
38. Ford AC, Bernstein CN, Khan KJ, Abreu MT, Marshall JK, Talley NJ, Moayyedi P. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2011;106:590–9; quiz 600.
39. Aytac E, Londono JM, Erem HH, Vogel JD, Costedio MM. Impact of stress dose steroids on the outcomes of restorative proctocolectomy in patients with ulcerative colitis. Dis Colon Rectum. 2013;56:1253–8.
40. Ritter KA, Burke JP, Stocchi L, Aiello A, Holubar S, Ashburn JH, Lipman JM, Shawki S, Hull T. Postoperative steroid taper is associated with pelvic sepsis after ileal pouch-anal anastomosis. Inflamm Bowel Dis. 2019;25:1383–9.
41. Zaghiyan K, Melmed G, Murrell Z, Fleshner P. Are high-dose perioperative steroids necessary in patients undergoing colorectal surgery treated with steroid therapy within the past 12 months? Am Surg. 2011;77:1295–9.
42. Zaghiyan K, Melmed G, Murrell Z, Fleshner P. Safety and feasibility of using low-dose perioperative intravenous steroids in inflammatory bowel disease patients undergoing major colorectal surgery: a pilot study. Surgery. 2012;152:158–63.
43. Chilkoti GT, Singh A, Mohta M, Saxena AK. Perioperative "stress dose" of corticosteroid: pharmacological and clinical perspective. J Anaesthesiol Clin Pharmacol. 2019;35:147–52.
44. Freudzon L. Perioperative steroid therapy: where's the evidence? Curr Opin Anaesthesiol. 2018;31:39–42.
45. Urmson K. Stress dose steroids: the dogma persists. Can J Anaesth. 2020;67:276–7.
46. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, Brown JP, Cohen A, Kim H. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013;9:30.
47. Bean RH. The treatment of chronic ulcerative colitis with 6-mercaptopurine. Med J Aust. 1962;49(2):592–3.
48. Sanderson J, Ansari A, Marinaki T, Duley J. Thiopurine methyltransferase: should it be measured before commencing thiopurine drug therapy? Ann Clin Biochem. 2004;41:294–302.
49. Chouchana L, Narjoz C, Beaune P, Loriot MA, Roblin X. Review article: the benefits of pharmacogenetics for improving thiopurine therapy in inflammatory bowel disease. Aliment Pharmacol Ther. 2012;35:15–36.
50. Ferraro S, Leonardi L, Convertino I, Blandizzi C, Tuccori M. Is there a risk of lymphoma associated with anti-tumor necrosis factor drugs in patients with inflammatory bowel disease? A systematic review of observational studies. Front Pharmacol. 2019;10:247.
51. Bourrier A, Carrat F, Colombel JF, Bouvier AM, Abitbol V, Marteau P, Cosnes J, Simon T, Peyrin-Biroulet L, Beaugerie L, CESAME Study Group. Excess risk of urinary tract cancers in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Aliment Pharmacol Ther. 2016;43:252–61.
52. Lopez A, Mounier M, Bouvier AM, Carrat F, Maynadie M, Beaugerie L, Peyrin-Biroulet L, CESAME Study Group. Increased risk of acute myeloid leukemias and myelodysplastic syndromes in patients who received thiopurine treatment for inflammatory bowel disease. Clin Gastroenterol Hepatol. 2014;12:1324–9.
53. Landerholm K, Kalman D, Wallon C, Myrelid P. Immunomodulators: friends or enemies in surgery for Crohn's disease? Curr Drug Targets. 2019;20:1384–98.
54. Hitchings GH Jr. Nobel lecture in physiology or medicine--1988. Selective inhibitors of dihydrofolate reductase. In Vitro Cell Dev Biol. 1989;25:303–10.
55. Kozarek RA, Patterson DJ, Gelfand MD, Botoman VA, Ball TJ, Wilske KR. Methotrexate induces clinical and histologic remission in patients with refractory inflammatory bowel disease. Ann Intern Med. 1989;110:353–6.
56. Bedoui Y, Guillot X, Selambarom J, Guiraud P, Giry C, Jaffar-Bandjee MC, Ralandison S, Gasque P. Methotrexate an old drug with new tricks. Int J Mol Sci. 2019;20(20):5023.
57. Tandon P, Govardhanam V, Leung K, Maxwell C, Huang V. Systematic review with meta-analysis: risk of adverse pregnancy-related outcomes in inflammatory bowel disease. Aliment Pharmacol Ther. 2020;51:320–33.
58. Restellini S, Biedermann L, Hruz P, Mottet C, Moens A, Ferrante M, Schoepfer AM. Update on the management of inflammatory bowel disease during pregnancy and breastfeeding. Digestion. 2020;101 Suppl 1:27–42.

59. Mahadevan U, Robinson C, Bernasko N, Boland B, Chambers C, Dubinsky M, Friedman S, Kane S, Manthey J, Sauberan J, Stone J, Jain R. Inflammatory bowel disease in pregnancy clinical care pathway: a report from the American Gastroenterological Association IBD Parenthood Project Working Group. Gastroenterology. 2019;156:1508–24.
60. Gaidos JKJ, Kane SV. Sexuality, fertility, and pregnancy in Crohn's disease. Gastroenterol Clin North Am. 2017;46:531–46.
61. Afzali A, Park CJ, Zhu K, Hu JK, Sharma P, Sinanan MN, Lee SD. Preoperative use of methotrexate and the risk of early postoperative complications in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2016;22:1887–95.
62. Yadav A, Foromera J, Feuerstein I, Falchuk KR, Feuerstein JD. Variations in health insurance policies regarding biologic therapy use in inflammatory bowel disease. Inflamm Bowel Dis. 2017;23:853–7.
63. Khanna R, Bressler B, Levesque BG, Zou G, Stitt LW, Greenberg GR, Panaccione R, Bitton A, Pare P, Vermeire S, D'Haens G, MacIntosh D, Sandborn WJ, Donner A, Vandervoort MK, Morris JC, Feagan BG, Investigators RS. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. Lancet. 2015;386:1825–34.
64. Stidham RW, Lee TC, Higgins PD, Deshpande AR, Sussman DA, Singal AG, Elmunzer BJ, Saini SD, Vijan S, Waljee AK. Systematic review with network meta-analysis: the efficacy of anti-TNF agents for the treatment of Crohn's disease. Aliment Pharmacol Ther. 2014;39:1349–62.
65. Cholapranee A, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. Aliment Pharmacol Ther. 2017;45:1291–302.
66. Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, Podolsky DK, Sands BE, Braakman T, DeWoody KL, Schaible TF, van Deventer SJ. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med. 1999;340:1398–405.
67. Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2011;106:644–59, quiz 60.
68. Singh S, Heien HC, Sangaralingham LR, Schilz SR, Kappelman MD, Shah ND, Loftus EV Jr. Comparative effectiveness and safety of anti-tumor necrosis factor agents in biologic-naive patients with Crohn's disease. Clin Gastroenterol Hepatol. 2016;14:1120–9 e6.
69. Targownik LE, Bernstein CN. Infectious and malignant complications of TNF inhibitor therapy in IBD. Am J Gastroenterol. 2013;108:1835–42, quiz 43.
70. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P, SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010;362:1383–95.
71. Cheifetz AS. Management of active Crohn disease. JAMA. 2013;309:2150–8.
72. Baumgart DC, Sandborn WJ. Crohn's disease. Lancet. 2012;380:1590–605.
73. Jones JL, Kaplan GG, Peyrin-Biroulet L, Baidoo L, Devlin S, Melmed GY, Tanyingoh D, Raffals L, Irving P, Kozuch P, Sparrow M, Velayos F, Bressler B, Cheifetz A, Colombel JF, Siegel CA. Effects of concomitant immunomodulator therapy on efficacy and safety of anti-tumor necrosis factor therapy for Crohn's disease: a meta-analysis of placebo-controlled trials. Clin Gastroenterol Hepatol. 2015;13:2233–40.e1–2; quiz e177–8.
74. Matsumoto T, Motoya S, Watanabe K, Hisamatsu T, Nakase H, Yoshimura N, Ishida T, Kato S, Nakagawa T, Esaki M, Nagahori M, Matsui T, Naito Y, Kanai T, Suzuki Y, Nojima M, Watanabe M, Hibi T, DIAMOND Study Group. Adalimumab monotherapy and a combination with azathioprine for Crohn's disease: a prospective, randomized trial. J Crohns Colitis. 2016;10:1259–66.
75. Sandborn WJ, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, Panaccione R, Sanders M, Schreiber S, Targan S, van Deventer S, Goldblum R, Despain D, Hogge GS, Rutgeerts P, International Efficacy of natalizumab as Active Crohn's Therapy Trial Group, Evaluation of Natalizumab as Continuous Therapy Trial Group. Natalizumab induction and maintenance therapy for Crohn's disease. N Engl J Med. 2005;353:1912–25.
76. Van Assche G, Van Ranst M, Sciot R, Dubois B, Vermeire S, Noman M, Verbeeck J, Geboes K, Robberecht W, Rutgeerts P. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. N Engl J Med. 2005;353:362–8.
77. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, Lukas M, Fedorak RN, Lee S, Bressler B, Fox I, Rosario M, Sankoh S, Xu J, Stephens K, Milch C, Parikh A, Group GS. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369:711–21.
78. Chandar AK, Singh S, Murad MH, Peyrin-Biroulet L, Loftus EV Jr. Efficacy and safety of natalizumab and vedolizumab for the management of Crohn's disease: a systematic review and meta-analysis. Inflamm Bowel Dis. 2015;21:1695–708.
79. Lin L, Liu X, Wang D, Zheng C. Efficacy and safety of antiintegrin antibody for inflammatory bowel disease: a systematic review and meta-analysis. Medicine (Baltimore). 2015;94:e556.
80. Sands BE, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Sy R, D'Haens G, Ben-Horin S, Xu J, Rosario M, Fox I, Parikh A, Milch C, Hanauer S. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology. 2014;147:618–27. e3.
81. Hazlewood GS, Rezaie A, Borman M, Panaccione R, Ghosh S, Seow CH, Kuenzig E, Tomlinson G, Siegel CA, Melmed GY, Kaplan GG. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. Gastroenterology. 2015;148:344–54.e5; quiz e14–5.
82. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, Blank MA, Johanns J, Gao LL, Miao Y, Adedokun OJ, Sands BE, Hanauer SB, Vermeire S, Targan S, Ghosh S, de Villiers WJ, Colombel JF, Tulassay Z, Seidler U, Salzberg BA, Desreumaux P, Lee SD, Loftus EV Jr, Dieleman LA, Katz S, Rutgeerts P, Group U-I-US. Ustekinumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2016;375:1946–60.
83. Papp K, Gottlieb AB, Naldi L, Pariser D, Ho V, Goyal K, Fakharzadeh S, Chevrier M, Calabro S, Langholff W, Krueger G. Safety surveillance for ustekinumab and other psoriasis treatments from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). J Drugs Dermatol. 2015;14:706–14.
84. Sandborn WJ, Gasink C, Gao LL, Blank MA, Johanns J, Guzzo C, Sands BE, Hanauer SB, Targan S, Rutgeerts P, Ghosh S, de Villiers WJ, Panaccione R, Greenberg G, Schreiber S, Lichtiger S, Feagan BG, Group CS. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med. 2012;367:1519–28.
85. Ye BD, Pesegova M, Alexeeva O, Osipenko M, Lahat A, Dorofeyev A, Fishman S, Levchenko O, Cheon JH, Scribano ML, Mateescu RB, Lee KM, Eun CS, Lee SJ, Lee SY, Kim H, Schreiber S, Fowler H, Cheung R, Kim YH. Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease: an international, randomised, double-blind, phase 3 non-inferiority study. Lancet. 2019;393:1699–707.
86. Ponsioen CY, de Groof EJ, Eshuis EJ, Gardenbroek TJ, PMM B, Hart A, Warusavitarne J, Buskens CJ, van Bodegraven AA, Brink

MA, ECJ C, van Wagensveld BA, MCM R, Crolla R, Noomen CG, APJ H, Mallant RC, Boom M, Marsman WA, Stockmann HB, Mol B, de Groof AJ, Stokkers PC, D'Haens GR, Bemelman WA, LIR!C Study Group. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. Lancet Gastroenterol Hepatol. 2017;2:785–92.

87. de Groof EJ, Stevens TW, Eshuis EJ, Gardenbroek TJ, Bosmans JE, van Dongen JM, Mol B, Buskens CJ, Stokkers PCF, Hart A, D'Haens GR, Bemelman WA, Ponsioen CY, LIR!C Study Group. Cost-effectiveness of laparoscopic ileocaecal resection versus infliximab treatment of terminal ileitis in Crohn's disease: the LIR!C trial. Gut. 2019;68:1774–80.
88. Peyrin-Biroulet L, Sandborn W, Sands BE, Reinisch W, Bemelman W, Bryant RV, D'Haens G, Dotan I, Dubinsky M, Feagan B, Fiorino G, Gearry R, Krishnareddy S, Lakatos PL, Loftus EV Jr, Marteau P, Munkholm P, Murdoch TB, Ordas I, Panaccione R, Riddell RH, Ruel J, Rubin DT, Samaan M, Siegel CA, Silverberg MS, Stoker J, Schreiber S, Travis S, Van Assche G, Danese S, Panes J, Bouguen G, O'Donnell S, Pariente B, Winer S, Hanauer S, Colombel JF. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. Am J Gastroenterol. 2015;110:1324–38.
89. Baert F, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, Stokkers P, Hommes D, Rutgeerts P, Vermeire S, D'Haens G, Belgian Inflammatory Bowel Disease Research Group, North-Holland Gut Club. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology. 2010;138:463–8; quiz e10–1.
90. De Cruz P, Kamm MA, Prideaux L, Allen PB, Moore G. Mucosal healing in Crohn's disease: a systematic review. Inflamm Bowel Dis. 2013;19:429–44.
91. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012;61:1619–35.
92. Rutgeerts P, Diamond RH, Bala M, Olson A, Lichtenstein GR, Bao W, Patel K, Wolf DC, Safdi M, Colombel JF, Lashner B, Hanauer SB. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointest Endosc. 2006;63:433–42; quiz 64.
93. Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, Hoffman I, Van Steen K, Vermeire S, Rutgeerts P. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis. 2009;15:1295–301.
94. Ungar B, Levy I, Yavne Y, Yavzori M, Picard O, Fudim E, Loebstein R, Chowers Y, Eliakim R, Kopylov U, Ben-Horin S. Optimizing anti-TNF-alpha therapy: serum levels of infliximab and adalimumab are associated with mucosal healing in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2016;14:550–7.e2.
95. Cornillie F, Hanauer SB, Diamond RH, Wang J, Tang KL, Xu Z, Rutgeerts P, Vermeire S. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. Gut. 2014;63:1721–7.
96. Mazor Y, Almog R, Kopylov U, Ben Hur D, Blatt A, Dahan A, Waterman M, Ben-Horin S, Chowers Y. Adalimumab drug and antibody levels as predictors of clinical and laboratory response in patients with Crohn's disease. Aliment Pharmacol Ther. 2014;40:620–8.
97. Vande Casteele N, Ferrante M, Van Assche G, Ballet V, Compernolle G, Van Steen K, Simoens S, Rutgeerts P, Gils A, Vermeire S. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology. 2015;148:1320–9.e3.
98. D'Haens G, Vermeire S, Lambrecht G, Baert F, Bossuyt P, Pariente B, Buisson A, Bouhnik Y, Filippi J, Vander Woude J, Van Hootegem P, Moreau J, Louis E, Franchimont D, De Vos M, Mana F, Peyrin-Biroulet L, Brixi H, Allez M, Caenepeel P, Aubourg A, Oldenburg B, Pierik M, Gils A, Chevret S, Laharie D, GETAID. Increasing infliximab dose based on symptoms, biomarkers, and serum drug concentrations does not increase clinical, endoscopic, and corticosteroid-free remission in patients with active luminal Crohn's disease. Gastroenterology. 2018;154:1343–51.e1.
99. Assa A, Matar M, Turner D, Broide E, Weiss B, Ledder O, Guz-Mark A, Rinawi F, Cohen S, Topf-Olivestone C, Shaoul R, Yerushalmi B, Shamir R. Proactive monitoring of adalimumab trough concentration associated with increased clinical remission in children with Crohn's disease compared with reactive monitoring. Gastroenterology. 2019;157:985–96.e2.
100. Torres J, Boyapati RK, Kennedy NA, Louis E, Colombel JF, Satsangi J. Systematic review of effects of withdrawal of immunomodulators or biologic agents from patients with inflammatory bowel disease. Gastroenterology. 2015;149:1716–30.
101. Olaison G, Smedh K, Sjodahl R. Natural course of Crohn's disease after ileocolic resection: endoscopically visualised ileal ulcers preceding symptoms. Gut. 1992;33:331–5.
102. Bernell O, Lapidus A, Hellers G. Risk factors for surgery and recurrence in 907 patients with primary ileocaecal Crohn's disease. Br J Surg. 2000;87:1697–701.
103. Nguyen GC, Loftus EV Jr, Hirano I, Falck-Ytter Y, Singh S, Sultan S, Committee AGAICG. American Gastroenterological Association Institute guideline on the management of Crohn's disease after surgical resection. Gastroenterology. 2017;152:271–5.
104. Ferrante M, Papamichael K, Duricova D, D'Haens G, Vermeire S, Archavlis E, Rutgeerts P, Bortlik M, Mantzaris G, Van Assche G, International Organization for Study of Inflammatory Bowel Diseases. Systematic versus endoscopy-driven treatment with azathioprine to prevent postoperative ileal Crohn's disease recurrence. J Crohns Colitis. 2015;9:617–24.
105. Ryan JM, Rogers AC, O'Toole A, Burke JP. Meta-analysis of histological margin positivity in the prediction of recurrence after Crohn's resection. Dis Colon Rectum. 2019;62:882–92.
106. Prantera C, Scribano ML, Falasco G, Andreoli A, Luzi C. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with Lactobacillus GG. Gut. 2002;51:405–9.
107. Ewe K, Bottger T, Buhr HJ, Ecker KW, Otto HF. Low-dose budesonide treatment for prevention of postoperative recurrence of Crohn's disease: a multicentre randomized placebo-controlled trial. German Budesonide Study Group. Eur J Gastroenterol Hepatol. 1999;11:277–82.
108. Hellers G, Cortot A, Jewell D, Leijonmarck CE, Lofberg R, Malchow H, Nilsson LG, Pallone F, Pena S, Persson T, Prantera C, Rutgeerts P. Oral budesonide for prevention of postsurgical recurrence in Crohn's disease. The IOIBD Budesonide Study Group. Gastroenterology. 1999;116:294–300.
109. Mottet C, Schoepfer AM, Juillerat P, Cosnes J, Froehlich F, Kessler-Brondolo V, Seibold F, Rogler G, Vavricka SR, Michetti P. Experts opinion on the practical use of azathioprine and 6-mercaptopurine in inflammatory bowel disease. Inflamm Bowel Dis. 2016;22(11):2733–47.

Anorectal Crohn's Disease

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Emily Steinhagen and Andrea Chao Bafford

Key Concepts

- Control sepsis: Infection must be addressed before starting immunosuppressive medications.
- Treat underlying luminal disease and control diarrhea, but avoid steroids for perianal Crohn's disease.
- Perineal care: Perineal hygiene should include gentle cleansing with sitz baths or showers and skin protection with barrier creams.
- Avoid surgery in patients who are asymptomatic or in the setting of active proctitis.
- In patients who are optimized, fistulas may be treated with long-term draining setons, advancement flaps, or LIFT.
- Skin tags or hemorrhoids should generally not be treated.
- Diversion may appropriate as component of the management of perianal Crohn's disease for some patients.

Introduction

Crohn's disease (CD) is a chronic, relapsing, inflammatory condition that can affect any part of the gastrointestinal tract, from mouth to anus. Perianal involvement was first described by Penner and Crohn in 1938 [1] and includes fistulizing (abscesses, fistulas) and non-fistulizing (hemorrhoids, skin tags, anal fissures/ulcers, anorectal stricture, malignancy) complications. Approximately 13–38% of CD patients have perianal involvement and more than 80% require surgery [2–5]. Perianal CD may cause a range of disabling symptoms, including pain, discharge, bleeding, and both sexual and defecatory dysfunction. The evaluation and treatment of patients with perianal CD requires a careful history and physical examination, endoscopic evaluation, occasional imaging, and often both medical and surgical intervention. Physicians should maintain close and candid relationships with patients and care approached in a multidisciplinary fashion. The overarching goal of treating patients with perianal CD is to provide symptom resolution while avoiding incontinence and proctectomy where possible.

General principles for management of patients with perianal CD:

- Control sepsis: Infection must be addressed before starting immunosuppressive medications.
- Treat underlying luminal disease.
- Control diarrhea.
- Perineal care: Perineal hygiene includes gentle cleansing with sitz baths or showers and skin protection with barrier creams.
- Avoid steroids: Steroids do not typically have a role in the treatment of perianal CD.
- Avoid surgery in patients who are asymptomatic.
- Avoid surgery in the setting of active proctitis when possible.

Fistulizing Complications

Epidemiology and Risk Factors

Perianal fistulas are a common feature of CD, accounting for 50–87% of perianal lesions [6]. In one population-based study, 20% of patients with CD had at least one anorectal fistula during a 25-year period [4]. Approximately 10% of CD patients present with perianal fistulas as their initial manifestation, most of whom go on to develop intestinal manifestations in the year following diagnosis [7–9]. Only about 5% of patients maintain disease isolated to the peri-

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anal region [10, 11]. The incidence of fistulizing perianal disease increases with greater disease duration and severity and more distal disease involvement [2–4, 10, 12]. Hellers reported the incidence of perianal fistulas to be 12% in patients with ileal disease, 15% in those with ileocolonic disease, 41% in patients with colonic disease sparing the rectum, and 92% in patients with colonic and rectal disease [2]. Tang found that patients with perineal fistulas had a more than threefold higher likelihood of having colonic rather than isolated ileal disease [13]. CD-related perianal fistulas frequently recur, with one prospective cohort study showing the risk of recurrent fistula activity being 48% at 1 year and 59% at 2 years [14].

Pathogenesis

Two leading mechanisms exist with regard to the pathogenesis of anorectal fistulas and abscesses: (1) Rectal inflammation causes ulcers and/or shallow fistulas, which then extend deeper with persistent exposure to feces and pressure caused by defecation [15]; and (2) infected anal glands penetrate the intersphincteric space and then progress to form fistulas or abscesses [16]. CD-related fistulas are thought to arise from the former, while the latter explains idiopathic fistulas.

Clinical Presentation and Classification

Patients with fistulizing perianal CD may present acutely with abscesses or chronically with draining fistulas. Abscesses typically cause acute onset pain, perianal swelling and tenderness, and fever. Additional signs of systemic sepsis may also occur. Fistulas without abscess typically cause chronic anorectal discomfort and mucoid, bloody, or feculent discharge from an external opening in the perianal skin, groin, or vagina or, in the case of urinary fistulization, may be associated with pneumaturia or fecaluria.

Abscess

Up to 62% of patients with perianal CD develop an anorectal abscess [17]. Abscesses occur in the perianal, ischiorectal, interspincteric, and supralevator spaces (Fig. 47.1). Ischiorectal abscesses are most common, accounting for 40% of CD-related perirectal abscesses [18]. Perianal and ischiorectal abscesses result in erythema, swelling, tenderness, induration (early), and fluctuance (late) on the affected side. Intersphincteric and supralevator abscesses may cause few overt clinical signs, and therefore imaging studies, such as CT [19], endorectal ultrasound [20], or MRI [21], are often needed for diagnosis.

Management

Prompt surgical drainage of perianal abscesses is required to control sepsis and limit damage to the sphincters and surrounding anorectal tissues [3, 22]. General anesthesia is typically advised except for the most superficial abscesses, which may be amenable to drainage under local anesthesia with incisions placed over areas of obvious fluctuance. Ischiorectal abscesses are best drained with incisions made close to the sphincter complex to result in shorter subsequent fistula tracts. Intersphincteric abscesses may be palpated via

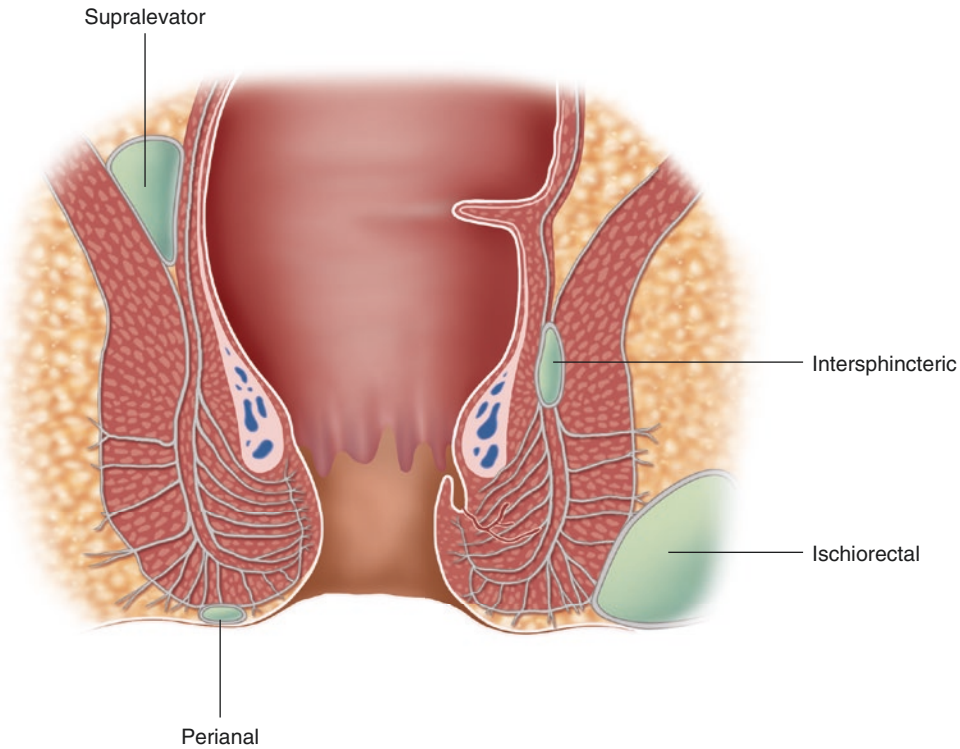

Fig. 47.1 Anorectal abscess locations

digital rectal examination as fluctuant masses within the anorectal wall. Drainage into the rectal lumen is accomplished via division of mucosa and internal sphincter muscle overlying the abscess. When fluctuance cannot be determined, needle aspiration may allow for localization of the abscess cavity. Larger abscesses are best treated with mushroom catheter drainage as wound healing is often poor in the face of acute inflammation and infection; wound packing can impede drainage and dressing changes are often poorly tolerated. For similar reasons, when an internal fistula opening is identified at the time of abscess drainage, seton drainage rather than fistulotomy should be performed even when fistulas are low-lying. The addition of aerobic and anaerobic culture and antibiotic treatment should be considered in immunosuppressed patients and those with significant cellulitis or systemic signs of sepsis.

Anorectal Fistula

A fistula is a chronic track of granulation tissue connecting two epithelial-lined surfaces. CD-related perianal fistulas can connect the anorectum with the perianal, buttock, perineal, thigh, or inguinal skin, the vagina, and the urinary tract. In 1976, Parks proposed an anatomical classification system for anal fistulas defined by their relationship to the external sphincter [16]. In order to also describe additional perianal manifestations of CD, the American Gastroenterological Association developed an empiric approach to fistula classification based on physical and endoscopic examinations [3]. Fistulas are classified as either "simple" or "complex." A simple fistula is low (superficial, low intersphincteric, low transsphincteric), has a single external opening, has no pain or fluctuance to suggest perianal abscess, is not a rectovaginal fistula, and is not associated with an anorectal stricture. A complex fistula is high (high intersphincteric, high transsphincteric, extrasphincteric, or suprasphincteric), may have multiple external openings, may be associated with the presence of pain or fluctuance suggestive of an abscess, may be associated with the presence of a rectovaginal fistula, may be associated with the presence of an anorectal stricture, and may be associated with the presence of active rectal disease at endoscopy.

Diagnosis

Precise determination of fistula anatomy is required for treatment of CD-related perianal fistulas. Fistula anatomy is typically determined using a multimodal approach combining physical examination, examination under anesthesia (EUA), and imaging techniques. On physical examination, external fistula openings may be visualized and underlying infection/inflammation determined by inspecting for erythema, purulence, and swelling, and palpating for induration, fluctuance, warmth, and tenderness. Occasionally, fistula tracks may be identified by palpating a firm "cord" of indurated tissue between the external fistula opening and the anus. Digital rectal examination may identify defects in the anorectal wall, fluctuance, an underlying stricture, or decreased sphincter tone. Anoscopy may identify internal fistula openings and underlying proctitis.

However, office examination, particularly DRE, and anoscopy are often limited by patient discomfort and are rarely therapeutic, making EUA favored in most situations. MRI and endorectal ultrasound (ERUS) have largely replaced CT and fistulography for imaging evaluation of perianal fistulas due to better accuracy. A triple blinded study comparing ERUS, MRI, and EUA showed excellent accuracy of all three modalities in determining fistula anatomy, rates being 91%, 87%, and 91%, respectively [23]. Combining any two modalities led to 100% accuracy. More recently, Sahni concluded that MRI exceeds EUA and ERUS in distinguishing complex from simple fistulas, based on a comprehensive review combining data from literature review, consensus guidelines, and consultations with experts [24]. The likelihood ratio for MRI confirming complex disease was found to be 22.7 compared to 2.1 and 6.2 for clinical examination and ERUS, respectively. Further, several societies, including the Shanghai Group and the European Society of Crohn's and Colitis (ECCO), also regard MRI as the gold standard imaging technique for perianal CD [25]. EUA without preceding imaging is likely adequate for patients with simple fistulas. For patients with complex fistulas, preoperative anatomic mapping via pelvic MRI should be considered prior to EUA.

Management

The first step in the management of patients with CD-related perianal fistulas is to eradicate infection. This is accomplished primarily with surgical drainage. Once sepsis is cleared, endoscopic evaluation is necessary to detect any luminal disease, in particular active proctitis also requiring treatment.

Medical Management

Antibiotics

Antibiotics are frequently used as the initial medical therapy for perianal CD in conjunction with treatment of underlying luminal disease; however the evidence for this is somewhat limited. Two randomized placebo-controlled trials (RCTs) have assessed antibiotic use combined with biologic therapy. Ciprofloxacin combined with infliximab had a higher response than infliximab alone (73% vs. 39%, $P = 0.12$) [26]. Given with adalimumab, ciprofloxacin also led to an improved 12-week clinical response (71% vs. 47%, $P = 0.047$) [27]. One small RCT comparing ciprofloxacin, metronidazole, and placebo was underpowered to detect any statistically significant effect [28].

In a prospective, open-label study, half of patients receiving either an 8-week regimen of ciprofloxacin (500–1000 mg/

day) or metronidazole (1000–1500 mg/day) in addition to azathioprine had significantly improved perianal disease scores (PDAI 8.4 ± 2.9 to 6 ± 4; $P < 0.0001$), with 25% achieving complete healing [29]. In a systemic review and meta-analysis including 3 trials of 123 patients with perianal CD fistula, treatment with either ciprofloxacin or metronidazole significantly reduced fistula drainage (RR = 0.8; 95% CI = 0.66–0.98), with a number needed to treat of 5 (95% CI = 3–20) [30]. In another meta-analysis, ciprofloxacin was effective in reducing perianal fistula drainage but not providing closure (RR, 1.64; 95% CI, 1.16–2.32; $P = 0.005$) [31]. However, recurrence following antibiotic discontinuation is common, and both side effects and potential for antibiotic resistance limit their use. Antibiotics should therefore be used primarily as a bridge to immunosuppressant therapy and not as sole therapy.

Thiopurines

Thiopurines are best used in combination with anti-TNF therapy or in patients who cannot tolerate anti-TNF therapy, rather than as first-line agents [32]. In a meta-analysis of RCTs comparing azathioprine (AZA) or 6-mercaptopurine (6-MP) to placebo, perianal fistula response, defined as complete healing or decreased discharge, was seen in 54% (22/49) of treated patients compared to 21% (6/29) in the placebo group (pooled OR 4.44, 95% CI 1.50–13.2) [33]. Lecomte found that 29% of patients with CD-related anal fistulas, fissures, and/or strictures responded to AZA or 6-MP; however, absence of fistula, age >40, and shorter disease duration predicted better response [34]. Due to delayed response times of 3 of more months, these immunomodulators should typically be initiated in conjunction with other medications and used to maintain rather than induce fistula closure [35].

Calcineurin Inhibitors

A small and short-term RCT by Sandborn showed that tacrolimus at 0.2 mg/kg/day was effective in improving fistula drainage (43% vs. 8%, $p < 0.05$), but not closure ($p = 0.86$) [36]. Cyclosporine has also been shown to have some efficacy in CD-related perianal fistulas in multiple non-controlled trials. In a retrospective study, intravenous cyclosporine followed by oral cyclosporine achieved symptomatic improvement in 80–85% of patients acutely and closure in 45% of patients chronically; however, recurrence occurred after discontinuation [37]. Present also reported high initial response (88%) and closure (44%) rates with parenteral and then oral cyclosporine with loss of response after treatment discontinuation [38]. These agents, however, have significant side effects including nephrotoxicity, and close drug monitoring is required. Their role appears to be limited to some patients with severe CD intolerant or unresponsive to multimodality therapy, including anti-TNF agents, in whom the options of fecal diversion or proctectomy are being considered as a last resort [3].

Biologics

Infliximab was the first anti-TNF agent to show efficacy in the treatment of CD-related perianal fistulas in two RCTs as well as in multiple non-controlled trials [39–43]. In an RCT, 85 patients with CD-related perianal fistulas were randomized to treatment with infliximab 5 or 10 mg/kg at 0, 2, and 6 weeks versus placebo [39]. Closure of at least 50% of fistulas was maintained for at least 4 weeks in 68% of patients treated with infliximab 5 mg/kg and 56% of patients treated with infliximab 10 mg/kg, compared with 26% of patients treated with placebo ($p = 0.002$ and $p = 0.02$, respectively). Closure of all fistulas was maintained for at least 4 weeks in 13% for placebo, 55% for infliximab 5 mg/kg, and 38% for infliximab 10 mg/kg ($p = 0.001$ and $p = 0.04$, respectively). The median time to response was 2 weeks and fistulas remained closed for approximately 3 months.

However, more patients treated with infliximab developed perianal abscesses than placebo-treated patients, thought possibly due to closure of the external fistula opening before the fistula tract itself. In the ACCENT II trial, 306 patients with fistulizing CD were treated with infliximab 5 mg/kg at weeks 0, 2, and 6. Patients who responded to therapy were then randomized into maintenance doses of placebo every 8 weeks beginning at week 14 or maintenance doses of infliximab 5 mg/kg every 8 weeks beginning at week 14 [40]. The median time to loss of response through week 54 was 14 weeks for patients in the placebo group and >40 weeks for patients treated with infliximab 5 mg/kg ($p < 0.001$). At week 54, 39% of patients in the infliximab maintenance group had complete closure of all draining fistulas compared to 19% of those in the placebo group ($p = 0.009$).

Adalimumab has also been shown to close CD-related fistulas in infliximab-naïve patients as well as those who previously failed infliximab treatment in two RCTs and multiple retrospective studies [44–49]. In the CHARM trial, 30% of patients with perianal fistulas treated with adalimumab for 26 weeks had fistula closure compared to 13% of patients treated with placebo ($p < 0.04$) [44]. Fistulas were closed in 33% of treated patients vs. 13% of controls at week 56 ($p < 0.02$). The efficacy of certolizumab in fistulizing perianal CD was evaluated within the PRECiSE trials [50, 51]. Fifteen of 28 (54%) of patients had fistula closure compared with 13/30 (43%) in the placebo group; this difference did not reach statistical significance ($p = 0.069$) [52].

Combining anti-TNF agents with additional therapies including thiopurines [53, 54], ciprofloxacin [26, 27], and exam under anesthesia [55] may further improve clinical response, remission durability, and patient tolerance. Feagan evaluated the efficacy of maintenance vedolizumab, an α4β7 integrin monoclonal antibody, in a subpopulation of patients

from the GEMINI 2 trial [56, 57]. Fistula closure was achieved in 28% of vedolizumab-treated patients versus 11% of control patients at 14 weeks. Vedolizumab-treated patients also had faster time to fistula closure and higher rates of fistula closure at week 52 (33% vs. 11%; HR 2.54; 95% CI, 0.54–11.96). Finally, in limited, small, retrospective studies, ustekinumab, an anti-IL12/23 IgG1 kappa human monoclonal antibody, has been shown to improve fistula symptoms and achieve closure in 61% and 31% of patients, respectively [58, 59].

Surgical Management

Fistula anatomy, underlying inflammation, and presence of complicating factors, such as proctitis and abscess, determine surgical options for CD-related perianal fistulas. In the setting of active proctitis or abscess, both fistulotomy and definite repair should be avoided due to risks of poor wound healing and failure. Unfortunately, complex fistulas are seen in 80% of CD patients, and these are associated with higher rates of recurrence and failure to heal [9, 60, 61]. As a result, patients with CD are more likely to have setons placed and less likely to undergo curative treatment for their anal fistulas [62].

Fistulotomy

Conventional fistulotomy by laying open the fistula tract and any side tracts can be safely performed in the absence of proctitis. This procedure is usually performed in the operating room under anesthesia in either prone or lithotomy position. A metal probe is passed from the external fistula to the internal fistula opening. Saline, diluted hydrogen peroxide, or diluted methylene blue injection may be used to help identify the internal fistula opening. The tissue overlying the probe is palpated and, if minimal or no sphincter muscle involvement is confirmed, divided with cautery. The wound is then gently debrided and may be marsupialized. In a study by Williams, 41 fistulotomies were performed in 33 patients with subcutaneous [17], intersphincteric [19], or low transsphincteric [5] fistulas with a 73% and 93% rate of wound healing at 3 and 6 months, respectively. Twelve percent of patients experienced minor degrees of incontinence [63]. Other retrospective studies have reported similar results [64–66]. A Crohn's Disease Activity Index (CDAI) of greater than 150 has been suggested as a contraindication to fistulotomy [67].

Draining Seton

Patients with complex perianal fistula without abscess typically require EUA with seton placement in conjunction with medical therapy. Loose, thin, silastic setons should be placed after identifying the fistula tracts as described above for fistulotomy. Draining setons maintain fistula tract patency, decrease inflammation around the tract, and often prevent the development of recurrent abscesses [62, 68]. Studies have demonstrated higher rates of fistula healing and longer duration of closure when draining setons are added to anti-TNF and other medical therapies [53, 69, 70]. A recent systematic review by de Groof included 10 non-controlled studies, with a total of 305 patients treated with setons and anti-TNF therapy. Complete fistula closure rate varied between 13.6% and 100% and recurrence ranged from 0% to 83% [71]. Setons may remain in place for months to years, or even permanently. After active proctitis is addressed medically, seton removal can occur in up to 98% of patients at a median of 33 weeks [53]. Timing of seton removal should be coordinated between the patient's colorectal surgeon and gastroenterologist, typically after anti-TNF induction is complete [68].

Endorectal Advancement Flap

Endorectal advancement flaps can be used in CD patients without active proctitis. The internal fistula opening is identified, and the crypt-bearing tissue as well as a rim of anoderm below is excised. The internal anal sphincter opening is then closed and a U-shaped flap of mucosa, submucosa, and internal anal sphincter advanced over this closure and sutured down without tension. Success rates of about 60–64% have been reported; however recurrence rates of 57% and incontinence rates of 9.4% were also found [72–74]. Joo showed that the presence of concomitant small bowel disease predicted poorer outcome [73]. Smoking has also been found to negatively impact results of flap repair [75]. In addition to proctitis, cavitating ulceration and anal stenosis are also considered relative contraindications to this technique [76]. The advancement rectal sleeve procedure involves circumferential excision, lifting the anal canal mucosa from the dentate line to the anorectal ring, mobilization of a full-thickness rectal flap, and anastomosis of the rectal sleeve to the dentate line; Marchesa described this as an alternative technique in patients with severe, complex fistulizing disease in whom proctectomy is being considered [77].

Ligation of the Internal Fistula Tract (LIFT)

The LIFT procedure involves ligating and transecting the fistula tract within the intersphincteric space. Two small retrospective studies examined the use of this technique in CD-related perianal fistulas. Gingold reported a 67% rate of clinical healing at 12 months in 15 patients, with no patient experiencing incontinence [78]. Kaminski reported healing in 6 of 8 (75%) patients at less than 1-year follow-up and 5 of 15 (33%) patients with more than 1-year follow-up [79]. In multifocal CD, success was higher in patients with small bowel disease ($p = 0.04$) compared with colonic disease ($p = 0.02$).

Fibrin Glue and Fistula Plugs

Fibrin glue treatment involves the injection of biodegradable glue into the fistula tract in order to stimulate fibroblasts to form a fibrin clot seal [80]. This technique has the advantage of maintaining the integrity of the anal sphincters, and therefore repeat injections can be performed. Highly variable success rate between 0% and 100% has been reported, and data in CD patients is limited to small case series with relatively short-term follow-up [80–82]. Anal fistula plugs are bioprosthetic grafts that provide a collagen scaffold over which a patient's endogenous cells populate. Similar to fibrin glue, published results vary widely with studies showing a 15–100% rate of healing [83–86]. In a systematic review, the success rate of the plug was 55% [85]. One multicenter RCT in 106 CD patients reported that fistula plug treatment had similar efficacy as seton removal alone [87].

Mesenchymal Stem Cell Therapy

Local injection of mesenchymal stem cells is a promising new therapy for nonhealing perianal fistulas. In a phase 3 trial of 212 CD patients with complex fistulas, higher rates of fistula closure were found for patients who received adipose-derived stem cell injection compared to placebo (56.3% vs. 38.6%, respectively; 95% CI 4.2–31.2, $p = 0.010$) [88]. Study patients also had significantly shorter time to clinical remission (6.7 vs. 14.6 weeks). Other trials have similarly shown this procedure is safe and efficacious in patients with CD [89–94].

In a recent systematic review and meta-analysis of 11 studies, Lightner reported improved healing with mesenchymal stem cells compared with placebo at primary end points of 6–24 weeks [OR = 3.06 (95% CI, 1.05–8.90); $p = 0.04$] and 24–52 weeks [OR = 2.37 (95% CI, 0.90–6.25); $p = 0.08$] [95]. Another meta-analysis showed higher healing and clinical response rates in patients with baseline CDAI >150 than those with baseline CDAI <50 (79.17 vs. 47.53, $P = 0.011$), higher healing rate and lower recurrence rate with a moderate dose of 2–4 × 107 cells/mL compared to other dosages, and lower recurrence with adipose-derived MSCs therapy compared to bone marrow-derived MSCs (RR 7.4 ± 4.28 vs. 13.39 ± 0.89) [96]. These studies, however, were limited by heterogeneous patient populations, variable medication dosing, non-standardized methods of drug delivery, and differing definitions of success. One study reported fistula relapse-free survival of 37% for 4 years after treatment and cumulative probabilities of surgery- and medical-free survival of 63% and 25% at 5 and 6 years, respectively; however, the majority of reports lack long-term follow-up [97].

Rectovaginal Fistula

The incidence of anovaginal or rectovaginal fistula (RVF) in women with CD is approximately 10%; the median age of onset is 34 years [4, 98]. They are caused by an inflammatory process in the anus or rectum that is severe enough to erode through the vaginal wall. The most frequent disease distribution associated with RVF is colonic rather than small bowel disease [99, 100]. While some RVFs cause minimal or no symptoms, many significantly impact quality of life. Patients may experience seepage or incontinence of gas or stool via the fistula, leading to vaginal and perineal irritation. Sexual dysfunction, including dyspareunia, and urinary tract infections may also be present.

Prior to considering repair of an RVF, control of perianal sepsis and optimization of medical management should be accomplished. Examination under anesthesia with drainage of any abscesses and placement of setons can often accomplish the former; close collaboration with a gastroenterologist is essential for the latter. It may be helpful to establish the extent of sphincter damage and whether it is intact either via MRI or ultrasound [101]. Options for repair include advancement flaps from the anal or vaginal side, interposition either with gracilis or Martius (bulbocavernosus) flaps, episioproctotomy, or abdominal approaches such as pull-through procedures. Other approaches that have been described include fibrin glue or stem cell injection, fistula plugs, mesh interposition, and other novel techniques. The data on outcomes following RVF repair tends to be small case series, including fewer than 20 patients. As such, predictors of successful healing are largely unknown.

One study of RVF repair with rectal advancement flap found a healing rate of 42% for initial repair in 12 patients; this rose to 83% after up to 3 attempts [102]. This technique is appropriate in women with an otherwise normal anal canal, as those with significant stricture or sphincter defect are less likely to heal. In cases of anal stenosis, a vaginal flap consisting of healthy, nondiseased tissue may be more appropriate [103]. Sphincter defects should be repaired simultaneously, when present.

The Martius flap utilizes a pedicle graft to interpose healthy tissue between the rectal and vaginal sides of the fistula. After perineal dissection separating the rectovaginal septum to above the fistula defect is completed, an incision is made over the labia majora and the bulbocavernosus muscle mobilized. A subcutaneous tunnel is then created to the mobilized rectovaginal septum and the anterior portion of the flap pulled through the tunnel and sutured to the posterior vaginal wall. Healing rates varying between 50% and 100%, with or without fecal diversion, have been reported [104, 105]. For gracilis flap repairs, the gracilis muscle is harvested from the thigh, preserving the neurovascular bundle. The flap is rotated into the rectovaginal space via a subcutaneous tunnel and secured in place. Series of RVF repair with gracilis flap formation report healing rates ranging from 33% to 80%; however none included more than 11 patients [106–109]. One study that assessed quality of life before and after gracilis flap repair found that while seven of eight women

were sexually active before surgery, only four remained active following repair [109].

There are two studies with just three and nine patients that described the use of biologic (porcine-derived) mesh for RVF; healing ranged from 50% to 78% [110, 111]. Plugs have a healing rate of 50% in CD patients based on limited studies [112]. In an RCT of stem cell injection, CD patients with RVF achieved a remission rate of 51% at 24 weeks compared to 35% in controls [113]. In studies that include more than one technique with the primary end point of overall fistula healing, success rates range from 50% to 80% at 5 years with a rate of proctectomy of about 20% [114, 115].

In general, starting with an advancement flap repair and proceeding to more complex procedures if there is failure often makes sense. In the setting of recurrent fistulas, diversion is more frequently considered. Stomas may also be used before repair to minimize symptoms and improve inflammation of the perineal tissues related to seepage and soilage. Up to 60% of CD patients with RVF require temporary fecal diversion, and up to half require a permanent stoma for their perianal disease [116].

Medical management plays an important role in healing of RVF. Immunomodulators improve healing rates, while smoking and steroid use decrease success [117, 118]. A study of RVF repair that included a number of different techniques in both CD and non-CD patients found that repair at a short interval from diagnosis, no previous repairs, major procedures, and fecal diversion were also prognostic of success [119].

Non-fistulizing Complications

Anal Fissures and Ulcers

In the setting of CD, the etiology of anal fissures may be similar to that in non-Crohn's patients – from repeated bowel movements traumatizing the anal canal – or as a sequelae of anal canal inflammation related to the disease itself. Idiopathic fissures are generally located in the anterior (10%) or posterior (90%) midline and are associated with sharp pain and bright red blood with bowel movements. These fissures are located between the anal verge and dentate line and are associated with a hypertonic internal anal sphincter. CD patients experience idiopathic fissures as well as atypical fissures, which are frequently multiple and located off midline [120]. Atypical fissures classically have a granulating base with overhanging edges and may extend beyond the verge onto the perianal skin (Fig. 47.2). Large cavitating ulcers with significant tissue loss may also be seen (Fig. 47.3).

Atypical fissures occur due to direct involvement of the perianal tissues with CD-related inflammation. They often cause pain, bleeding, and, occasionally, pruritus. Unlike idiopathic fissures, they are not associated with increased internal anal sphincter tone. Biopsies demonstrate non-necrotizing epithelioid cell granulomas in about three-quarters of cases [121]. When these lesions present in healthy patients not known to have CD, other ulcer-related anal diseases such as carcinoma, radiation-related changes, syphilis, herpes, AIDS, gonorrhea, chlamydia, tuberculosis, and leukemia must be ruled out [122].

If fissures appear to be idiopathic in nature, even in patients with CD, they should be treated with the same algorithm used in non-CD patients. When fissures are present in the context of numerous bowel movements, controlling stool frequency is an appropriate first goal. This is accomplished by treating the underlying luminal disease and may be aided by anti-diarrheal or bulking agents, such as psyllium-based fiber. Minimizing toilet time, gentle perianal skin care, and topical agents such as nitroglycerine, calcium channel block-

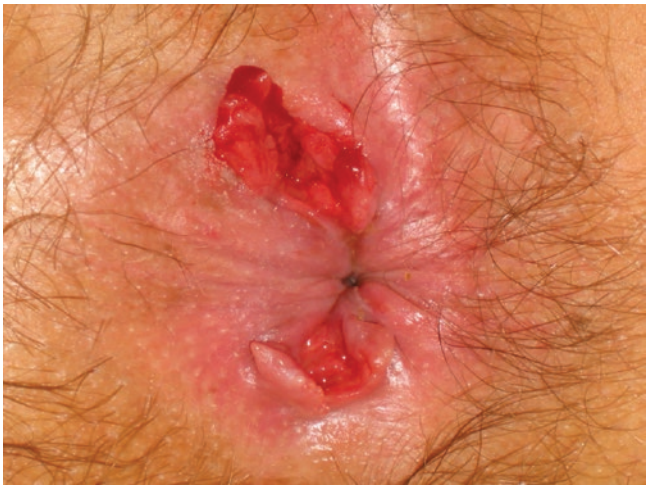

Fig. 47.2 Severe fissures and ulcers

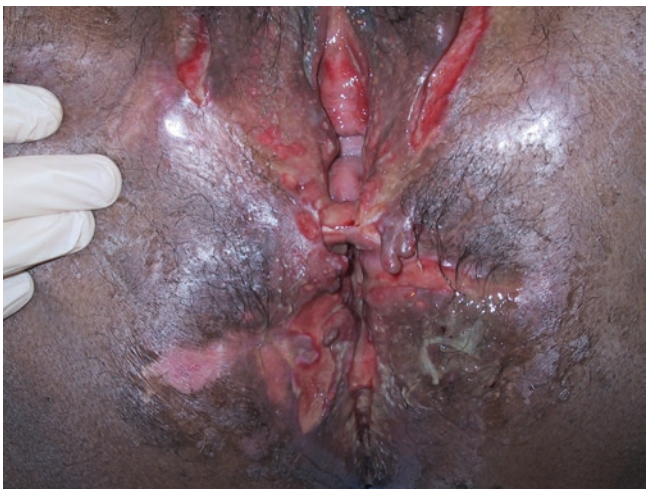

Fig. 47.3 Cavitating ulcers

ers, and botulinum toxin injections may also be useful. Hot baths and perianal hygiene may relieve symptoms as well. While these measures are highly successful in non-CD patients, data regarding their use in CD patients is limited.

The safety and efficacy of lateral internal sphincterotomy (LIS) in patients with CD has been studied in a small series by Fleshner [120]. The authors concluded that if patients have a single, characteristic midline fissure associated with a hypertonic sphincter and a disease-free rectum, LIS is appropriate. Additionally, when medical management was compared to LIS combined with fissurectomy in 56 CD patients, there was 67% short-term healing in the surgical group compared to 50% in the medical group. In the subset of patients with luminal disease, the healing rate fell to 43%. In long-term follow-up, 60% of the surgical group healed compared with 49% of the medical group. Of the patients with non-healed fissures, one quarter eventually developed a fistula. However, in other series, nearly 60% of CD patients treated surgically for fissure (botulinum toxin +/− fissurectomy, or LIS) experienced complications, including poor wound healing, recurrence, and fistulas [123].

Fissures and ulcers associated with CD inflammation are challenging to treat. In the absence of sphincter hypertonicity, strategies that decrease tone should be avoided, both because they will not help and because they can threaten continence in patients who may already have impaired control and are prone to loose bowel movements. Topical metronidazole 10% has demonstrated improvement in pain, drainage, induration, and CDAI at 4 weeks [124]. Tacrolimus 0.1% has also been used successfully. Systemic treatments such as steroids, antibiotics, aminosalicylates, and immunomodulators have shown inconsistent results [125–129]. Other small studies have reported some success with thalidomide [130], cyclosporine [37], hyperbaric oxygen [131], and local infiltration of infliximab [132].

Systemic anti-TNF medications have become the gold standard for the treatment of perianal CD, including fissures and ulcers. One large retrospective study demonstrated a 43% rate of complete healing and symptom resolution with anti-TNF therapy; healing was maintained in 73% of responders at 175 weeks [53]. Local infliximab injection adds minimal benefit in patients already receiving systemic infliximab [132].

The presence of CD-related fissures and ulcers is not insignificant; the likelihood of anoproctectomy is approximately 80% in patients with cavitating ulcers [133].

Skin Tags

CD-related skin tags can be classified by their appearance [3]. Type 1 skin tags are edematous and hard and may be cyanotic and tender (Fig. 47.4). These typically arise as sequelae of fissures, ulcers, or hemorrhoids when there is lymphedema secondary to lymphatic obstruction. Type 2 skin tags are raised lesions with a range of shapes from broad to narrow and soft or firm; these painless tags are often referred to as "elephant ear tags" and generally occur in multiplicity (Fig. 47.4b). The cumulative 10-year incidence of skin tags among CD patients is about 19% [134]. Skin tags may be asymptomatic or cause discomfort, pruritus related to difficulty with hygiene, or poor cosmesis. Additionally, symptomatic skin tags may signify active intraluminal disease [135].

Patients with symptomatic skin tags and active proctitis should have treatment directed at controlling inflammation. This has the dual purpose of improving bowel movements and decreasing inflammation of the tags themselves. Sitz baths, moistened wipes for hygiene, and careful cleansing also help reduce the symptoms of irritated skin tags.

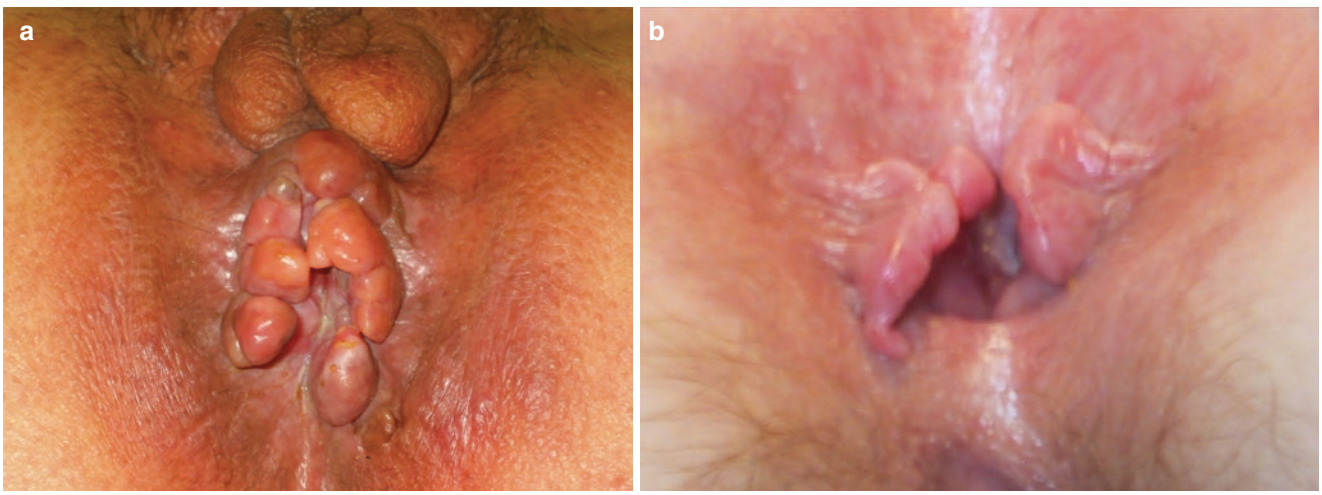

Fig. 47.4 (**a**, **b**) Type 1 and Type 2 skin tags

For patients in remission complaining of hygiene issues and impaired quality of life due to large or multiple skin tags, excision can be considered, particularly when tags are narrow-based and resulting defects will be small. However, it is difficult to truly quantify the risk in this situation, and a good understanding of the potential complications is critical.

Hemorrhoids

Hemorrhoidal disease is uncommon in the setting of CD; in a cohort of 50,000 hemorrhoid patients, only 20 had CD [136]. In studies specifically of IBD patients, 3–20% are reported to have hemorrhoids [137].

Studies show poor outcomes following hemorrhoid surgery in patients with CD; however the quality of this data is limited. Multiple early reports describe high rates of proctectomy following hemorrhoid surgery [137]. However, these studies likely demonstrate an association between hemorrhoids and skin tags with severe distal disease, rather than implicate that complications of hemorrhoid surgery lead to proctectomy. In other words, proctectomy is a reflection of the natural progression of severe disease rather than the hemorrhoid excision itself. Despite the dictum to avoid hemorrhoid surgery in CD patients, some authors have suggested that carefully selected patients may have acceptable outcomes [138]. While historically, poor wound healing has limited the application of hemorrhoid surgery to CD patients [137], a more recent study showed that of 36 patients who underwent excisional hemorrhoidectomy, only 4 had complications of nonhealing wound, anal stenosis, abscess/fistula, and recurrent bleeding. Three patients (8%) required fecal diversion for their perianal disease at a median follow-up of 31 months [139].

In patients with CD, addressing hemorrhoids surgically may be reasonable in those with luminal remission without the need for corticosteroids and a CDAI <150 [123]. However, conservative management is generally preferred.

Anal Stricture

Anal or rectal strictures typically arise as a consequence of prolonged transmural inflammation. They occur in 17% of patients with perianal CD and rarely occur without concurrent perianal disease [133]. While some patients are asymptomatic, most report symptoms of hematochezia, constipation, pain, or incontinence [140]. Digital rectal exam or proctoscopy easily establishes the diagnosis. Asymptomatic strictures do not require any specific treatment, although underlying proctitis or other perianal manifestations should be treated. When strictures obstruct defecation, dilation can be performed either manually or with balloon or Hegar dilators. Repeat dilations are frequently needed as strictures tend to recur. However, this should not be regarded as treatment failure so long as the patient experiences symptomatic relief between dilations. Rectal advancement has also been described for anal stricture with some success [141]. Nevertheless, about half of patients with an anorectal stricture eventually undergo proctectomy [140, 142].

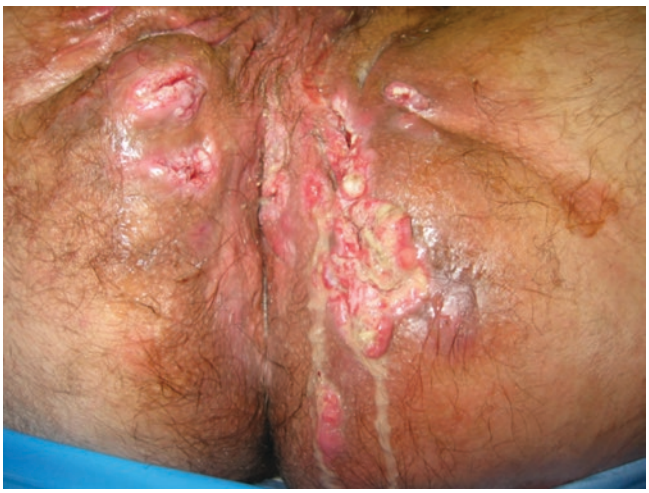

Fig. 47.5 Squamous cell carcinoma in multiple fistula tracts

Anal Cancer

The risk of both adenocarcinoma and squamous cell carcinoma is increased in patients with long-standing perianal CD [143, 144]. These occur in the anal canal itself or within chronic fistula tracts (Fig. 47.5). Diagnosis is made by biopsy. Cancers are often discovered late and require a high index of suspicion [145]. A long-standing previously asymptomatic fistula that acutely causes symptoms is suspicious for malignant degeneration as is a newly inflamed chronic fissure. The treatment of anal cancer in patients with perianal CD mirrors that for sporadic cancer.

Diversion and Proctectomy for Perianal Crohn's Disease

Severe perianal CD may require temporary or permanent fecal diversion (Fig. 47.6). This occurs at a rate of 10–20% [22]. Risk is increased with active rectal disease and anal stricture [146]. Patients with active colonic CD and an anal stricture are also at increased risk of permanent diversion as well as proctectomy.

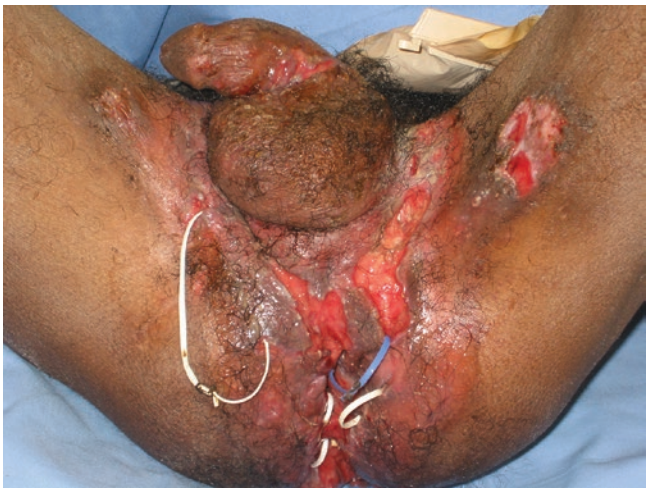

Fig. 47.6 Severe perianal CD requiring diversion

The risk of perineal wound complications following primary closure is up to 36% in patients with CD [147, 148]. Risk is higher with active inflammation and in patients with extensive perianal disease causing a "watering-can" perineum. Even after prolonged healing, some patients will have chronic perineal sinuses [149].

Depending on the presence of active inflammation, a staged approach to complete proctectomy may be most appropriate. During the first stage, the rectum is transected at the level of the levator muscles, and a permanent stoma is created. Once the patient has recovered, the perianal disease is often substantially improved allowing for a limited perineal anoproctectomy with decreased risk of wound complications [150]. An intersphincteric dissection sparing the external sphincter muscle should be utilized when feasible to minimize the risk and size of the perineal wound. Primary closure is associated with poor healing in up to one-third of patients [151]. Nonhealing wounds lead to significant morbidity and may necessitate skin grafting or myocutaneous flap reconstruction.

Conclusions

Perianal CD is a source of significant morbidity for those affected by it. Early treatment of perianal sepsis is essential. Straightforward problems, such as skin tags, hemorrhoids, and simple fistulas, can often be managed similarly to their non-CD forms. Combined medical and surgical therapy and close collaboration between surgeons and gastroenterologists are essential for optimal outcomes, particularly in more complex cases. The goals of treatment should be elimination of infection, adequate symptomatic control, preservation of continence and function, and maximizing quality of life.

References

1. Penner A, Crohn BB. Perianal fistulae as a complication of regional ileitis. Ann Surg. 1938;108(5):867–73.
2. Hellers G, Bergstrand O, Ewerth S, Holmström B. Occurrence and outcome after primary treatment of anal fistulae in Crohn's disease. Gut. 1980;21:525–7.
3. Sandborn WJ, Fazio VW, Feagan BG, Hanauer SB, American Gastroenterological Association Clinical Practice Committee. AGA technical review on perianal Crohn's disease. Gastroenterology. 2003;125(5):1508–30.
4. Schwartz DA, Loftus EV Jr, Tremaine WJ, et al. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. Gastroenterology. 2002;122(4):875–80.
5. Lapidus A, Bernell O, Hellers G, Lofberg R. Clinical course of colorectal Crohn's disease: a 35-year follow-up study of 507 patients. Gastroenterology. 1998;114(6):1151–60.
6. Geltzeiler CB, Wieghard N, Tsikitis VL. Recent developments in the surgical management of perianal fistula for Crohn's disease. Ann Gastroenterol. 2014;27(4):320–30.
7. Kotze PG, Shen B, Lightner A, et al. Modern management of perianal fistulas in Crohn's disease: future directions. Gut. 2018;67(6):1181–94.
8. Williams DR, Coller JA, Corman ML, Nugent FW, Veidenheimer MC. Anal complications in Crohn's disease. Dis Colon Rectum. 1981;24(1):22–4.
9. Molendijk I, Nuij VJ, van der Meulen-de Jong AE, van der Woude CJ. Disappointing durable remission rates in complex Crohn's disease fistula. Inflamm Bowel Dis. 2014;20(11):2022–8.
10. Farmer RG, Hawk WA, Turnbull RB Jr. Clinical patterns in Crohn's disease (a statistical study of 615 cases). Gastroenterology. 1975;68(4 Pt 1):627–35.
11. Lockhart-Mummery HE. Symposium. Crohn's disease: anal lesions. Dis Colon Rectum. 1975;18(3):200–2.
12. Cosnes J, Cattan S, Blain A, et al. Long-term evolution of disease behavior of Crohn's disease. Inflamm Bowel Dis. 2002;8(4):244–50.
13. Tang LY, Rawsthorne P, Bernstein CN. Are perineal and luminal fistulas associated in Crohn's disease? A population-based study. Clin Gastroenterol Hepatol. 2006;4(9):1130–4.
14. Makowiec F, Jehle EC, Starlinger M. Clinical course of perianal fistulas in Crohn's disease. Gut. 1995;37(5):696–701.
15. Hughes LE. Surgical pathology and management of anorectal Crohn's disease. J R Soc Med. 1978;71(9):644–51.
16. Parks AG. Pathogenesis and treatment of fistula-in-ano. Br Med J. 1961;1(5224):463–9.
17. Wolff BG, Culp CE, Beart RW, Ilstrup DM, Ready RL. Anorectal Crohn's disease. A long-term perspective. Dis Colon Rectum. 1985;28(10):709–11.
18. Solomon MJ. Fistulae and abscesses in symptomatic perianal Crohn's disease. Int J Color Dis. 1996;11(5):222–6.
19. Khati NJ, Sondel Lewis N, et al. CT of acute perianal abscesses and infected fistulae: a pictorial essay. Emerg Radiol. 2015;22(3):329–35. https://doi.org/10.1007/s10140-014-1284-3.
20. Visscher AP, Felt-Bersma RJ. Endoanal ultrasound in perianal fistulae and abscesses. Ultrasound Q. 2015;31(2):130–7. https://doi.org/10.1097/RUQ.0000000000000124.
21. O'Malley RB, Al-Hawary MM, Kaza RK, Wasnik AP, Liu PS, Hussain HK. Rectal imaging: part 2, Perianal fistula evaluation on pelvic MRI--what the radiologist needs to know. AJR Am J Roentgenol. 2012;199(1):W43–53. https://doi.org/10.2214/AJR.11.8361.
22. Singh B, McC Mortensen NJ, Jewell DP, George B. Perianal Crohn's disease. Br J Surg. 2004;91(7):801–14.

23. Schwartz DA, Wiersema MJ, Dudiak KM. A comparison of endoscopic ultrasound, magnetic resonance imaging, and exam under anesthesia for evaluation of Crohn's perianal fistulas. Gastroenterology. 2001;121(5):1064–72.
24. Sahni V, Ahmad R. Which method is best for imaging of perianal fistula? Abdom Imaging. 2008;33(1):26–30. https://doi.org/10.1007/s00261-007-9309-y.
25. Gallego JC, Echarri A. Role of magnetic resonance imaging in the management of perianal Crohn's disease. Insights Imaging. 2018;9(1):47–58. https://doi.org/10.1007/s13244-017-0579-9.
26. West RL, van der Woude CJ, Hansen BE, et al. Clinical and endosonographic effect of ciprofloxacin on the treatment of perianal fistulae in Crohn's disease with infliximab: a double-blind placebo-controlled study. Aliment Pharmacol Ther. 2004;20(11–12):1329–36.
27. Dewint P, Hansen BE, Verhey E, et al. Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistula closure in Crohn's disease: a randomised, double-blind, placebo controlled trial (ADAFI). Gut. 2014;63(2):292–9.
28. Thia KT, Mahadevan U, Feagan BG, et al. Ciprofloxacin or metronidazole for the treatment of perianal fistulas in patients with Crohn's disease: a randomized, double-blind, placebo-controlled pilot study. Inflamm Bowel Dis. 2009;15(1):17–24.
29. Dejaco C, Harrer M, Waldhoer T, et al. Antibiotics and azathioprine for the treatment of perianal fistulas in Crohn's disease. Aliment Pharmacol Ther. 2003;18(11–12):1113–20.
30. Khan KJ, Ullman TA, Ford AC, et al. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol. 2011;106(4):661–73.
31. Su JW, Ma JJ, Zhang HJ. Use of antibiotics in patients with Crohn's disease: a systematic review and meta-analysis. J Dig Dis. 2015;16(2):58–66.
32. Steinhart AH, Panaccione R, Targownik L, et al. Clinical practice guideline for the medical management of perianal fistulizing Crohn's disease: the Toronto consensus. Inflamm Bowel Dis. 2019;25(1):1–13.
33. Pearson DC, May GR, Fick GH, Sutherland LR. Azathioprine and 6-mercaptopurine in Crohn disease. A meta-analysis. Ann Intern Med. 1995;123(2):132–42.
34. Lecomte T, Contou JF, Beaugerie L, et al. Predictive factors of response of perianal Crohn's disease to azathioprine or 6-mercaptopurine. Dis Colon Rectum. 2003;46(11):1469–75.
35. Present DH, Korelitz BI, Wisch N, Glass JL, Sachar DB, Pasternack BS. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. N Engl J Med. 1980;302(18):981–7.
36. Sandborn WJ, Present DH, Isaacs KL, et al. Tacrolimus for the treatment of fistulas in patients with Crohn's disease: a randomized, placebo-controlled trial. Gastroenterology. 2003;125(2):380–8.
37. Cat H, Sophani I, Lemann M, Modiglani R, Solue JC. Cyclosporin treatment of anal and perianal lesions associated with Crohn's disease. Turk J Gastroenterol. 2003;14(2):121–7.
38. Present DH, Lichtiger S. Efficacy of cyclosporine in treatment of fistula of Crohn's disease. Dig Dis Sci. 1994;39(2):374–80.
39. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med. 1999;340(18):1398–405.
40. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med. 2004;350(9):876–85.
41. Ricart E, Panaccione R, Loftus EV, Tremaine WJ, Sandborn WJ. Infliximab for Crohn's disease in clinical practice at the Mayo Clinic (the first 100 patients). Am J Gastroenterol. 2001;96(3):722–9.
42. Cohen RD, Tsang JF, Hanauer SB. Infliximab in Crohn's disease (first anniversary clinical experience). Am J Gastroenterol. 2000;95(12):3469–77.
43. Farrell RJ, Shah SA, Lodhavia PJ, et al. Clinical experience with infliximab therapy in 100 patients with Crohn's disease. Am J Gastroenterol. 2000;95(12):3490–7.
44. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007;132(1):52–65.
45. Lichtiger S, Binion DG, Wolf DC, et al. The CHOICE trial: adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohn's disease who failed prior infliximab therapy. Aliment Pharmacol Ther. 2010;32(1):1228–39.
46. Castaño-Milla C, Chaparro M, Saro C, et al. Effectiveness of adalimumab in perianal fistulas in Crohn's disease patients naive to anti-TNF therapy. J Clin Gastroenterol. 2015;49(1):34–40.
47. Fortea-Ormaechea JI, González-Lama Y, Casis B, et al. Adalimumab is effective in long-term real life clinical practice in both luminal and perianal Crohn's disease. The Madrid experience. Gastroenterol Hepatol. 2011;34(7):443–8.
48. Kotze PG, Spinelli A. Adalimumab for perianal fistulizing Crohn's disease: real-world data adds important information for clinical practice. J Clin Gastroenterol. 2015;49(2):174–5.
49. Echarri A, Castro J, Barreiro M, Carpio D, Pereira S, Lorenzo A. Evaluation of adalimumab therapy in multidisciplinary strategy for perianal Crohn's disease patients with infliximab failure. J Crohns Colitis. 2010;4(6):654–60.
50. Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al.; PRECISE 2 Study Investigators. Maintenance therapy with certolizumab pegol for Crohn's disease. N Engl J Med. 2007;357(3):239–50.
51. Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease. N Engl J Med. 2007;357(3):228–38.
52. Schreiber S, Lawrance IC, Thomsen O, Hanauer SB, Bloomfield R, Sandborn WJ. Randomised clinical trial: certolizumab pegol for fistulas in Crohn's disease - subgroup results from a placebo-controlled study. Aliment Pharmacol Ther. 2011;33(2):185–93.
53. Bouguen G, Siproudhis L, Gizard E, et al. Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab. Clin Gastroenterol Hepatol. 2013;11(8):975–8. e1–e4.
54. Ochsenkuhn T, Goke B, Sackmann M. Combining infliximab with 6-mercaptopurine/azathioprine for fistula therapy in Crohn's disease. Am J Gastroenterol. 2002;97(8):2022–5.
55. Regueiro M, Mardini H. Treatment of perianal fistulizing Crohn's disease with infliximab alone or as an adjunct for exam under anesthesia with seton placement. Inflamm Bowel Dis. 2003;9(2):98–103.
56. Feagan B, Schwartz D, Danese S, et al. Efficacy of Vedolizumab in fistulising Crohn's disease: exploratory analysis of data from GEMINI 2. J Crohns Colitis. 2018;12(5):621–6.
57. Sandborn WJ, Feagan BG, Rutgeerts P, et al.; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369(8):711–21.
58. Ma C, Fedorak RN, Kaplan GG, et al. Clinical, endoscopic and radiographic outcomes with ustekinumab in medically-refractory Crohn's disease: real world experience from a multicentre cohort. Aliment Pharmacol Ther. 2017;45(9):1232–43.
59. Khorrami S, Ginard D, Marín-Jiménez I, et al. Ustekinumab for the treatment of refractory Crohn's disease: the Spanish experience in a large multicentre open-label cohort. Inflamm Bowel Dis. 2016;22(7):1662–9.
60. Pittet V, Juillerat P, Michetti P, et al. Appropriateness of therapy for fistulizing Crohn's disease: findings from a national

inflammatory bowel disease cohort. Aliment Pharmacol Ther. 2010;32(8):1007–16.
61. Loffler T, Welsch T, Muhl S, Hinz U, Schmidt J, Kienle P. Long-term success rate after surgical treatment of anorectal and rectovaginal fistulas in Crohn's disease. Int J Color Dis. 2009;24(5):521–6.
62. Gecse KB, Bemelman W, Kamm MA, et al.; World Gastroenterology Organization International Organisation for Inflammatory Bowel Diseases IOIBD European Society of Coloproctology and Robarts Clinical Trials. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. Gut. 2014;63(9):1381–92.
63. Williams JG, Rothenberger DA, Nemer FD, Goldberg SM. Fistula-in-ano in Crohn's disease. Results of aggressive surgical treatment. Dis Colon Rectum. 1991;34(5):378–84.
64. Sangwan YP, Schoetz DJ Jr, Murray JJ, Roberts PL, Coller JA. Perianal Crohn's disease. Results of local surgical treatment. Dis Colon Rectum. 1996;39(5):529–35.
65. Levien DH, Surrell J, Mazier WP. Surgical treatment of anorectal fistula in patients with Crohn's disease. Surg Gynecol Obstet. 1989;169(2):133–6.
66. Morrison JG, Gathright JB Jr, Ray JE, Ferrari BT, Hicks TC, Timmcke AE. Surgical management of anorectal fistulae in Crohn's disease. Dis Colon Rectum. 1989;32(6):492–6.
67. Lozynskyy YS. Treatment algorithms in the case of perianal complications of Crohn's disease. Dig Dis. 2009;27(4):565–70.
68. Hyder SA, Travis SP, Jewell DP, McC Mortensen NJ, George BD. Fistulating anal Crohn's disease: results of combined surgical and infliximab treatment. Dis Colon Rectum. 2006;49(12):1837–41.
69. Regueiro M, Mardini H. Treatment of perianal fistulizing Crohn's disease with infliximab alone or as an adjunct to exam under anesthesia with seton placement. Inflamm Bowel Dis. 2003;9(2):98–103.
70. Topstad DR, Panaccione R, Heine JA, Johnson DR, MacLean AR, Buie WD. Combined seton placement, infliximab infusion, and maintenance immunosuppressives improve healing rate in fistulizing anorectal Crohn's disease: a single center experience. Dis Colon Rectum. 2003;46(5):577–83.
71. de Groof EJ, Sahami S, Lucas C, Ponsioen CY, Bemelman WA, Buskens CJ. Treatment of perianal fistula in Crohn's disease: a systematic review and meta-analysis comparing seton drainage and anti-tumour necrosis factor treatment. Color Dis. 2016;18(7):667–75.
72. Mizrahi N, Wexner SD, Zmora O, et al. Endorectal advancement flap: are there predictors of failure? Dis Colon Rectum. 2002;45(12):1616–21.
73. Joo JS, Weiss EG, Nogueras JJ, Wexner SD. Endorectal advancement flap in perianal Crohn's disease. Am Surg. 1998;64(2):147–50.
74. Soltani A, Kaiser AM. Endorectal advancement flap for cryptoglandular or Crohn's fistula-in-ano. Dis Colon Rectum. 2010;53(4):486–95.
75. Zimmerman DD, Delemarre JB, Gosselink MP, Hop WC, Briel JW, Schouten WR. Smoking affects the outcome of transanal mucosal advancement flap repair of trans-sphincteric fistulas. Br J Surg. 2003;90(3):351–4.
76. Sordo-Mejia R, Gaertner WB. Multidisciplinary and evidence-based management of fistulizing perianal Crohn's disease. World J Gastrointest Pathophysiol. 2014;5(3):239–51.
77. Marchesa P, Hull TL, Fazio VW. Advancement sleeve flaps for treatment of severe perianal Crohn's disease. Br J Surg. 1998;85(12):1695–8.
78. Gingold DS, Murrell ZA, Fleshner PR. A prospective evaluation of the ligation of the intersphincteric tract procedure for complex anal fistula in patients with Crohn disease. Ann Surg. 2013;260(6):1057–61.
79. Kamiński JP, Zaghiyan K, Fleshner P. Increasing experience of LIFT procedure for patients with Crohn's disease: what have we learned? Color Dis. 2017;19(8):750–5.
80. Grimaud J, Munoz-Bongrand N, Siproudhis L, et al. Fibrin glue is effective healing perianal fistulas in patients with Crohn's disease. Gastroenterology. 2010;138(7):2275–81.
81. Cirocchi R, Farinella E, La Mura F, et al. Fibrin glue in the treatment of anal fistula: a systematic review. Ann Surg Innov Res. 2009;3:12.
82. Zmora O, Mizrahi N, Rotholtz N, et al. Fibrin glue sealing in the treatment of perianal fistulas. Dis Colon Rectum. 2003;46(5):584–9.
83. Ky AJ, Sylla P, Steinhagen R, Steinhagen E, Khaitov S, Ly EK. Collagen fistula plug for the treatment of anal fistulas. Dis Colon Rectum. 2008;51(6):838–43.
84. Taxonera C, Schwartz DA, García-Olmo D. Emerging treatments for complex perianal fistula in Crohn's disease. World J Gastroenterol. 2009;15(34):4263–72.
85. O'Riordan JM, Datta I, Johnston C, Baxter NN. A systematic review of the anal fistula plug for patients with Crohn's and non- Crohn's related fistula-in-ano. Dis Colon Rectum. 2012;55(3):351–8.
86. O'Connor L, Champagne B, Ferguson M, Orangio G, Schertzer M, Armstrong D. Efficacy of anal fistula plug in closure of Crohn's anorectal fistulae. Dis Colon Rectum. 2006;49(10):1569–73.
87. Senéjoux A, Siproudhis L, Abramowitz L, et al. Fistula plug in fistulising ano-perineal Crohn's disease: a randomised controlled trial. J Crohns Colitis. 2016;10(2):141–8.
88. Panés J, García-Olmo D, Van Assche G, et al.; ADMIRE CD Study Group Collaborators. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. Lancet. 2016;388(10051):1281–90.
89. Lee WY, Park KJ, Cho YB, et al. Autologous adipose tissue-derived stem cells treatment demonstrated favorable and sustainable therapeutic effect for Crohn's fistula. Stem Cells. 2013;31(11):2575–81.
90. Ciccocioppo R, Bernardo ME, Sgarella A, et al. Autologous bone marrow-derived mesenchymal stromal cells in the treatment of fistulising Crohn's disease. Gut. 2011;60(6):788–98.
91. de la Portilla F, Alba F, García-Olmo D, Herrerías JM, González FX, Galindo A. Expanded allogeneic adipose-derived stem cells (eASCs) for the treatment of complex perianal fistula in Crohn's disease: results from a multicenter phase I/IIa clinical trial. Int J Color Dis. 2013;28(3):313–23.
92. Molendijk I, Bonsing BA, Roelofs H, et al. Allogeneic bone marrow–derived mesenchymal stromal cells promote healing of refractory perianal fistulas in patients with Crohn's disease. Gastroenterology. 2015;149(4):918–27.e6.
93. García-Olmo D, García-Arranz M, Herreros D, Pascual I, Peiro C, Rodríguez-Montes JA. A phase I clinical trial of the treatment of Crohn's fistula by adipose mesenchymal stem cell transplantation. Dis Colon Rectum. 2005;48(7):1416–23.
94. Cho YB, Lee WY, Park KJ, Kim M, Yoo HW, Yu CS. Autologous adipose tissue-derived stem cells for the treatment of Crohn's fistula: a phase I clinical study. Cell Transplant. 2013;22(2):279–85.
95. Lightner AL, Wang Z, Zubair AC, Dozois EJ. "A systematic review and meta-analysis of mesenchymal stem cell injections for the treatment of perianal crohn's disease: progress made and future directions. Dis Colon Rectum. 2018;61(5):629–40. https://doi.org/10.1097/DCR.0000000000001093.
96. Cao Y, Ding Z, Han C, Shi H, Cui L, Lin R. Efficacy of mesenchymal stromal cells for fistula treatment of Crohn's disease: a systematic review and meta-analysis. Dig Dis Sci. 2017;62(4):851–60.
97. Ciccocioppo R, Gallia A, Sgarella A, Kruzliak P, Gobbi PG, Corazza GR. Long-term follow-up of Crohn disease fistulas after

local injections of bone marrow–derived mesenchymal stem cells. Mayo Clin Proc. 2015;90(6):747–55.
98. Radcliffe AG, Ritchie JK, Hawley PR, Lennard-Jones JE, Northover JMA. Anovaginal and rectovaginal fistulas in Crohn's disease. Dis Colon Rectum. 1988;31:94. https://doi.org/10.1007/BF02562636.
99. Ritchie JK, Lennard Jones JE. Crohn's disease of the distal large bowel. Scand J Gastroenterol. 1976;11:433.
100. Van Patter WN, Bargen JA, Dockerty MB, Feldman WH, Mayo CW, Waugh JM. Regional enteritis. Gastroenterology. 1954;26:347. https://doi.org/10.1016/S0016-5085(54)80024-2.
101. Deleon MF, Hull TL. Treatment strategies in Crohn's-associated rectovaginal fistula. Clin Colon Rectal Surg. 2019;32:261. https://doi.org/10.1055/s-0039-1683908.
102. Jarrar A, Church J. Advancement flap repair: a good option for complex anorectal fistulas. Dis Colon Rectum. 2011;54:1537. https://doi.org/10.1097/DCR.0b013e31822d7ddd.
103. Sher ME, Bauer JJ, Gelernt I. Surgical repair of rectovaginal fistulas in patients with Crohn's disease: transvaginal approach. Dis Colon Rectum. 1991;34(8):641–8. http://www.ncbi.nlm.nih.gov/pubmed/1855419.
104. Songne K, Scotté M, Lubrano J, et al. Treatment of anovaginal or rectovaginal fistulas with modified Martius graft. Color Dis. 2007;9:653. https://doi.org/10.1111/j.1463-1318.2007.01232.x.
105. Pitel S, Lefevre JH, Parc Y, Chafai N, Shields C, Tiret E. Martius advancement flap for low rectovaginal fistula: short- and long-term results. Color Dis. 2011;13:e112. https://doi.org/10.1111/j.1463-1318.2011.02544.x.
106. Wexner SD, Ruiz DE, Genua J, Nogueras JJ, Weiss EG, Zmora O. Gracilis muscle interposition for the treatment of recto-urethral, rectovaginal, and pouch-vaginal fistulas: results in 53 patients. Ann Surg. 2008;248:39. https://doi.org/10.1097/SLA.0b013e31817d077d.
107. Fürst A, Schmidbauer C, Swol-Ben J, Iesalnieks I, Schwandner O, Agha A. Gracilis transposition for repair of recurrent anovaginal and rectovaginal fistulas in Crohn's disease. Int J Color Dis. 2008;23:349. https://doi.org/10.1007/s00384-007-0413-9.
108. Ulrich D, Roos J, Jakse G, Pallua N. Gracilis muscle interposition for the treatment of recto-urethral and rectovaginal fistulas: a retrospective analysis of 35 cases. J Plast Reconstr Aesthet Surg. 2009;62:352. https://doi.org/10.1016/j.bjps.2008.11.067.
109. Lefèvre JH, Bretagnol F, Maggiori L, Alves A, Ferron M, Panis Y. Operative results and quality of life after gracilis muscle transposition for recurrent rectovaginal fistula. Dis Colon Rectum. 2009;52:1290. https://doi.org/10.1007/DCR.0b013e3181a74700.
110. Schwandner O, Fuerst A, Kunstreich K, Scherer R. Innovative technique for the closure of rectovaginal fistula using SurgisisTM mesh. Tech Coloproctol. 2009;13:135. https://doi.org/10.1007/s10151-009-0470-x.
111. Mege D, Frasson M, Maggiori L, Panis Y. Is biological mesh interposition a valid option for complex or recurrent rectovaginal fistula? Color Dis. 2016;18(2):O61–5. https://doi.org/10.1111/codi.13242.
112. Gajsek U, McArthur DR, Sagar PM. Long-term efficacy of the button fistula plug in the treatment of ileal pouch-vaginal and Crohn's-related rectovaginal fistulas. Dis Colon Rectum. 2011;54:999. https://doi.org/10.1097/DCR.0b013e31821df266.
113. Panés J, García-Olmo D, Van Assche G, et al. Long-term efficacy and safety of stem cell therapy (Cx601) for complex perianal fistulas in patients with Crohn's disease. Gastroenterology. 2018;154:1334. https://doi.org/10.1053/j.gastro.2017.12.020.
114. Löffler T, Welsch T, Mühl S, Hinz U, Schmidt J, Kienle P. Long-term success rate after surgical treatment of anorectal and rectovaginal fistulas in Crohn's disease. Int J Color Dis. 2009;24:521. https://doi.org/10.1007/s00384-009-0638-x.
115. O'Leary DP, Milroy CE, Durdey P. Definitive repair of anovaginal fistula in Crohn's disease. Ann R Coll Surg Engl. 1998;80(4):250–2.
116. Mueller MH, Geis M, Glatzle J, et al. Risk of fecal diversion in complicated perianal Crohn's disease. J Gastrointest Surg. 2007;11:529. https://doi.org/10.1007/s11605-006-0029-3.
117. El-Gazzaz G, Hull T, Mignanelli E, Hammel J, Gurland B, Zutshi M. Analysis of function and predictors of failure in women undergoing repair of Crohn's related rectovaginal fistula. J Gastrointest Surg. 2010;14(5):824–9. https://doi.org/10.1007/s11605-010-1167-1.
118. Penninckx F, Moneghini D, D'Hoore A, Wyndaele J, Coremans G, Rutgeerts P. Success and failure after repair of rectovaginal fistula in Crohn's disease: analysis of prognostic factors. Color Dis. 2001;3:406. https://doi.org/10.1046/j.1463-1318.2001.00274.x.
119. Corte H, Maggiori L, Treton X, Lefevre JH, Ferron M, Panis Y. Rectovaginal fistula: what is the optimal strategy?: an analysis of 79 patients undergoing 286 procedures. Ann Surg. 2015;262:855. https://doi.org/10.1097/SLA.0000000000001461.
120. Fleshner PR, Schoetz DJ Jr, Roberts PL, Murray JJ, Coller JA, Veidenheimer MC. Anal fissure in Crohn's disease: a plea for aggressive management. Dis Colon Rectum. 1995;38(11):1137–43. http://www.ncbi.nlm.nih.gov/pubmed/7587755.
121. Figg RE, Church JM. Perineal Crohn's disease: an indicator of poor prognosis and potential proctectomy. Dis Colon Rectum. 2009;52:646. https://doi.org/10.1007/DCR.0b013e3181a0a5bf.
122. Pfenninger JL, Zainea GG. Common anorectal conditions. Obstet Gynecol. 2001;98:1130. https://doi.org/10.1016/S0029-7844(01)01687-8.
123. D'Ugo S, Franceschilli L, Cadeddu F, et al. Medical and surgical treatment of haemorrhoids and anal fissure in Crohn's disease: a critical appraisal. BMC Gastroenterol. 2013;13 https://doi.org/10.1186/1471-230X-13-47.
124. Stringer EE, Nicholson TJ, Armstrong D. Efficacy of topical metronidazole (10 percent) in the treatment of anorectal Crohn's disease. Dis Colon Rectum. 2005;48:970. https://doi.org/10.1007/s10350-004-0873-8.
125. Hart AL, Plamondon S, Kamm MA. Topical tacrolimus in the treatment of perianal Crohn's disease: exploratory randomized controlled trial. Inflamm Bowel Dis. 2007;13:245. https://doi.org/10.1002/ibd.20073.
126. Sweeney JL, Ritchie JK, Nicholls RJ. Anal fissure in Crohn's disease. Br J Surg. 1988;75:56. https://doi.org/10.1002/bjs.1800750120.
127. Buchmann P, Michael Keighley SR, Robert Allan EN, Henry Thompson E, John Alexander-Williams E. Natural history of perianal Crohn's disease ten year follow-up: a plea for conservatism. https://ac.els-cdn.com/0002961080900483/1-s2.0-0002961080900483-main.pdf?_tid=8326e71b-f774-40bd-9b4f-05bd7da49ac5&acdnat=1530544446_63b178098fc8836b3e4565a596c4256d. Accessed 2 July 2018.
128. Kruis W, Katalinic A, Klugmann T, et al. Predictive factors for an uncomplicated long-term course of Crohn's disease: a retrospective analysis. J Crohn's Colitis. 2013; https://doi.org/10.1016/j.crohns.2012.10.012.
129. Siproudhis L, Mortaji A, Mary JY, Juguet F, Bretagne JF, Gosselin M. Anal lesions: any significant prognosis in Crohn's disease? Eur J Gastroenterol Hepatol. 1997;9:239. https://doi.org/10.1097/00042737-199703000-00004.
130. Plamondon S, Ng SC, Kamm MA. Thalidomide in luminal and fistulizing Crohn's disease resistant to standard therapies. Aliment Pharmacol Ther. 2007;25:557. https://doi.org/10.1111/j.1365-2036.2006.03239.x.
131. Colombel JF, Mathieu D, Bouault JM, et al. Hyperbaric oxygenation in severe perineal Crohn's disease. Dis Colon Rectum. 1995;38:609. https://doi.org/10.1007/BF02054120.

132. Poggioli G, Laureti S, Pierangeli F, et al. Local injection of infliximab for the treatment of perianal Crohn's disease. Dis Colon Rectum. 2005;48(4):768–74. https://doi.org/10.1007/s10350-004-0832-4.
133. Keighley MRB, Allan RN. Current status and influence of operation on perianal Crohn's disease. Int J Color Dis. 1986;1(2):104–7. https://doi.org/10.1007/BF01648416.
134. Peyrin-Biroulet L, Loftus EV, Tremaine WJ, Harmsen WS, Zinsmeister AR, Sandborn WJ. Perianal Crohn's disease findings other than fistulas in a population-based cohort. Inflamm Bowel Dis. 2012;18:43. https://doi.org/10.1002/ibd.21674.
135. Alexander-Williams J, Buchmann P. Perianal Crohn's disease. World J Surg. 1980;4(2):203–8. http://www.ncbi.nlm.nih.gov/pubmed/7405258. Accessed 2 July 2018.
136. Jeffery PJ, Ritchie J, Parks AG. Treatment of haemorrhoids in patients with inflammatory bowel disease. Lancet. 1977;309(8021):1084–5. https://doi.org/10.1016/S0140-6736(77)92337-6.
137. Cracco N, Zinicola R. Is haemorrhoidectomy in inflammatory bowel disease harmful? An old dogma re-examined. Color Dis. 2014;16:516. https://doi.org/10.1111/codi.12555.
138. Wolkomir AF, Luchtefeld MA. Surgery for symptomatic hemorrhoids and anal fissures in Crohn's disease. Dis Colon Rectum. 1993;36(6):545–7. http://www.ncbi.nlm.nih.gov/pubmed/8500370. Accessed 2 July 2018.
139. Lightner AL, Kearney D, Giugliano D, et al. Excisional hemorrhoidectomy: safe in patients with Crohn's disease? Inflamm Bowel Dis. 2019;26:1390. https://doi.org/10.1093/ibd/izz255.
140. Linares L, Moreira LF, Andrews H, Allan RN, Alexander-Williams J, Keighley MR. Natural history and treatment of anorectal strictures complicating Crohn's disease. Br J Surg. 1988;75(7):653–5. http://www.ncbi.nlm.nih.gov/pubmed/3416120. Accessed 5 Jan 2017.
141. Simmang CL, Lacey SW, Huber PJ. Rectal sleeve advancement: repair of rectovaginal fistula associated with anorectal stricture in Crohn's disease. Dis Colon Rectum. 1998;41:787. https://doi.org/10.1007/BF02236270.
142. Bauer JJ, Gelernt IM, Salk BA, Kreel I. Proctectomy for inflammatory bowel disease. Am J Surg. 1986;151:157. https://doi.org/10.1016/0002-9610(86)90026-7.
143. Slesser AAP, Bhangu A, Bower M, Goldin R, Tekkis PP. A systematic review of anal squamous cell carcinoma in inflammatory bowel disease. Surg Oncol. 2013;22:230. https://doi.org/10.1016/j.suronc.2013.08.002.
144. Shwaartz C, Munger JA, Deliz JR, et al. Fistula-associated anorectal cancer in the setting of Crohn's disease. Dis Colon Rectum. 2016;59(12):1168–73. https://doi.org/10.1097/DCR.0000000000000700.
145. Vermeire S, Van Assche G, Rutgeerts P. Perianal Crohn's disease: classification and clinical evaluation. Dig Liver Dis. 2007;39:959. https://doi.org/10.1016/j.dld.2007.07.153.
146. Galandiuk S, Kimberling J, Al-Mishlab TG, Stromberg AJ. Perianal Crohn disease: predictors of need for permanent diversion. Ann Surg. 2005;241(5):796–801; discussion 801–2. https://doi.org/10.1097/01.sla.0000161030.25860.c1.
147. Corman ML, Veidenheimer MC, Coller JA, Ross VH. Perineal wound healing after proctectomy for inflammatory bowel disease. Dis Colon Rectum. 1978;21:155. https://doi.org/10.1007/BF02586557.
148. Baudot P, Keighley MRB, Alexander-Williams J. Perineal wound healing after proctectomy for carcinoma and inflammatory disease. Br J Surg. 1980;67:275. https://doi.org/10.1002/bjs.1800670415.
149. Yamamoto T, Bain LM, Allan RN, Keighley MRB. Persistent perineal sinus after proctocolectomy for Crohn's disease. Dis Colon Rectum. 1999;42:96. https://doi.org/10.1007/BF02235190.
150. Sher ME, Bauer JJ, Gorphine S, Gelernt I. Low Hartmann's procedure for severe anorectal Crohn's disease. Dis Colon Rectum. 1992;35:975. https://doi.org/10.1007/BF02253501.
151. Yamamoto T, Allan RN, Keighley MRB. Audit of single-stage proctocolectomy for Crohn's disease: postoperative complications and recurrence. Dis Colon Rectum. 2000;43:249. https://doi.org/10.1007/BF02236990.

Crohn's Disease: Surgical Management

48

Lisa M. Cannon and Alessandro Fichera

Key Concepts

- Despite significant advances in medical management, surgery for Crohn's disease remains a vital component of many treatment paradigms.
- Optimal timing of surgery is critical in order to achieve the best outcome.
- Preoperative patient optimization is of critical importance.
- The surgeon treating Crohn's disease should be familiar with bowel-sparing principles and properly apply them while not compromising long-lasting remissions.
- Different anastomotic configurations should be considered based on severity and location of the disease.
- For all the abovementioned aspects, Crohn's disease requires a multidisciplinary approach to achieve optimal and lasting outcomes.
- Risk stratification should guide postoperative medical management.

Introduction

Medical therapy and our understanding of the pathophysiology of Crohn's disease have advanced during the last two decades. Surgical treatment has become less invasive, selective, and targeted. Now more than ever, it must be properly timed and planned. Patients affected by the disease ought to be managed in the context of a multidisciplinary approach. Surgery should be performed by properly trained surgical teams, and like our gastroenterology colleagues, many colorectal surgeons have subspecialized to become "surgical IBDologists" working in the context of a specialty medical home (SMH). It has been shown that an IBD SMH significantly reduces unplanned care and disease activity and increases patient quality of life [1].

Changing Trends in the Surgical Management of Crohn's Disease

Crohn's disease is not cured by surgery; however, surgery retains an important role in disease management. The goals of a well-timed surgical intervention are to relieve symptomatic complications such as obstruction or fistula, improve quality of life, preserve small bowel, and minimize treatment interruptions in order to reduce risk of surgical recurrence.

Significant advances in medical therapy including the advent of immunomodulators and biologic therapies have altered the natural history of Crohn's disease. The need for surgery based on time from diagnosis has declined compared to patients managed in earlier decades. For example, in a population-based cohort of patients diagnosed with Crohn's between 1955 and 1989, 73% of patients overall required surgery: 44% at 1 year, 61% at 5 years, and 71% at 10 years after the diagnosis [2]. In a cohort of patients diagnosed from 2003 to 2004 and followed to 2011, 29% of patients required surgery: 14.6% at 1 year, 24.6% at 5 years, and 28.5% at 7 years after diagnosis [3]. Comparably numbers are seen in other studies based on decade. Interestingly, the largest drop in need for surgery predates the introduction of biologics and appears reflective of the increased use of corticosteroids. Immunomodulators and biologics have likely decreased the need for surgery, but the attributable impact is hard to measure. Improved diagnostic modalities in this same timeframe have led to earlier diagnosis and initiation of therapy, and treatment paradigms have shifted to individualized and risk-stratified medical management algorithms. Both of these evolutions have likely decreased the rate of complicated surgical disease.

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After recovery from intestinal resection, health-related quality of life improves as early as 2 weeks after surgery and remains high in the long term. Postoperative complications and disease recurrence may limit improvement in quality of life [4]. Overall, patients are satisfied with their surgery and generally wish they had undergone surgery earlier in their disease course [5].

Indications for Surgery

The indications for operative management of Crohn's disease are varied and listed in Table 48.1. Free perforation, toxic colitis, and major hemorrhage are true surgical emergencies; these are far less common than the host of nonemergent Crohn's complications that require individualized surgical decision-making.

Failed Medical Therapy

Despite the introduction of entirely new classes of Crohn's therapies in the past decade, failure of medical management remains a common indication for surgical intervention. The phrase "failure of medical therapy" carries multiple meanings. Some patients are unable to achieve acceptable symptom control despite aggressive medical therapy; the patient is transitioned to the next medical agent or combination of agents until all options have been exhausted. Other patients may be able to achieve good symptom control but suffer side effects or reactions to the medications. In pediatric inflammatory bowel disease, growth retardation is a manifestation of failure of medical therapy as well. Steroid-refractory patients are those who have active disease despite prednisolone up to 1 mg/kg/day for a period of 4 weeks. Steroid-dependent patients are those who are unable to reduce their steroid dose below the equivalent of prednisolone 10 mg/day without disease reactivation or who have relapse within 3 months of stopping steroids [6].

Table 48.1 Operative indications for Crohn's disease

Failure of medical management
Pediatric growth retardation
Bowel obstruction
Free perforation
Penetrating disease/fistula/phlegmon/abscess
Cancer/dysplasia
Toxic colitis
Bleeding

Bowel Obstruction

Several Crohn's phenotypes can lead to bowel obstruction; taken together, about one-quarter of Crohn's disease surgery is secondary to obstructive symptomatology. Untreated and poorly controlled Crohn's disease causes progressive transmural intestinal injury. Histologic examination of a Crohn's stricture reveals thickening of the muscularis mucosa and muscularis propria with fibrotic change, as well as increased volume and density of the submucosa [7]. There is a slow evolution, and the bowel slowly accommodates to the progressive obstruction. The patient experiences intermittent abdominal pain, bloating, and progressive food intolerance. Eventually intervention is necessary due to acute on chronic obstruction or intolerable symptoms as the occlusive disease progresses. Currently no antifibrotic therapies for stricturing disease exist. Other etiologies of Crohn's disease-related obstruction include anastomotic stricture and neoplasm.

Once the diagnosis of obstruction has been established, the relative contribution of fibrosis and inflammation is assessed. CT or MR enterography is the current standard for assessing the small intestine. CT enterography findings of tissue inflammation include mucosal hyperenhancement, mesenteric fat stranding ("comb sign"), and mesenteric hypervascularity. However, CT enterography is not as successful at identifying degree of fibrosis, and upstream dilation is not reliable at distinguishing inflammation from fibrosis. On multivariate analysis, mesenteric hypervascularity was the only CT radiologic finding that predicted fibrosis. This highlights the pathophysiologic continuum between inflammation and fibrosis [8]. MRI findings indicative of inflammation include T2 hypersignal, mucosal enhancement, presence of ulceration, and blurred margins. A homogenous pattern of enhancement, and the percent of enhancement gain over time, can discriminate severe fibrosis deposition. Again, most lesions have a mixed pattern of fibrosis and inflammation [9].

Inflammatory stenoses are likely to respond to medical therapy, while fibrotic strictures typically require surgery. For localized ileocecal disease with obstruction, surgery is indicated if the patient does not respond to a trial of medical management with bowel rest and intravenous corticosteroids; upfront surgical management is indicated if clinical and radiologic findings suggest marked fibrosis with low levels of inflammation (Fig. 48.1). Ileocecectomy for Crohn's disease has a high rate of disease control. Retrospective studies performed even prior to the era of biologic therapy indicated that over half of patients never require another surgery [10]. Though postoperative endo-

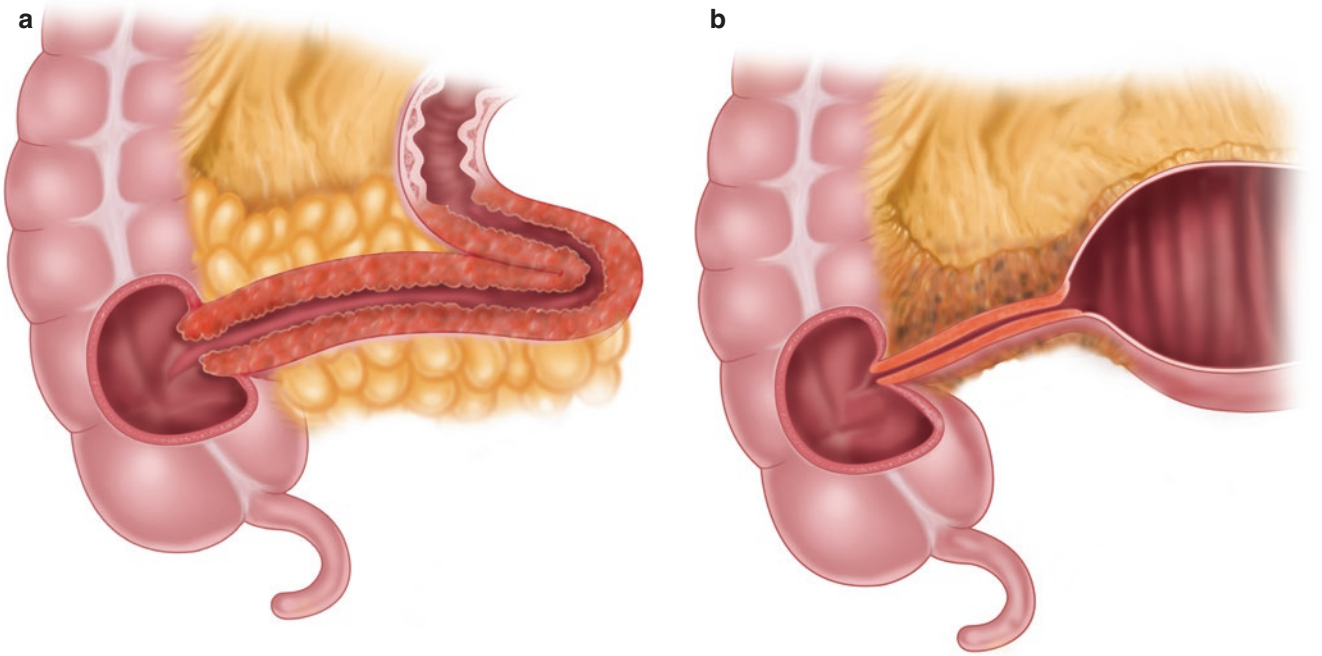

Fig. 48.1 (**a**, **b**) Crohn's-related bowel obstruction (**a**). Active inflammation with creeping fat, mural thickening, and luminal narrowing representing active disease which may respond to medical therapy. (**b**) Fibrotic change with luminal narrowing and upstream dilation, representing fibrotic stricture that is unlikely to respond to medical therapy

scopic recurrence is the rule, aggressive postoperative medical management paradigms based on endoscopic, disease-related, and patient-related risk stratification enable many patients to avoid the disease progression that led to their initial operation [11].

Endoscopic balloon dilation is an alternative therapeutic option for bowel obstruction due to stricturing disease in some patients and has been shown to delay and even prevent the need for surgery when successful. The ideal candidate for this procedure is a patient with a single short-segment (<4 cm) fibrostenotic stricture or a patient with an anastomotic stricture. The stricture should not be associated with marked angling of the bowel lumen and be without associated fistula or abscess [12]. Dilation diameter should be at least 14 mm; dilation to 16–18 mm is associated with the need for less frequent follow-up procedures; dilation of small bowel strictures to greater than 20 mm may contribute to increased rates of perforation and bleeding [12, 13]. Multifocal stricturing disease is an independent risk factor for clinical failure of balloon dilation [14].

In a recent pooled analysis, Bettenworth evaluated 1463 patients with Crohn's disease who underwent over 3000 balloon dilation procedures. Overall technical success was achieved in 89% of cases. Anastomotic strictures comprised 62% of the procedures. At 2-year follow-up, three-quarters of patients had required re-dilation, and half had undergone surgical resection. Major adverse events including perforation, bleeding, and sepsis occurred in 2.8% of patients and highlight the need for a skilled and capable endoscopist in close communication with the surgical team [15].

Perforation

Free perforation in Crohn's disease is a rare occurrence. It is typically associated with toxic colitis or complete obstruction due to multifocal small bowel stricturing disease. If the perforation is associated with small bowel strictures, it is usually immediately proximal to a completely obstructing stricture, when a more proximal stricture has created a relative closed loop obstruction. This is best treated with resection and primary anastomosis if the patient's condition allows. In the setting of an obstructing colonic stricture, the site of perforation is more commonly the cecum; this is best treated with total abdominal colectomy and ileostomy. The extent of distal resection may be tailored somewhat to the site of the stricture if the distal colon and rectum are free of disease. Toxic colitis leading to perforation is managed with total abdominal colectomy and ileostomy.

Penetrating Disease: Fistula and Abscess Formation

Approximately 11–16% of adult patients have penetrating intestinal disease manifestations [16–18]. Risk factors for penetrating disease include a number of serologic and genetic markers and tobacco [19]. Transmural inflammation of the bowel wall promotes phlegmon, abscess, or fistula formation to a nearby organ or viscera. Hirten characterized the relative frequency of fistula formation by location; 29% are enterocolonic, 18–24% enteroenteric, 6–16% enterocutaneous, 4–9% rectovaginal, and 2–8% enterovesical, and rarely enterosalpingeal and enterogastric. The originating site is usually the ileocecal region and terminal ileum [17]. Only fistulas that are symptomatic require intervention (Fig. 48.2). When surgery is indicated, the diseased segment of bowel requires resection, but often the targeted organ or bowel can be primarily repaired or a small patch excision and transverse closure performed. Penetration to the retroperitoneum can cause a psoas abscess, which requires special mention. These cavities are prone to epithelialize and become a recalcitrant source of recurrent abscess and usually require surgical intervention. After resection of the diseased bowel, the psoas abscess cavity may be unroofed and curetted; an omental pedicle flap may facilitate healing.

Patients with small abscesses or phlegmon should typically be initiated on antibiotic therapy. When a phlegmon is associated with active inflammatory disease, it is safe to administer antibiotics in combination with corticosteroids. Felder examined 24 patients with Crohn's disease and palpable inflammatory mass treated with high-dose corticosteroids. Two-thirds of patients resolved their phlegmon completely, and in the remaining 1/3, it reduced in size by greater than 50%. Though 58% of the patients did require resection for persistence or recurrence of symptoms, most were performed in the elective setting [20].

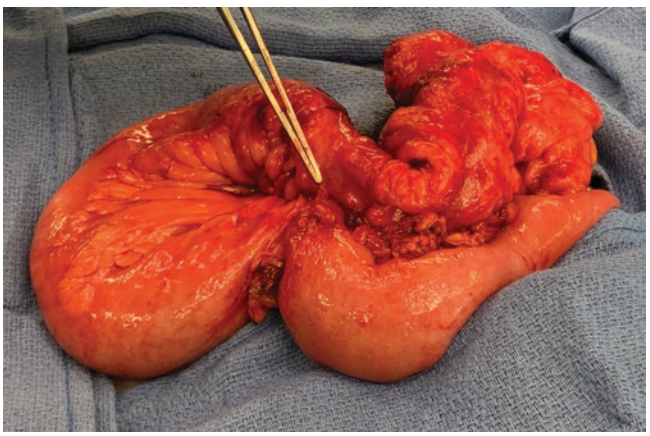

Fig. 48.2 Enteroenteric fistula. The targeted loop of otherwise normal bowel is in the foreground. (Reproduced with permission from F Michelassi, MD)

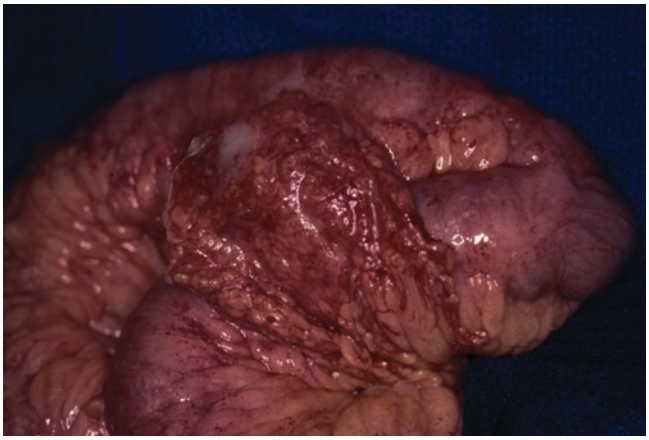

Fig. 48.3 Crohn's interloop abscess found during operative exploration. (Reproduced with permission from F Michelassi, MD)

Intra-abdominal abscess in the setting of active disease often presents a management dilemma (Fig. 48.3). Patients with accessible abscesses greater than 3 cm in average diameter should usually undergo percutaneous drainage and be initiated on antibiotic therapy. The technical success of percutaneous drainage is >90% [21, 22]. A meta-analysis by Clancy performed in 2016 of 333 patients from 6 studies compared the outcomes of primary surgery versus percutaneous drainage alone. Intra-abdominal abscess was defined as extra-luminal fluid collections identified on various imaging modalities [23]. Primary surgical resection was performed in 184 (55%) patients, and percutaneous drainage was performed in 149 patients (45%). There was a significantly higher rate of recurrent abscess in the percutaneous drainage group (OR 6.54), and the pooled proportion of these patients requiring subsequent surgery was 70.7%. The proportion of patients who underwent initial surgery and required surgery for recurrence was 17.9%.

Patients whose abscess resolves both clinically and radiologically with percutaneous drainage may present more of a therapeutic dilemma; it is unclear whether they should all proceed to elective resection. There is much interest in identifying patients who may be able to avoid surgery in the setting of successful percutaneous drainage or medical management. The prior meta-analysis suggested that up to 30% of patients undergoing percutaneous drainage can avoid surgery [23]. The MICA trial is prospectively examining predictive factors of anti-TNF response in luminal Crohn's disease complicated by abscess formation. This trial is sponsored by the Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives (GETAID).

There are a number of studies that have examined percutaneous drainage as a bridge to surgery for Crohn's-related abscess. Müller-Wille examined the influence of preoperative percutaneous abscess drainage on postoperative septic complications. Twenty-five of the patients with spontaneous

intra-abdominal abscess were treated with percutaneous abscess drainage (48%) on average 37 days (range 6–83 days) before surgery. The rate of postoperative septic complications was significantly lower in the group who underwent preoperative intra-abdominal abscess drainage (25% versus 69%) [24].

Similarly, Zhang demonstrated that intra-abdominal abscess, not penetrating behavior, is associated with poorer outcome after resection. In this study, 288 patients, 180 of whom had penetrating behavior including 54 with intra-abdominal sepsis, underwent surgical resection. Patients with intra-abdominal sepsis, not penetrating behavior alone, were more likely to have postoperative septic complications, superficial surgical site infection, and stoma formation [25]. Percutaneous drainage may improve the nutritional and general medical conditional of the patient and enable a less invasive operation. Given that penetrating disease is a risk factor for recurrence, initiation of prophylactic therapy is typically recommended after intestinal resection [6].

Cancer and Dysplasia

Patients with Crohn's disease are at increased risk of developing both intestinal and non-intestinal cancers, compared to the general population. Colorectal cancer is the cause of 1 in every 12 deaths of patients with inflammatory bowel disease [26]. Colitis-associated cancer has many of the molecular alterations also found sporadic colorectal cancer, but with different timing and frequency. For example, loss of adenomatous polyposis coli (APC) functions occurs early in sporadic colon cancer and late in colitis-associated cancer. In contrast, loss of p53 function occurs early in colitis-associated cancer [27]. Development of cancer in chronic colitis is accelerated by inflammatory activity [26]. Patients with Crohn's disease have a twofold to threefold increase in colorectal cancer compared to the general population. The mean age at diagnosis is 51.5 years, about 20 years earlier than the general population [28]. The risk of cancer is also associated with disease duration; the cumulative risk of colorectal cancer in Crohn's disease is 2.9% at 10 years, 5.6% at 20 years, and 8.3% after 30 years with the disease [27]. With equivalent disease duration, the risk of colorectal cancer in Crohn's disease appears to be lower than that of ulcerative colitis, but this may be informed by differences in disease distribution [28].

Colorectal strictures in the setting of Crohn's disease are particularly associated with an increased risk of cancer. Yamazaki analyzed 132 patients with 175 strictures identified between 1959 and 1980. A total of ten malignant strictures were identified *in nine patients*, three with ileocolic and six with colonic disease. The frequency of cancer in patients with a stricture was 6.8% [29]. The authors further observed that all of the malignant strictures were short-segment. A group out of Hungary similarly analyzed 640 patients with Crohn's disease over a 30-year period, including 62 patients with ileocolic or colonic strictures. The group observed a 6.5% rate of colorectal cancer in those patients with stricture. The authors observed that all four patients with stricture-associated colorectal cancer were male smokers [30].

The surgical management of colitis-associated dysplasia in Crohn's disease follows the same principles as ulcerative colitis and is reviewed elsewhere in this textbook.

Toxic Colitis

Up to 50% of cases of toxic colitis from IBD may be attributed to Crohn's colitis. Severe colitis is defined by Truelove and Witt as six or more bloody bowel movements daily, temperature greater than 37.8 °C, heart rate greater than 90 beats per minute, anemia with a hemoglobin less than 10.5 g/dL, and an elevated erythrocyte sedimentation rate greater than 30 mm/h. These criteria, combined with imaging demonstrating dilation of the colon and a disturbed or absent haustral pattern, constitute toxic megacolon. The medical management of toxic colitis is covered in another section of this textbook. When surgery is required due to clinical deterioration or failure to respond to rescue therapy, total abdominal colectomy with end ileostomy is indicated, with or without mucous fistula. The extent of resection and surgical management in the setting of medically refractory colitis is reviewed later in this chapter, under operative considerations for colonic and rectal disease.

Bleeding

Acute severe gastrointestinal hemorrhage is a rare complication of Crohn's disease, with an incidence of 1–2%. There are few studies that describe the epidemiology of this condition. Bleeding does not always correlate with disease activity. The site of bleeding can be duodenal, jejunoileal, ileocolic, or colic. Surgery is typically successful when the site of bleeding has been localized. In those that resolve without surgery, recurrent hemorrhage is not rare [31–33].

A patient with Crohn's disease presenting with acute gastrointestinal bleeding should be initially managed using the usual resuscitative algorithms for gastrointestinal bleeding, including nasogastric lavage to begin the process of source localization. In contrast to ulcerative colitis where bleeding is due to widespread mucosal ulceration, hemorrhage in the setting of Crohn's disease is more often due to a focal erosion into an intestinal vessel or occasionally an inflammatory pseudopolyp. Source localization therefore is extremely important to minimize unnecessary bowel resection should surgery be required. Up to 30% of patients with Crohn's disease and hemorrhage will have a bleeding duodenal ulcer and positive gastric lavage should trigger upper endoscopy [34]. Colonoscopy within 24 hours of bleeding can successfully locate the bleeding source 60–78% of the time [31, 32]; endoscopic control is not often successful, but will localize

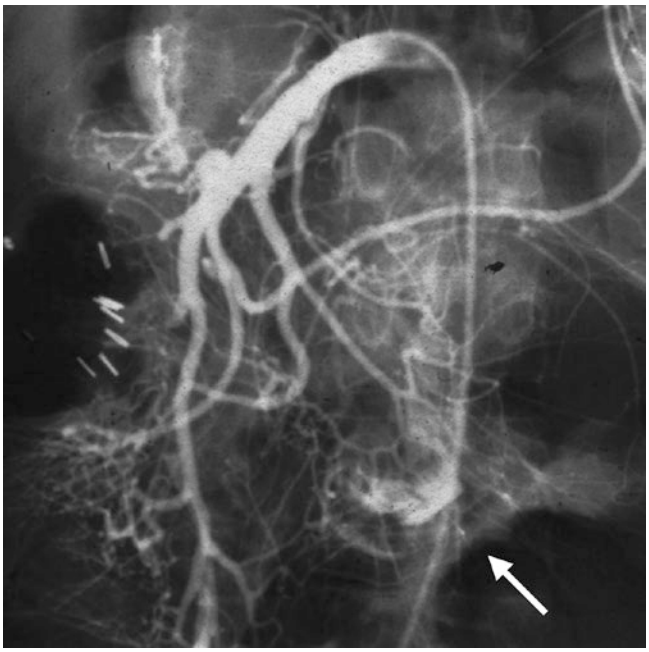

Fig. 48.4 Contrast extravasation (arrow) seen on angiography from an intestinal segment in a patient with Crohn's disease. (Reproduced with permission from F Michelassi, MD)

the site for guided resection. CT angiography and traditional mesenteric angiography have also been successfully utilized for source localization (Fig. 48.4). When mesenteric angiography localizes bleeding, methylene blue injection can be used to identify the segment of involved bowel so that it may be readily identified during operative exploration. This approach will typically stain a 10–40 cm segment of bowel for resection [35].

Surgical Considerations

Crohn's disease cannot be cured by surgical therapy, and thus surgery, like medical treatment, should be considered palliative. It is paramount to keep in mind the recurrent and chronic nature of the disease that is typically diagnosed in a young patient population with a long life expectancy. The pendulum has swung from an emphasis on margin-negative resection to bowel-sparing approaches largely based on a landmark paper from Fazio. The authors randomized 152 patients undergoing ileocolic resection to 2 groups in which the proximal line of resection was 2 cm (limited resection) or 12 cm (extended resection) from the macroscopically involved area. They showed that there was no difference in recurrence rates between the two groups; further, recurrence rates did not increase when microscopic disease was present at the resection margins [36]. Similar to medical treatment, the goal of surgical treatment of Crohn's disease is to provide long-lasting symptomatic relief while avoiding excessive morbidity. Complete extirpation of microscopic disease should not be the primary goal of surgery, as this does not produce cure and is frequently counterproductive. Rather, treatment of complications and relief of disease-related symptoms coupled with bowel preservation should be the main aims of surgical treatment.

To avoid excessive loss of small intestine, nonresectional techniques such as strictureplasty may be required. On the other hand, in patients with isolated Crohn's colitis, especially if multifocal and associated with perianal disease, a more aggressive approach is often indicated [37–39]. Understanding the natural history of different patient cohorts is key to optimal decision-making.

Nutritional Support and Total Parenteral Nutrition

Exclusive enteral nutrition has been shown to induce remission in the pediatric Crohn's population and to be as effective as systemic corticosteroids in inducting remission both in newly diagnosed and established patients. In fact, intestinal healing was significantly more likely among patients receiving exclusive enteral nutrition compared to corticosteroids (OR = 4.5 [95% CI 1.64,12.32]) in a recent meta-analysis [40]. In the adult patient population, exclusive enteral nutrition is not as effective in inducing remission, but it may be useful for maintaining remission in patients with quiescent Crohn's disease [41].

In the adult literature, nutritional support has been evaluated primarily for preoperative optimization. Crohn's patients are at increased risk for malnutrition, which can result in adverse clinical outcomes. In a recent study from China, 59.0% of screened patients were deemed to be at risk for malnutrition [42]. If we consider that surgical patients have failed medical management, that percentage is probably even higher in the operative cohort. Crohn's disease patients with serious nutritional deficits, based on weight loss >10% in the last 3–6 months, body mass index <18.5 kg/m, or albumin levels <30 g/L, have been shown to benefit from intensive enteral or parenteral nutritional support, thereby reducing the risk of surgical site infections and postoperative septic complications [43]. Malnutrition has been shown to be an independent risk factor for postoperative morbidity and mortality irrespective of immunosuppressive and biologic therapy [44]. The duration of preoperative nutritional support depends on the urgency of the operation and the suitability of the gastrointestinal tract for enteral administration [45, 46].

Overview of Operative Considerations

Minimally Invasive Surgery

Crohn's disease may present both real and perceived challenges to a minimally invasive surgical approach. A Crohn's-related inflammatory mass and secondary phlegmon can increase the risk of bowel injury during minimally invasive manipulation and dissection. Thick, inflamed mesentery may be difficult to divide with a vessel-sealing device. With limited tactile feedback, it may be difficult to determine whether a fistula requires resection versus debridement and repair. Despite these challenges, evidence has accumulated in favor of a tailored approach to minimally invasive surgery (MIS) in Crohn's disease.

Milsom and Maartense both conducted prospective randomized trials in selected Crohn's patients undergoing ileocecectomy, concluding that MIS patients enjoy improved postop pulmonary function, morbidity, and reduced length of stay [47, 48]. Analysis of long-term outcomes in these two trial populations supported improved body image perception and cosmesis, as well as a decreased risk of bowel obstruction and hernia [49, 50]. Evidence does not support the concern that diminished tactile feedback will lead to missed strictures or increased disease recurrence due to incomplete resection [51]. MIS approaches for complex Crohn's disease, defined as reoperative disease, presence of phlegmon, abscess and/or fistula, or immunosuppressed state, can be accomplished with acceptable outcomes, albeit with generally higher conversion rates [52–55].

Robotic MIS for Crohn's disease is technically feasible. Like the laparoscopic approach, morbidity and length of stay are reduced compared to open approach [56], but operative times are longer [57]. The conversion rate is lower than with laparoscopy in some series [58]. All in all, there is not yet a clear demonstrated advantage of robotic over laparoscopic MIS in Crohn's disease [59].

The general advantage of MIS versus open approach in Crohn's disease is no longer disputed. Widespread acceptance of MIS approach is cultivating advanced near-term technologies and techniques, such as single-incision surgery and intracorporeal anastomosis. Inability to deliver a foreshortened Crohn's mesentery through a small extraction site in order to perform an extracorporeal anastomosis makes intracorporeal anastomotic technique enticing and may reduce the surgical site infection rate [60]. Heimann demonstrated that it may be possible to decrease and possibly eliminate incisional hernia in Crohn's disease patients undergoing bowel resection using an intracorporeal anastomosis and small (<4 cm) transverse extraction incision [61]. Tou described a robotic-assisted strictureplasty, and Scaringi illustrated a robotic approach to stricturing disease that is in essence a nonresectional, intracorporeal, side-to-side isoperistaltic anastomosis [62, 63]. Further studies and long-term analysis are needed to understand how these techniques may influence disease recurrence.

Single-incision laparoscopic surgery utilizes only one abdominal incision and an incisional platform through which a 5-mm camera and two working instrument ports are inserted. A number of small studies support the safety of this approach in Crohn's disease, but there is no clear benefit over conventional laparoscopy [64].

IBD surgeons should tailor the approach to the individual patient and be willing to utilize a hybrid or open approach if there is a lack of progress in complex cases. The hybrid approach is attractive when circumstances prohibit a fully MIS procedure. If a Crohn's terminal ileal phlegmon is fixed to the retroperitoneum, the surgeon can mobilize the proximal bowel and distal colon in order to limit the incision required to complete the procedure. If the mesentery is noted to be too thick and unwieldy for laparoscopic vessel sealers, it may be possible to perform minimally invasive mobilization and then divide this mesentery extracorporeally using more traditional clamp and suture ligature technique [65].

Enhanced Recovery Pathways

Very little disease-specific data exists supporting the application of enhanced recovery pathways (ERPs) after colorectal resection in inflammatory bowel disease. A recent review identified only a dozen English-language studies on ERPs that included any proportion of patients with IBD in their analysis, and only 28.9% of the total number of patients within these studies had a stated surgical indication of IBD [66]. Most studies did not provide important IBD-specific demographic information such as biologic therapy, steroids, or immune modulations. Still, all available evidence to date suggests that application of ERPs to patients undergoing colorectal surgery for IBD is safe and likely leads to decreased length of stay without an increase in the rate of readmission or morbidity. Inflammatory bowel disease is a known risk factor for prolonged length of stay, and this should be taken into account when setting postoperative expectations for recovery [67].

Perioperative Medical Management

In steroid-treated and steroid-dependent patients, concern over postoperative adrenal insufficiency and adrenal crisis has traditionally led to the liberal utilization of stress-dose steroids in the perioperative setting. Truong noted that much of the evidence around dosing, duration, and indications for steroid supplementation is poorly supported and anecdotal [68]. The dose and duration of steroid therapy do not correlate with the degree and duration of hypothalamic-pituitary-

adrenal (HPA) axis suppression. Recovery of HPA axis function after cessation of steroid therapy can be as short as 2 days and as long as 1 year, which is the basis for recommending stress-dose steroids for a patient who has required steroid therapy within the past year [69].

As perioperative high-dose steroids are associated with impaired wound healing, reducing or omitting stress-dose steroids in Crohn's disease surgery is desirable. In a small pilot study, Zaghiyan did not administer any perioperative steroids to IBD patients who had received steroids within the year but were not on steroids at the time of surgery. All cases of hypotension, bradycardia, and tachycardia spontaneously resolved without the need for fluid bolus, vasopressor, or steroid administration [70]. Further studies support the notion that steroid-treated patients can be maintained on their usual preoperative steroid dose in the perioperative period. Patients who have been treated with steroids within the year probably do not need precautionary perioperative steroid supplementation at all. High "stress-dose" perioperative steroids are unnecessary and may increase perioperative risk [71, 72].

There is a dose-dependent relationship between steroid use and infectious complications. The highest risk of complications occurs in patients on >40 mg prednisolone or equivalent [73, 74]. If the surgery is elective or semi-elective, an attempt to wean steroids should be undertaken, with the goal to have patients off steroids for 1 week prior to surgery [75]. If complete cessation is not possible, an attempt to wean to their lowest possible dose, with a target of less than 20 mg prednisolone or equivalent, is recommended [6].

There have been few studies examining whether immunomodulator use leads to increased complications. Patients on 6-mercaptopurine/azathioprine (6-MP/AZA) alone do not have an increase in complication rates, and concurrent use of 6-MP/AZA and corticosteroids does not further elevate complication rates as compared to the known risk of corticosteroids alone [73]. In a recent review, Rosen did not find any literature suggesting an increased complication rate with methotrexate. Discontinuing immunomodulator therapy prior to surgery appears unnecessary. These medications are typically held on the morning of surgery and resumed as per the gastroenterologist treatment plan [76].

Since the approval of infliximab in 1998 for treatment of inflammatory bowel disease, biologic therapy has vastly advanced medical treatment options for Crohn's disease. The influence of biologic therapy on surgical timing, morbidity, and intraoperative surgical decision-making is a ripe area of clinical interest. Tumor necrosis factor-α (TNFα) is a central cytokine in the pathogenesis of IBD, and anti-TNFα therapies including infliximab, adalimumab, and certolizumab pegol are some of the most successful Crohn's therapies available.

Table 48.2 Risk factors for postoperative septic complications in patient with Crohn's disease undergoing surgical resection [79, 154, 155]

Corticosteroid use
Malnutrition/hypoalbuminemia
Anemia/acute blood loss
Emergency surgery
Anti-TNFα therapy
Vedolizumab therapy
Penetrating disease/fistula/intraoperative abscess
Recurrent disease Smoking

Several studies had sought to describe the relationship between anti-TNFα therapy and postoperative outcomes, with mixed results. Interpretation of the impact of biologics is complicated by drug pharmacokinetics and associated drug levels, as these medications are typically protein-bound and prone to be lost in the stool in patients with active disease. One study showed that 50% of patients on anti-TNFα at the time of surgery did not have detectable drug levels immediately preoperatively [77]. Complications do not appear to correlate with anti-TNFα serum trough levels [78]. There are several, heterogeneous, retrospective, and prospective studies that either support or refute the hypothesis that anti-TNFα therapy leads to a significant increase in postoperative complications. Thought leaders in this area recommend considering biologic therapy as one of the several risk factors (Table 48.2) that negatively influence postoperative complications.

A reasonable elective strategy is to delay surgery by 4 weeks (allowing for washout period of two half-lives) from the last anti-TNFα dose. If this is not possible due to the patient's clinical circumstances, temporary diversion may be considered if the patient has two or more risk factors [79].

Vedolizumab, a monoclonal antibody to α4β7 integrin, has been approved for medical treatment of Crohn's disease since 2015. Literature is also conflicted regarding the influence of postoperative septic complications in patients receiving vedolizumab therapy. Vedolizumab has been associated with an increased rate of postoperative surgical site infections [80]. A reasonable strategy is to delay surgery by 6 weeks (two half-lives) from the last vedolizumab dose and, if this is not possible, consider temporary diversion if the patient has additional risk factors for septic complications. Ustekinumab, a monoclonal antibody targeting interleukin-12 and interleukin-23, does not appear to increase the risk of postoperative septic complications [81].

Anastomotic Type

Different anastomotic techniques in Crohn's disease may be compared based on safety (i.e., anastomotic leak rates) and risk of recurrence. When looking at leak rates, one very

important component that is hard to factor in is the surgeon's experience with the applicable technique. With the advent and wide acceptance of the surgical staplers, many are less facile at sewing the anastomosis, and that may result in higher complication rates for the hand-sewn technique.

Despite anastomotic construction being a critical aspect of Crohn's disease management, there is limited level 1 evidence in the literature. Muñoz-Juárez [82] performed the first case-controlled comparative analysis of 138 patients divided evenly into wide-lumen stapled side-to-side anastomoses and hand-sewn end-to-end anastomoses. Clinical recurrence occurred in 16 (24%) of the side-to-side anastomosis group and in 39 (57%) of the end-to-end anastomosis. The cumulative surgical recurrence rates at 5 years were 11% after side-to-side anastomosis and 20% after conventional end-to-end anastomosis ($p = 0.017$). A 2007 meta-analysis [83] comprising only 8 studies with 661 patients who underwent 712 anastomoses compared the outcomes of end-to-end anastomoses (53.8%) and other types of anastomotic configurations (46.2%), including stapled side-to-side in the vast majority. There were no significant differences between the groups regarding overall complications, anastomotic recurrence, or surgical anastomotic recurrence. When comparing only side-to-side and end-to-end anastomosis, a lower leak rate as well as reduction in postoperative complications was demonstrated in the side-to-side anastomosis group. However, there was no difference in overall recurrence or surgical recurrence rates. These data were confirmed in a subsequent Cochrane review by Choy [84].

Two more recent systematic reviews [85, 86], however, demonstrated no difference in anastomotic leak rates between side-to-side and end-to-end anastomotic configurations. In terms of surgical recurrence, Guo [85] reported no differences between the two anastomoses, while Feng [86] reported superiority of the side-to-side anastomosis. The results from these reviews should be interpreted with caution given the retrospective nature of most studies included in each analysis.

In 2009, the first randomized study comparing anastomotic type, the CAST trial [87], was published. Patients were randomized to either side-to-side anastomosis or end-to-end anastomosis. A total of 139 patients were included, and after a mean follow-up of 11.9 months, the endoscopic recurrence rate was 37.9% in the side-to-side anastomosis group and 42.5% in the end-to-end anastomosis group ($p = 0.55$). The symptomatic recurrence rate was also similar between the two groups (22.7% and 21.9%, $p = 0.92$). In 2013, another prospective, randomized trial from Germany was planned with a primary endpoint to investigate whether stapled side-to-side anastomosis resulted in lower recurrence rates compared to hand-sewn end-to-end anastomosis. The secondary endpoint was early postoperative complications. The study was terminated early due to insufficient patient recruitment; while they did not have an adequate number of patients to draw conclusion for the primary endpoint, there was no difference in terms of postoperative complications, length of surgery, and length of hospital stay between the two techniques [88].

In 2011, Kono [89] developed a new hand-sewn antimesenteric functional end-to-end anastomosis with the intent of reducing surgical recurrence in CD. The rationale behind this anastomotic configuration is centered on preservation of the mesenteric vascularization and innervation and a posterior supporting column created by suturing the two staple lines together in order to maintain the three-dimensional structure. In the original paper, the authors performed Kono-S anastomosis in 69 CD patients and compared this group with a historical cohort of 73 CD patients. They found significantly lower endoscopic recurrence rates in the Kono group than in the conventional one, with a lower probability of anastomotic surgical recurrence in the Kono group at 5 years (0% vs 15%; $P < 0.0013$) [89].

In brief, a small window in the mesentery is created at the level of the proximal and distal resection margins. The mesentery is divided using a tissue -device close to the intestinal wall to preserve vascularization and innervation [89]. At this point, the bowel is divided transversely, placing the stapler perpendicular to the intestinal lumen and the mesentery, so that the mesentery is located in the middle of the staple lines. The corners of the two stapled lines are imbricated and reinforced with 4/0 silk Lembert sutures, and the two stumps are approximated by tying together the corresponding corner sutures. The two stapled lines are now sewn together with interrupted 4/0 silk sutures spaced apart, thus creating the so-called supporting column. At this point, an antimesenteric longitudinal enterotomy (or colotomy) is performed on each stump to allow a transverse lumen of 7 cm on the small bowel or closer to 8 cm on the colon, starting no more than 1 cm away from the staple line. The anastomosis is now completed by closing the longitudinal opening transversely in two layers (Fig. 48.5).

This anastomotic configuration has been evaluated in two large multicenter studies [90, 91] and more recently in a prospective randomized trial [92]. Kono reported only 2 surgical anastomotic recurrences in the Kono group with a follow-up of 65 months and a 5 and 10 years' surgical recurrence-free survival rate of 98.6% [90]. Shimada reported a surgical recurrence rate of 3.4% in the Kono-S group versus 24.4% in the end-to-end group, as well as an increased risk of anastomotic leak in the end-to-end group (17.3% vs 5.1%). Kono-S anastomosis had a significantly lower risk of anastomotic surgical recurrence at 1 year (OR 0.14). The 5-year surgery-free survival rate on the anastomosis site (95.0%) was significantly higher with the Kono-S than with the end-to-end anastomosis (95% vs 81.3%; $P < 0.001$) [91]. The first published randomized controlled trial (RCT) [92] confirmed the

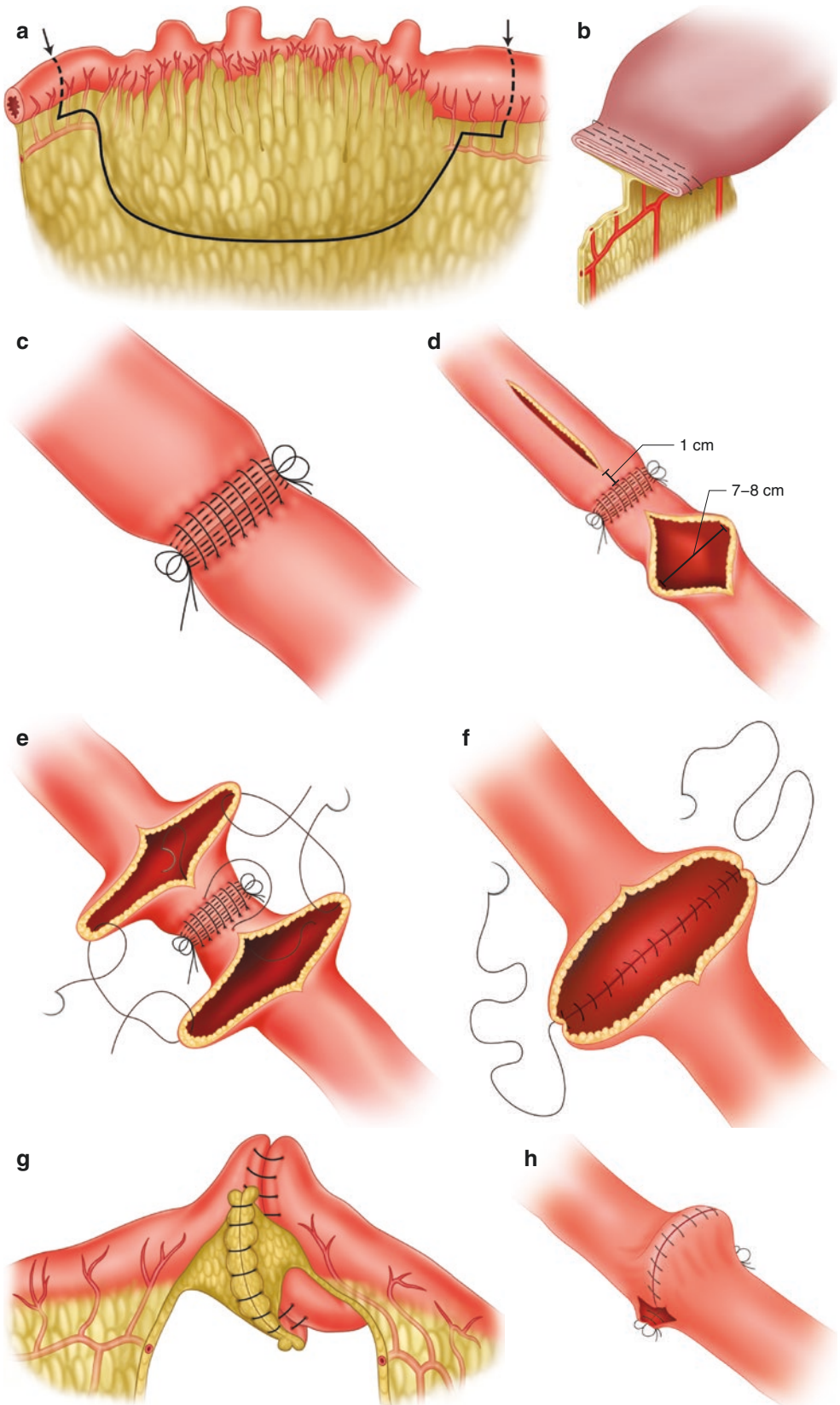

Fig. 48.5 Kono-S anastomosis. (**a**) Resection of diseased segment preserves mesentery at resection margin. (**b**) Transverse division of bowel with orientation of mesentery perpendicular to staple line. (**c**) Creation of supporting column. (**d**) Longitudinal enterotomy. (**e**, **f**) Transverse two-layer anastomosis. (**g**, **h**) Posterior and antimesenteric view of completed Kono-S anastomosis. (Courtesy of T. Kono, MD)

early reports showing lower rates of endoscopic recurrence, reduced severity of endoscopic scores, and lower rate of clinical recurrence in favor of the Kono-S anastomosis.

The mesentery has been thought by some to be involved with the initiation and recurrence of the disease as early ulcers develop typically on the mesenteric side of the bowel with the corresponding "creeping fat." A recent report from Ireland [93] compared wide excision of the mesentery with the conventional closer division in 64 patients. They reported surgical recurrence rates of 40% and 2.9% in favor of the wide excision group ($p = 0.003$). This study has several limitations. The conventional group was a historical control with longer follow-up, postoperative medical prophylaxis of recurrence was not standardized, and there is no data on anastomotic technique. In summary, there is no definitive evidence supporting superior safety of one anastomotic technique over the other. In regard to the risk of recurrence, the role of radical mesenteric excision and the promising results reported with the Kono-S anastomosis will require further study.

Disease Recurrence Trends and Surveillance

After an ileocolic resection with an anastomosis, recurrent Crohn's disease at the anastomotic site is noted in 70–90% of patients within 1 year on endoscopy [94], and 20–30% of these patients will require additional operations within 5 years [95]. Many factors have been cited as potential culprits in the recurrence of the disease at the anastomotic site, including fecal stasis, alteration in the microbiome, and local ischemia, just to mention a few [96, 97].

Over the years, a number of strategies to prevent postoperative recurrence have been proposed. On the medical side, postoperative biologic therapy has been shown to be effective [98, 99]. Regueiro [100] in a small prospective randomized trial comparing early administration of infliximab (5 mg/kg), for 1 year versus placebo, showed that the rate of endoscopic recurrence at 1 year was significantly lower in the infliximab group (1 of 11 patients, 9.1%) compared with the placebo group (11 of 13 patients, 84.6%) ($P = 0.0006$). In a larger multicenter follow-up study, the PREVENT trial [101], the primary endpoint of lower clinical recurrence was not met, but patients on infliximab had lower endoscopic scores and recurrence. The questions of optimal patient selection and timing of administration for prophylaxis remain unanswered.

Attempts at risk stratification based on clinical disease-specific factors and early colonoscopy findings have been proposed to guide postoperative medical management. De Cruz [102] randomized 174 high-risk patients to early colonoscopy vs standard clinical observation and noted that treatment based on clinical risk of recurrence, including early colonoscopy and treatment step-up for recurrence, is better than conventional drug therapy alone for prevention of postoperative recurrence. Selective therapy, adjusted for risk of early recurrence rather than routine use, leads to disease control in most patients. The authors also noted that although clinical risk factors predicted recurrence, patients at low risk also should undergo monitoring and early remission did not preclude the need for ongoing surveillance.

Operative Considerations for Specific Locations

Gastroduodenal Disease

Clinically significant Crohn's disease of the foregut is rare, affecting 0.5–4% of patients [103]. Advances in digestive endoscopy have improved detection of this entity; 30–50% of patients with Crohn's disease have macroscopic UGI disease, and 40–70% have histologically visible UGI disease [104–106]. At least 2/3 of these patients are asymptomatic, and over 90% have coexisting Crohn's in the more distal GI tract [107, 108]. Patients may note insidious gastritis-like symptoms [109]. Early satiety, postprandial pain or emesis, and weight loss can indicate stricture, by far the most common pathology of gastroduodenal Crohn's disease. Fecal calprotectin is not a reliable indicator of gastroduodenal disease [105].

Aphthous erosions, longitudinal ulcers, and bamboo joint-like appearances in the cardia are characteristic of gastric Crohn's, while longitudinal and notch-like erosions of Kerckring folds characterize duodenal disease [106] (Fig. 48.6). Dynamic radiologic studies may reveal a rigid antrum or reduced duodenal peristalsis, while CT or MR enterography may demonstrate disease activity and stricturing (Fig. 48.7). Therapy for symptomatic gastroduodenal Crohn's mirrors that of more distal disease, with the addition of acid suppression [110].

Surgery for gastroduodenal Crohn's is uncommon and comprises <1% of surgery for Crohn's at tertiary centers [111]. Indications for surgery include obstruction and fistula. Almost all instances of gastroduodenal fistula result from penetration of the gastric or duodenal wall originating from another site, such as the terminal ileum or transverse colon. Fistula takedown requires thorough exposure, including Kocherization of the duodenum. The defect can be repaired primarily in one or two layers with low morbidity. A jejunal serosal patch is used for larger defects [112].

Strictures are the most common indication for intervention in gastroduodenal Crohn's disease. Successful endoscopic hydrostatic balloon dilation is feasible for short-segment strictures with a low rate of perforation. Patients are often able to avoid surgery, but multiple dilations are required, and

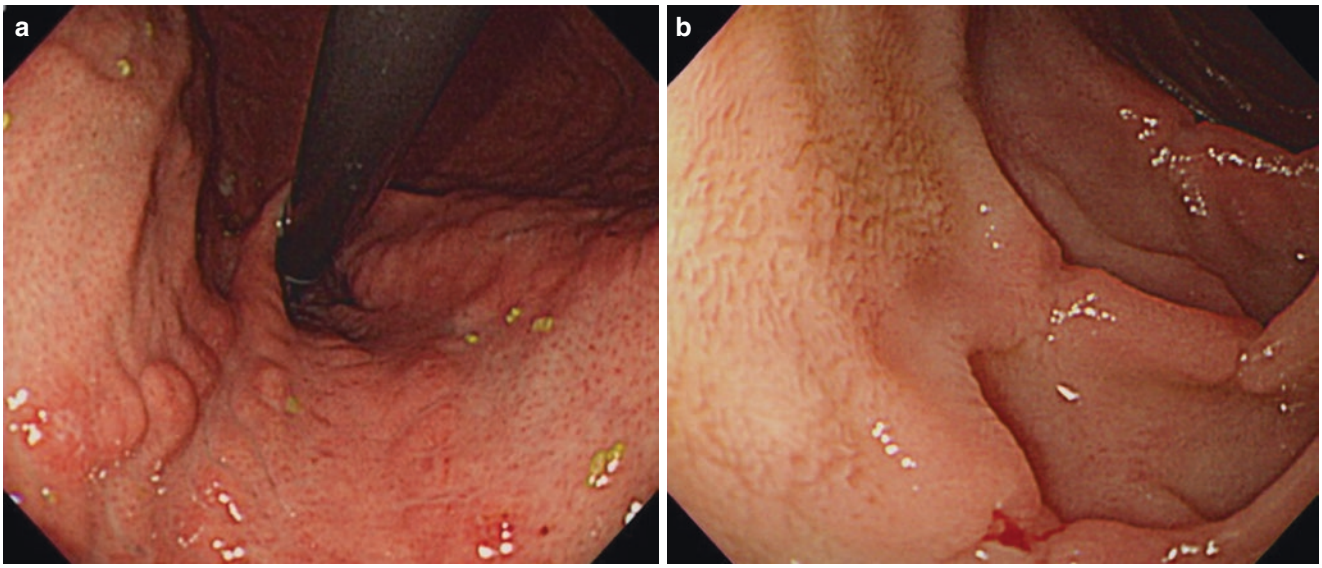

Fig. 48.6 Gastroduodenal disease. (**a**) Bamboo joint-like appearance in the gastric cardia. (**b**) Duodenal notching of Kerckring folds. (Courtesy of A. Sakuraba, MD)

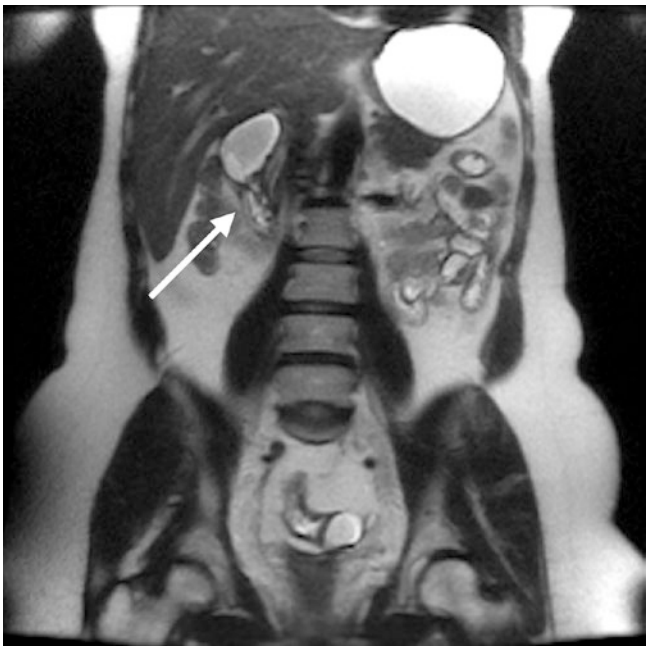

Fig. 48.7 T2-weighted MRI demonstrating a duodenal stricture (arrow). (Courtesy of A. Oto, MD)

recurrence is the rule. Surgical intervention for duodenal stricture includes strictureplasty and bypass. Both procedures are effective with low morbidity. Pancreaticoduodenectomy should be reserved only for instances of severe ampullary dysfunction and/or cholangitis.

Duodenal strictureplasty is a good option for short-segment strictures or if proximal jejunal inflammation prohibits consideration for gastrojejunostomy. After Kocherizing the duodenum, the stricture is assessed by visual inspection and palpation. A Heineke-Mikulicz or Finney strictureplasty is then performed in two layers. These techniques are described in the next section. A 20-mm Foley balloon may be floated in to trawl for more distal strictures. In instances of dense scarring around the stricture, stricturing in the first or fourth portion of the duodenum, or more than two strictures, bypass is preferred [111, 113].

Bypass procedures include gastroduodenostomy, gastrojejunostomy, and duodenojejunostomy predicated on the site of stricture. These procedures are safe with low morbidity. One-quarter to one-third of patients require reoperation for marginal ulceration or disease recurrence [114, 115]. Vagotomy does not decrease the rate of marginal ulceration in this population and need not be performed.

Upper Small Bowel Disease

The jejunum and ileum, not including the terminal ileum, are affected by Crohn's disease in 3–10% of patients [116, 117]. The two most common indications for surgical treatment of patients with disease in these locations are obstruction and sepsis; massive hemorrhage and carcinoma are much less common. The approach to small bowel Crohn's disease has shifted from extensive resections, with the intent to achieve negative microscopic surgical margin, to the resection of only the macroscopically diseased bowel segment [36], and/or to perform bowel-sparing strictureplasty to preserve intestinal length [6, 118, 119]. In the last decade, attention has been directed to the type of anastomosis as an important variable from the standpoint of endoscopic and surgical recurrence [120].

In very general terms, resection of grossly involved bowel segments remains the most common approach when dealing with an inflammatory or penetrating phenotype. On the other hand, strictureplasty is often preferred for quiescent stricturing disease and in patients at risk of developing short bowel syndrome. Patients with jejunoileitis typically have disease recurrence and a need for a second operation in as many as 30% of patients; short bowel syndrome has been reported in 8.5% of cases 20 years after the index surgery [121].

A significant proportion of small bowel strictures are not identified on preoperative workup, and the entire small bowel should be examined at exploration. When dealing with multifocal small bowel disease, assessment of bowel lumen can be done by running a calibration sphere through the bowel or, more simply, by inserting a cuffed catheter. Fibrostenotic strictures with a luminal diameter less than 20 mm are clear indications for strictureplasty or resection, although these cutoffs may vary depending on patient size and normal bowel diameter. Less critical strictures, especially in patients with previous resections and extensive disease, may not mandate operative treatment in an era of effective medical therapy. Strictures may be marked with metal clips for future reference; measurements of remaining intestinal length and location of the strictures in the operative report are important for long-term management.

In an attempt to preserve bowel length and function, Lee and Papaioannou in 1982 and, subsequently, Alexander Williams and Haynes in 1985 described the use of strictureplasty techniques, which had been previously described in India to correct tuberculous stricture of the terminal ileum and cecum [95, 122]. Currently, the most commonly performed strictureplasty techniques are the Heineke-Mikulicz, Finney, Jaboulay, and the side-to-side isoperistaltic strictureplasties. Strictureplasty procedures were adopted from the experience of treating peptic ulcer disease of the duodenum and were initially thought to be risky procedures for Crohn's patients.

However, after Lee [123] published their report proving the safety of strictureplasties, the Heineke-Mikulicz has become the most commonly performed strictureplasty performed in Crohn's patients. It is particularly suited for short-segment (<10 cm) chronic intestinal strictures [124]. A single longitudinal incision is made over the antimesenteric side of the affected small bowel, extending 2 cm beyond both proximal and distal thickened portions, and is closed transversely to create a wide lumen (Fig. 48.8). Finney strictureplasty is used for strictures that are longer than 10 cm but shorter than 25 cm (Fig. 48.9) [124]. Strictures longer than 25 cm if treated with this technique would result in a functional large blind loop leading to bacterial overgrowth and blind loop syndrome [124]. The segment of diseased is folded on itself, and a long, longitudinal enterotomy is made over the antimesenteric border. The anterior and posterior walls of the long enterotomy are sutured separately to create a wide lumen. The Jaboulay strictureplasty is also used for medium-sized (>10 and <25 cm) strictures. With this technique, bowel length is spared; however, there is the creation of a lateral diverticulum with resulting blind loop and potential for stasis in the strictured segment [124]. This short-segment "bypass" was also described in Lee's 1982 report [123], in which a shorter length of small bowel was involved. Both Jaboulay and Finney have the potential for stasis and bacterial overgrowth potentially resulting in a need for revision [125].

Michelassi proposed an isoperistaltic side-to-side strictureplasty for significantly long-segment strictures (>20 cm) or a long portion of bowel containing multiple short strictures in tandem, making the creation of multiple Heineke-Mikulicz strictureplasties unsafe [126]. The procedure involves dividing the bowel and its mesentery in the midpoint of the strictured bowel segment. The two loops are then approximated by a layer of interrupted seromuscular Lembert stitches, using nonabsorbable sutures. A longitudinal enterotomy is performed on both loops, with the intestinal ends tapered to avoid blind stumps. The outer suture line is reinforced with an internal row of running full-thickness 3–0 absorbable sutures, continued anteriorly as a running Connell suture; this layer is reinforced by an outer layer of interrupted seromuscular Lembert stitches using nonabsorbable 3–0 sutures (Fig. 48.10) [127]. This technique avoids sacrificing long segments of bowel and has achieved excellent long-term results [118, 119, 128]. With follow-up extending to 7.5 years in 20 patients, it has provided radiographic, endoscopic, and histopathologic evidence of regression of previously active Crohn's disease with restoration of intestinal function (Fig. 48.11) [129].

Several studies have confirmed the safety and efficacy of both short and longer strictureplasties [125, 128, 130–133]. Early postoperative complications, like bleeding and sepsis, have been reported in between 8% and 15% of cases [125]. Mucosal biopsies and marking the site with a metal clip should be considered, especially in long-standing disease, as cases of cancer at the strictureplasty site have been reported [125, 134, 135]. Reese [131] compared recurrence rates between patients undergoing strictureplasty or resection and found that surgical recurrence was more likely after strictureplasty ($p = 0.09$), and there was a significantly longer recurrence-free interval after resection ($p = 0.01$). Overall recurrence rates have been reported to be between 18% and 29% [130, 136, 137], but with only 4.6% of them at the previous strictureplasty site in one study [136].

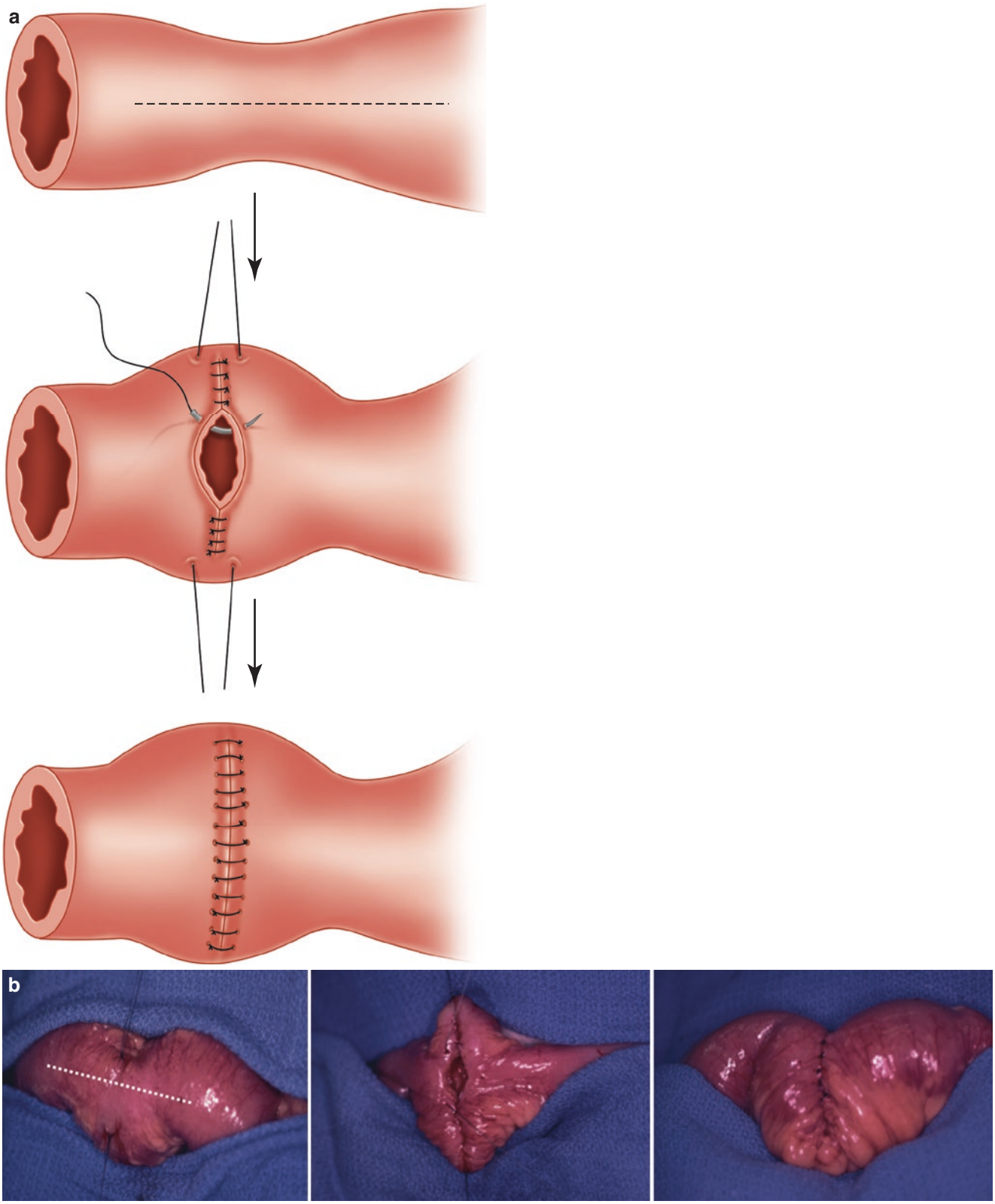

Fig. 48.8 (**a**) Heineke-Mikulicz strictureplasty. (**b**) The longitudinal incision (dashed line) is made over the antimesenteric border and closed transversely. (Courtesy of F. Michelassi, MD)

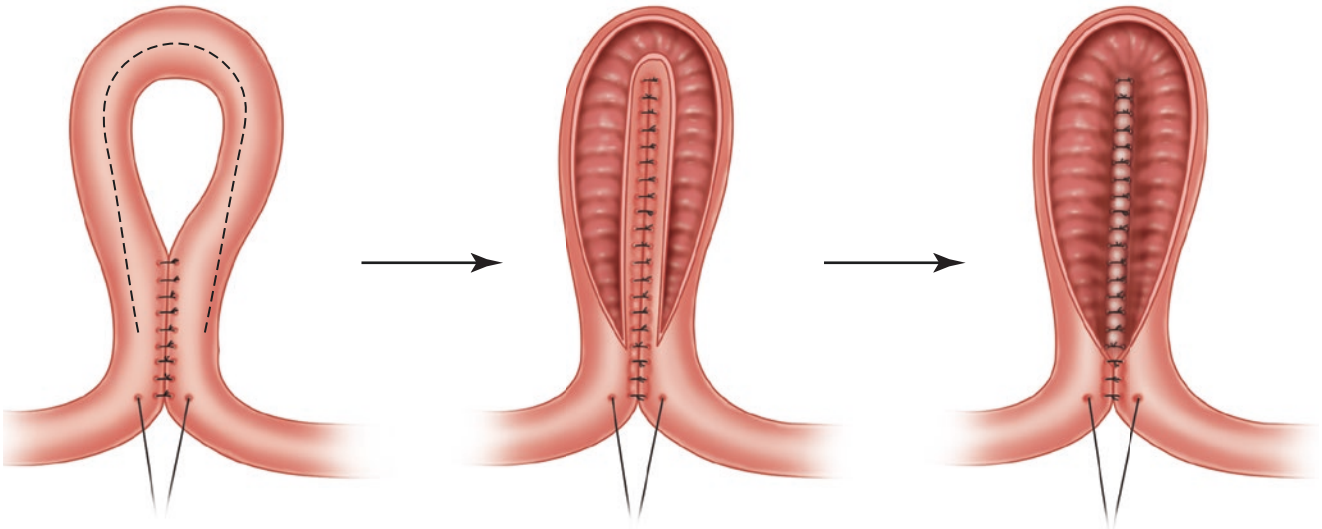

Fig. 48.9 Finney strictureplasty

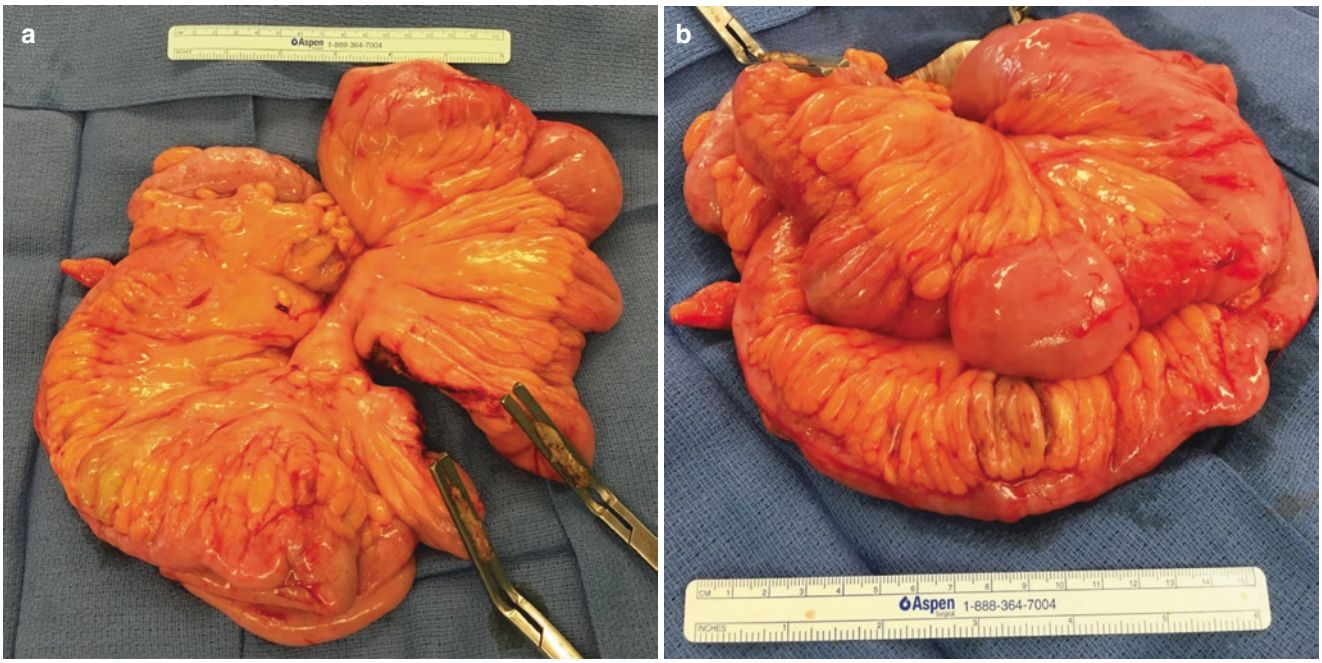

Fig. 48.10 Michelassi isoperistaltic side-to-side strictureplasty (**a**). The bowel is divided at the midpoint of the strictured segment. (**b**) The two loops are approximated. (**c**) A layer of interrupted seromuscular Lembert stiches is placed. (**d**) A longitudinal enterotomy is performed on both loops. (**e**) The anastomosis is completed with the circumferential luminal layer of suture followed by an outer layer of interrupted seromuscular Lembert stitches. (Courtesy from F. Michelassi, MD)

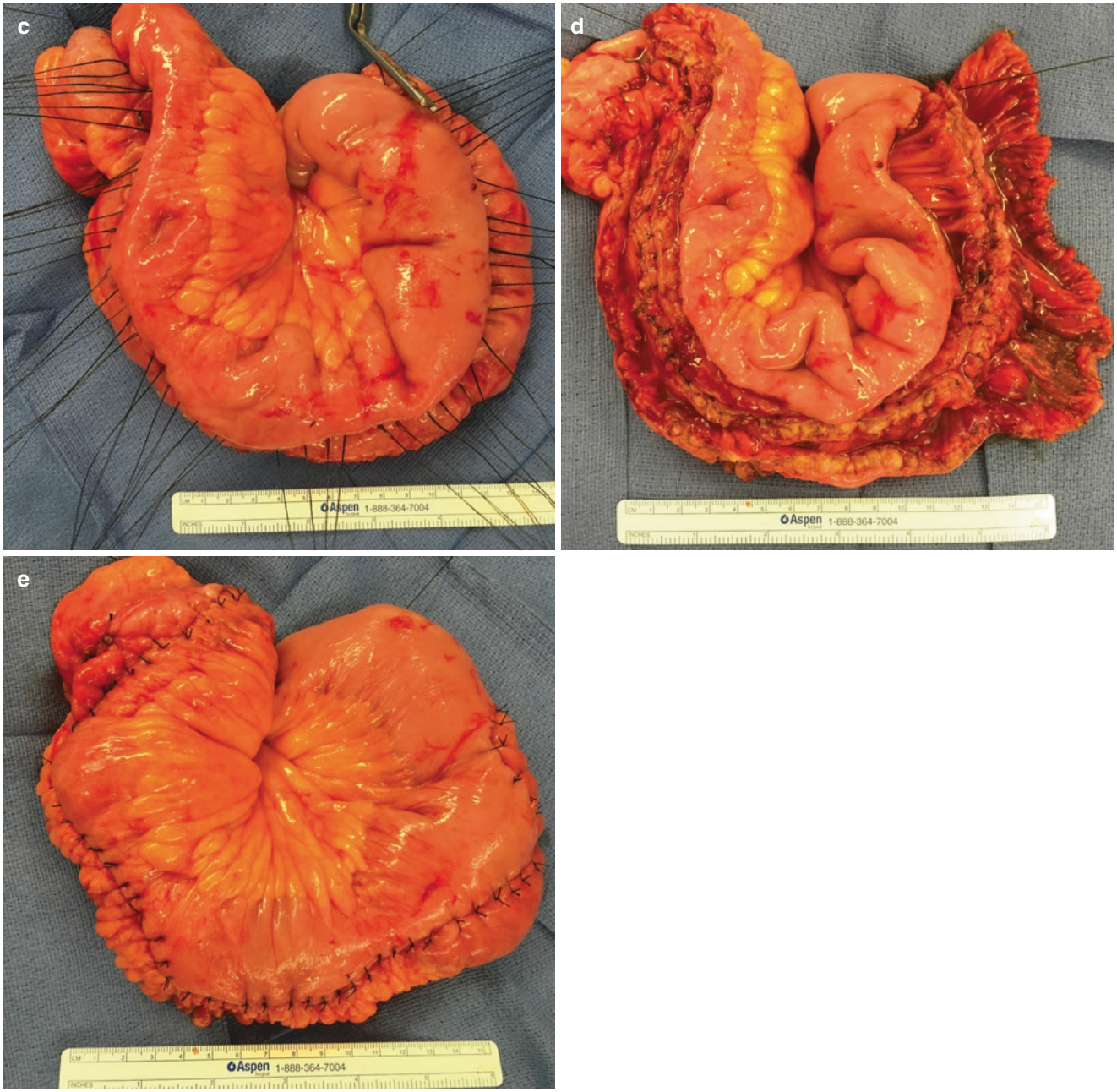

Fig. 48.10 (continued)

Colonic and Rectal Disease

The operations used to treat Crohn's disease of the colon and rectum include total proctocolectomy, total abdominal colectomy with ileostomy or ileorectal anastomosis, and segmental resection. Patients who present with toxic colitis typically require total abdominal colectomy with end ileostomy irrespective of rectal involvement. If the rectum has significant inflammation, there are several options to mitigate against rectal stump leak. If the stump is left intraperitoneally, a rectal tube may be added for decompression. The rectal staple line can also be buried extraperitoneally in the left lower quadrant or fixed above the fascia in the lower midline; as such, the staple line leak will manifest as an abdominal wall, rather than pelvic abscess. The rectal stump may also be matured as a mucus fistula. A systematic review of rectal stump management, albeit in ulcerative colitis, reports that subcutaneous placement is associated with the lowest morbidity [138]. The decision to ultimately perform an ileorectal anastomosis or completion proctectomy can be determined at a later date.

The best operation to perform for a patient with medically refractory Crohn's colitis is less clear. Patients who present with rectal involvement in addition to their colitis are not good candidates for limited resection as there is no good distal target to establish an anastomosis; total proctocolectomy with end ileostomy is typically the indicated procedure. If the patient has poor nutritional status or is on high-dose steroids, a near-total proctocolectomy with an ultralow Hartmann pouch and end ileostomy may be performed to avoid the high risk of perineal wound sepsis. In this instance, the rectum is divided at the anorectal junction; a completion perineal proctectomy can be performed at a later date via perineal approach. Alternatively, a total abdominal colectomy with end ileostomy can be performed and the completion proctectomy accomplished at a later date.

For patients with short-segment Crohn's colitis and rectal-sparing, segmental resection is an option. Numerous retrospective studies have evaluated the outcomes of segmental resection for short-segment Crohn's colitis as compared to total colectomy or total proctocolectomy, reporting on recurrence rates, need for further surgery, and permanent stoma formation. The perioperative complication rate is similar, with no approach emerging with clear benefit. The range of recurrence rate, reoperation rates, and permanent stoma formation are shown in Table 48.3.

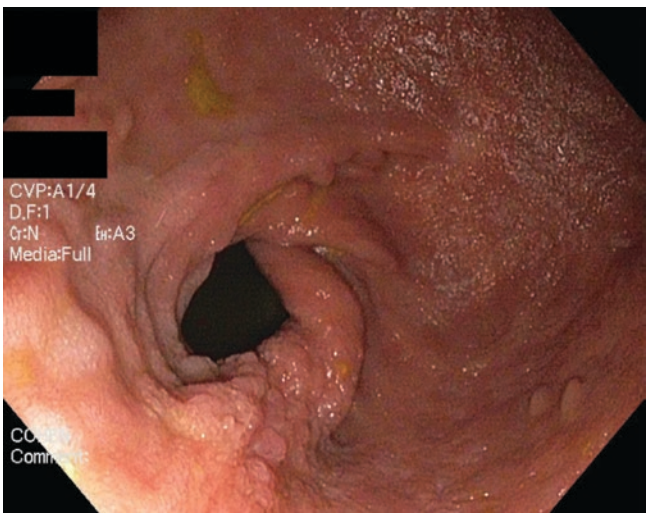

Fig. 48.11 Endoscopic evidence of regression of previously active Crohn's disease after Michelassi strictureplasty. (Courtesy of F. Michelassi, MD)

Patients undergoing segmental resection or total abdominal colectomy with anastomosis experience relatively high rates of colon or rectal recurrence. Up to half of patients will ultimately require a permanent stoma in the long term.

The correct operation for Crohn's colitis remains intrinsically dependent on the distribution of disease. The initial surgical approach should usually be to resect colonic segments that are grossly involved with disease. Patients with two contiguous intestinal segments with disease involvement should undergo resection of these segments in continuity, not two separate segmental resections.

Smoking appears to be associated with the need for further intestinal surgery and need for eventual proctectomy [38]. Patients with isolated distal disease are significantly more likely to require a permanent stoma than patients with isolated proximal disease. Perianal disease, young age, and female sex are independent risk factors for disease recurrence and eventual permanent stoma, and these may inform the consent process [139, 140].

Though it is true that some patients require completion proctectomy after a more limited colonic resection, for many, this can be deferred for several years [38]. The only operation that minimizes risk of disease recurrence is total proctocolectomy with end ileostomy. However, even after total proctocolectomy with end ileostomy, there is an up to 39% rate of recurrence in the small bowel, with up to 32% of patients requiring surgical intervention at 10 years [38, 139, 141–143].

It is important to again note that these recommendations are for Crohn's colitis with rectal-sparing, and not applicable to patients with dysplasia.

Ileal Pouch-Anal Anastomosis in Crohn's Disease

Because of the difficulty in distinguishing Crohn's disease from ulcerative colitis in various settings, some patients with

Table 48.3 Rates of disease recurrence, need for further intestinal surgery, and permanent stoma formation in patients with Crohn's colitis undergoing segmental resection, total abdominal colectomy, and total proctocolectomy

	Colon or rectal disease recurrence	Small bowel disease recurrence	Further intestinal surgery	Permanent stoma
Segmental resection [38, 156–160]	26–55%	4–14%	11–66%	5–44%
Total abdominal colectomy [38, 161–163]	24–66%	8–21%	30%	25–50%
Total proctocolectomy [38, 139, 141, 143]	n/a	Up to 39%	9–32%	Up to 100%

Crohn's disease inevitably undergo a restorative ileal pouch-anal anastomosis (IPAA). Older retrospective studies analyzing patients who were thought to have ulcerative colitis but were subsequently proven to have Crohn's disease demonstrated high complication and pouch failure rates; up to 56% required pouch excision, and a further proportion underwent indefinite diversion [144–146]. Patients with preoperative features suggestive of Crohn's, such as subtle perianal disease or discontinuous inflammation, do very poorly with no meaningful symptom-free intervals after ileal pouch formation. The authors of these studies did observe that a proportion of patients with Crohn's disease who underwent IPAA did well and enjoyed similar functional results as those patients with ulcerative colitis undergoing IPAA.

Two more recent studies suggest lower rates of pouch loss or indefinite diversion. A large prospective series of pouch patients from the Cleveland Clinic published in 2013 reported a 13.3% rate of pouch failure in Crohn's patients, versus only 5.1% in those with ulcerative colitis [147]. Li evaluated intentional IPAA and ileorectal anastomosis for Crohn's, noting that these two patient populations have distinctly different disease characteristics. They reported a 15.5% rate of indefinite diversion in the IPAA group [148]. Taking the above data into consideration, highly selected patients with Crohn's colitis with no perianal disease and no small bowel disease may consider restorative IPAA, provided the risk tolerance and shared decision-making priorities of both the patient and surgeon are aligned.

Special Considerations

Ileosigmoid Fistula

Ileosigmoid fistula is a common complication of perforating Crohn's disease of the terminal ileum. Typically, the inflamed terminal ileum adheres to the sigmoid colon that is otherwise normal and free of primary involvement with Crohn's disease. Most ileosigmoid fistulas are small, may be asymptomatic, and do not in and of themselves require operative management. On the other hand, large ileosigmoid fistulas can result in bypass of the intestinal contents from the terminal ileum to the distal colon and thus give rise to debilitating diarrhea. Such symptomatic fistulas often fail to respond to medical therapy and should be managed surgically.

More than half of the ileosigmoid fistulas from Crohn's disease are not recognized prior to surgery despite imaging and endoscopic evaluation [149]. For this reason, the surgeon should be prepared to deal with this complication in any case of Crohn's disease that involves the terminal ileum. Ileosigmoid fistulas can be managed by simple division of the fistulous adhesion and standard resection of the ileal disease [150]. The defect in the sigmoid colon is then debrided, and simple closure is undertaken; 75% of ileosigmoid fistulas can be thusly managed [149, 151]. The remainder requires resection of the sigmoid colon. Sigmoid colon resection is necessary when primary closure of the fistula is at risk for poor healing. This is the case either when the sigmoid is also involved with Crohn's disease, when the fistulous opening is particularly large, or when there is extensive fibrosis extending along the sigmoid colon. Also, fistulous tracts that enter the sigmoid colon in proximity to the mesentery may be difficult to close and often require resection and primary anastomosis.

Complex Perineal Wounds

Perianal Crohn's disease is common and occurs in one-third of the patients who suffer from intestinal Crohn's disease; this is covered in the chapter on perianal Crohn's disease. Complicated and active rectal disease significantly increases the need for proctectomy [152]; aggressive medical management with antibiotics and biologics [153] is a mainstay along with drainage of local sepsis when required in the attempt to avoid proctectomy.

Conclusion

Management of Crohn's disease is complex and requires a multidisciplinary team approach. Surgical intervention is reserved for refractory disease or complications of the disease. While significant progress has been made over the past 30 years and new medications are changing the course of treatment, much more work remains to be done including understanding how these medications will shift surgical treatment and whether specific surgical techniques lower the risk of recurrent disease.

References

1. Regueiro M, et al. Reduced unplanned care and disease activity and increased quality of life after patient enrollment in an inflammatory bowel disease medical home. Clin Gastroenterol Hepatol. 2018;16(11):1777–85.
2. Bernell O, Lapidus A, Hellers G. Risk factors for surgery and postoperative recurrence in Crohn's disease. Ann Surg. 2000;231(1):38–45.
3. Vester-Andersen MK, et al. Disease course and surgery rates in inflammatory bowel disease: a population-based, 7-year follow-up study in the era of immunomodulating therapy. Am J Gastroenterol. 2014;109(5):705–14.
4. Ha FJ, Thong L, Khalil H. Quality of life after intestinal resection in patients with Crohn disease: a systematic review. Dig Surg. 2017;34(5):355–63.

5. Scott NA, Hughes LE. Timing of ileocolonic resection for symptomatic Crohn's disease – the patient's view. Gut. 1994;35(5):656–7.
6. Gionchetti P, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 2: Surgical management and special situations. J Crohns Colitis. 2017;11(2):135–49.
7. Stenke E, Bourke B, Knaus U. Crohn's strictures-moving away from the knife. Front Pediatr. 2017;5:141.
8. Adler J, et al. Computed tomography enterography findings correlate with tissue inflammation, not fibrosis in resected small bowel Crohn's disease. Inflamm Bowel Dis. 2012;18(5):849–56.
9. Rimola J, et al. Characterization of inflammation and fibrosis in Crohn's disease lesions by magnetic resonance imaging. Am J Gastroenterol. 2015;110(3):432–40.
10. Kim NK, et al. Long-term outcome after ileocecal resection for Crohn's disease. Am Surg. 1997;63(7):627–33.
11. Bhattacharya A, Shen B, Regueiro M. Endoscopy in postoperative patients with Crohn's disease or ulcerative colitis. Does it translate to better outcomes? Gastrointest Endosc Clin N Am. 2019;29(3):487–514.
12. Klag T, Wehkamp J, Goetz M. Endoscopic balloon dilation for Crohn's disease-associated strictures. Clin Endosc. 2017;50(5):429–36.
13. Reutemann BA, et al. Endoscopic balloon dilation size and avoidance of surgery in stricturing Crohn's disease. Inflamm Bowel Dis. 2017;23(10):1803–9.
14. Nishida Y, et al. Analysis of the risk factors of surgery after endoscopic balloon dilation for small intestinal strictures in Crohn's disease using double-balloon endoscopy. Intern Med. 2017;56(17):2245–52.
15. Bettenworth D, et al. A pooled analysis of efficacy, safety, and long-term outcome of endoscopic balloon dilation therapy for patients with Stricturing Crohn's disease. Inflamm Bowel Dis. 2017;23(1):133–42.
16. Bossuyt P, et al. The operative risk and natural history after the diagnosis of ileal penetrating Crohn's disease. Eur J Gastroenterol Hepatol. 2018;30(5):539–45.
17. Hirten RP, et al. The management of intestinal penetrating Crohn's disease. Inflamm Bowel Dis. 2018;24(4):752–65.
18. Patil SA, Cross RK. Medical versus surgical management of penetrating Crohn's disease: the current situation and future perspectives. Expert Rev Gastroenterol Hepatol. 2017;11(9):843–8.
19. Feagins LA, et al. Current strategies in the management of intra-abdominal abscesses in Crohn's disease. Clin Gastroenterol Hepatol. 2011;9(10):842–50.
20. Felder JB, Adler DJ, Korelitz BI. The safety of corticosteroid therapy in Crohn's disease with an abdominal mass. Am J Gastroenterol. 1991;86(10):1450–5.
21. Bafford AC, et al. The clinical impact of preoperative percutaneous drainage of abdominopelvic abscesses in patients with Crohn's disease. Int J Color Dis. 2012;27(7):953–8.
22. Gervais DA, et al. Percutaneous abscess drainage in Crohn disease: technical success and short- and long-term outcomes during 14 years. Radiology. 2002;222(3):645–51.
23. Clancy C, et al. A meta-analysis of percutaneous drainage versus surgery as the initial treatment of Crohn's disease-related intra-abdominal abscess. J Crohns Colitis. 2016;10(2):202–8.
24. Muller-Wille R, et al. Influence of percutaneous abscess drainage on severe postoperative septic complications in patients with Crohn's disease. Int J Color Dis. 2011;26(6):769–74.
25. Zhang T, et al. Preoperative intra-abdominal sepsis, not penetrating behavior itself, is associated with worse postoperative outcome after bowel resection for Crohn disease: a retrospective cohort study. Medicine (Baltimore). 2015;94(45):e1987.
26. Garg SK, Velayos FS, Kisiel JB. Intestinal and nonintestinal cancer risks for patients with Crohn's disease. Gastroenterol Clin N Am. 2017;46(3):515–29.
27. Hnatyszyn A, et al. Colorectal carcinoma in the course of inflammatory bowel diseases. Hered Cancer Clin Pract. 2019;17:18.
28. Laukoetter MG, et al. Intestinal cancer risk in Crohn's disease: a meta-analysis. J Gastrointest Surg. 2011;15(4):576–83.
29. Yamazaki Y, et al. Malignant colorectal strictures in Crohn's disease. Am J Gastroenterol. 1991;86(7):882–5.
30. Lovasz BD, et al. Risk of colorectal cancer in Crohn's disease patients with colonic involvement and stenosing disease in a population-based cohort from Hungary. J Gastrointestin Liver Dis. 2013;22(3):265–8.
31. Belaiche J, et al. Acute lower gastrointestinal bleeding in Crohn's disease: characteristics of a unique series of 34 patients. Belgian IBD Research Group. Am J Gastroenterol. 1999;94(8):2177–81.
32. Pardi DS, et al. Acute major gastrointestinal hemorrhage in inflammatory bowel disease. Gastrointest Endosc. 1999;49(2):153–7.
33. Robert JR, Sachar DB, Greenstein AJ. Severe gastrointestinal hemorrhage in Crohn's disease. Ann Surg. 1991;213(3):207–11.
34. Goldstone RN, Steinhagen RM. Abdominal emergencies in inflammatory bowel disease. Surg Clin North Am. 2019;99(6):1141–50.
35. Remzi FH, et al. Combined use of preoperative provocative angiography and highly selective methylene blue injection to localize an occult small-bowel bleeding site in a patient with Crohn's disease: report of a case. Dis Colon Rectum. 2003;46(2):260–3.
36. Fazio VW, et al. Effect of resection margins on the recurrence of Crohn's disease in the small bowel. A randomized controlled trial. Ann Surg. 1996;224(4):563–71; discussion 571–3.
37. Angriman I, et al. A systematic review of segmental vs subtotal colectomy and subtotal colectomy vs total proctocolectomy for colonic Crohn's disease. Color Dis. 2017;19(8):e279–87.
38. Fichera A, et al. Long-term outcome of surgically treated Crohn's colitis: a prospective study. Dis Colon Rectum. 2005;48(5):963–9.
39. Fumery M, et al. Systematic review with meta-analysis: recurrence of Crohn's disease after total colectomy with permanent ileostomy. Aliment Pharmacol Ther. 2017;45(3):381–90.
40. Swaminath A, et al. Systematic review with meta-analysis: enteral nutrition therapy for the induction of remission in paediatric Crohn's disease. Aliment Pharmacol Ther. 2017;46(7):645–56.
41. Yamamoto T, Shiraki M. Efficacy of enteral nutrition during infliximab maintenance therapy in patients with Crohn's disease. Dig Dis Sci. 2013;58(6):1802–3.
42. Cao Q, et al. The prevalence and risk factors of psychological disorders, malnutrition and quality of life in IBD patients. Scand J Gastroenterol. 2019;54(12):1458–66.
43. Reindl W, et al. Reducing perioperative risks of surgery in Crohn's disease. Visc Med. 2019;35(6):348–54.
44. Gibbs J, et al. Preoperative serum albumin level as a predictor of operative mortality and morbidity: results from the National VA Surgical Risk Study. Arch Surg. 1999;134(1):36–42.
45. Gustafsson UO, et al. Guidelines for perioperative care in elective colorectal surgery: enhanced recovery after surgery (ERAS((R))) society recommendations: 2018. World J Surg. 2019;43(3):659–95.
46. Waitzberg DL, et al. Postsurgical infections are reduced with specialized nutrition support. World J Surg. 2006;30(8):1592–604.
47. Maartense S, et al. Laparoscopic-assisted versus open ileocolic resection for Crohn's disease: a randomized trial. Ann Surg. 2006;243(2):143–9; discussion 150–3.
48. Milsom JW, et al. Prospective, randomized trial comparing laparoscopic vs. conventional surgery for refractory ileocolic Crohn's disease. Dis Colon Rectum. 2001;44(1):1–8; discussion 8–9.
49. Eshuis EJ, et al. Long-term outcomes following laparoscopically assisted versus open ileocolic resection for Crohn's disease. Br J Surg. 2010;97(4):563–8.

50. Stocchi L, Milsom JW, Fazio VW. Long-term outcomes of laparoscopic versus open ileocolic resection for Crohn's disease: follow-up of a prospective randomized trial. Surgery. 2008;144(4):622–7; discussion 627–8.
51. Lowney JK, et al. Is there any difference in recurrence rates in laparoscopic ileocolic resection for Crohn's disease compared with conventional surgery? A long-term, follow-up study. Dis Colon Rectum. 2006;49(1):58–63.
52. Alves A, et al. Factors that predict conversion in 69 consecutive patients undergoing laparoscopic ileocecal resection for Crohn's disease: a prospective study. Dis Colon Rectum. 2005;48(12):2302–8.
53. Beyer-Berjot L, et al. Laparoscopic approach is feasible in Crohn's complex enterovisceral fistulas: a case-match review. Dis Colon Rectum. 2013;56(2):191–7.
54. Goyer P, et al. Impact of complex Crohn's disease on the outcome of laparoscopic ileocecal resection: a comparative clinical study in 124 patients. Dis Colon Rectum. 2009;52(2):205–10.
55. Wu JS, et al. Laparoscopic-assisted ileocolic resections in patients with Crohn's disease: are abscesses, phlegmons, or recurrent disease contraindications? Surgery. 1997;122(4):682–8; discussion 688–9.
56. Raskin ER, et al. Robotic-assisted ileocolic resection for Crohn's disease: outcomes from an early national experience. J Robot Surg. 2019;13(3):429–34.
57. Renshaw S, et al. Perioperative outcomes and adverse events of robotic colorectal resections for inflammatory bowel disease: a systematic literature review. Tech Coloproctol. 2018;22(3):161–77.
58. Moghadamyeghaneh Z, et al. Comparison of open, laparoscopic, and robotic approaches for total abdominal colectomy. Surg Endosc. 2016;30(7):2792–8.
59. Rencuzogullari A, et al. Case-matched comparison of robotic versus laparoscopic proctectomy for inflammatory bowel disease. Surg Laparosc Endosc Percutan Tech. 2016;26(3):e37–40.
60. Martinek L, et al. Does laparoscopic intracorporeal ileocolic anastomosis decreases surgical site infection rate? A propensity score-matched cohort study. Int J Color Dis. 2018;33(3):291–8.
61. Heimann TM, et al. Can laparoscopic surgery prevent incisional hernia in patients with Crohn's disease: a comparison study of 750 patients undergoing open and laparoscopic bowel resection. Surg Endosc. 2017;31(12):5201–8.
62. Scaringi S, et al. Totally robotic intracorporeal side-to-side isoperistaltic strictureplasty for Crohn's disease. J Minim Access Surg. 2018;14(4):341–4.
63. Tou S, et al. Robotic-assisted strictureplasty for Crohn's disease. Tech Coloproctol. 2015;19(4):253–4.
64. Maeda K, et al. A review of reports on single-incision laparoscopic surgery for Crohn's disease. Surg Today. 2019;49(5):361–8.
65. Schwartzberg DM, Remzi FH. The role of laparoscopic, robotic, and open surgery in uncomplicated and complicated inflammatory bowel disease. Gastrointest Endosc Clin N Am. 2019;29(3):563–76.
66. Cannon LM. The use of enhanced recovery pathways in patients undergoing surgery for inflammatory bowel disease. In: Fleshner P, Hyman N, Strong S, editors. Mastery of IBD surgery. Springer Nature Switzerland AG Switzerland; 2019. p. 29–38.
67. de Campos Lobato LF, Ferreira P, Wick EC, Kiran RP, Remzi FH, Kalady MF, Vogel JD. Risk factors of prolonged length of stay after colorectal surgery. J Coloproctol. 2013;33(1):22–7.
68. Troung A, Zaghiyan K. Perioperative steroid management in IBD patients undergoing colorectal surgery. In: Fleshner P, Hyman N, Strong S, editors. Mastery of IBD surgery. Cham: Springer Nature Switzerland AG; 2019. p. 39–49.
69. Lamberts SW, Bruining HA, de Jong FH. Corticosteroid therapy in severe illness. N Engl J Med. 1997;337(18):1285–92.
70. Zaghiyan KN, et al. High-dose perioperative corticosteroids in steroid-treated patients undergoing major colorectal surgery: necessary or overkill? Am J Surg. 2012;204(4):481–6.
71. Aytac E, et al. Impact of stress dose steroids on the outcomes of restorative proctocolectomy in patients with ulcerative colitis. Dis Colon Rectum. 2013;56(11):1253–8.
72. Zaghiyan K, et al. A prospective, randomized, noninferiority trial of steroid dosing after major colorectal surgery. Ann Surg. 2014;259(1):32–7.
73. Aberra FN, et al. Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients. Gastroenterology. 2003;125(2):320–7.
74. Subramanian V, et al. Preoperative steroid use and risk of postoperative complications in patients with inflammatory bowel disease undergoing abdominal surgery. Am J Gastroenterol. 2008;103(9):2373–81.
75. Zangenberg MS, et al. Preoperative optimization of patients with inflammatory bowel disease undergoing gastrointestinal surgery: a systematic review. Int J Color Dis. 2017;32(12):1663–76.
76. Rosen DR, Smith R. Managing immunomodulators perioperatively. In: Fleshner P, Hyman N, Strong S, editors. Mastery of IBD surgery. Switzerland: Springer Nature Switzerland AG; 2019. p. 51–8.
77. Lau C, et al. The impact of preoperative serum anti-TNFalpha therapy levels on early postoperative outcomes in inflammatory bowel disease surgery. Ann Surg. 2015;261(3):487–96.
78. Fumery M, et al. Postoperative complications after ileocecal resection in Crohn's disease: a prospective study from the REMIND group. Am J Gastroenterol. 2017;112(2):337–45.
79. Lightner AL. Managing biologics perioperatively. In: Fleshner P, Hyman N, Strong S, editors. Mastery in IBD surgery. Switzerland: Springer Nature Switzerland AG; 2019.
80. Lightner AL, et al. Postoperative outcomes in vedolizumab-treated Crohn's disease patients undergoing major abdominal operations. Aliment Pharmacol Ther. 2018;47(5):573–80.
81. Lightner AL, et al. Postoperative outcomes in Ustekinumab-treated patients undergoing abdominal operations for Crohn's disease. J Crohns Colitis. 2018;12(4):402–7.
82. Munoz-Juarez M, et al. Wide-lumen stapled anastomosis vs. conventional end-to-end anastomosis in the treatment of Crohn's disease. Dis Colon Rectum. 2001;44(1):20–5; discussion 25–6.
83. Simillis C, et al. A meta-analysis comparing conventional end-to-end anastomosis vs. other anastomotic configurations after resection in Crohn's disease. Dis Colon Rectum. 2007;50(10):1674–87.
84. Choy PY, et al. Stapled versus handsewn methods for ileocolic anastomoses. Cochrane Database Syst Rev. 2011;(9):CD004320.
85. Guo Z, et al. Comparing outcomes between side-to-side anastomosis and other anastomotic configurations after intestinal resection for patients with Crohn's disease: a meta-analysis. World J Surg. 2013;37(4):893–901.
86. Feng JS, et al. Stapled side-to-side anastomosis might be benefit in intestinal resection for Crohn's disease: a systematic review and network meta-analysis. Medicine (Baltimore). 2018;97(15):e0315.
87. McLeod RS, et al. Recurrence of Crohn's disease after ileocolic resection is not affected by anastomotic type: results of a multicenter, randomized, controlled trial. Dis Colon Rectum. 2009;52(5):919–27.
88. Zurbuchen U, et al. Complications after end-to-end vs. side-to-side anastomosis in ileocecal Crohn's disease – early postoperative results from a randomized controlled multicenter trial (ISRCTN-45665492). Langenbeck's Arch Surg. 2013;398(3):467–74.
89. Kono T, et al. A new antimesenteric functional end-to-end handsewn anastomosis: surgical prevention of anastomotic recurrence in Crohn's disease. Dis Colon Rectum. 2011;54(5):586–92.

90. Kono T, et al. Kono-S anastomosis for surgical prophylaxis of anastomotic recurrence in Crohn's disease: an international multicenter study. J Gastrointest Surg. 2016;20(4):783–90.
91. Shimada N, et al. Surgical recurrence at anastomotic site after bowel resection in Crohn's disease: comparison of Kono-S and end-to-end anastomosis. J Gastrointest Surg. 2019;23(2):312–9.
92. Luglio G, et al. Surgical prevention of anastomotic recurrence by excluding mesentery in Crohn's disease: the SuPREMe-CD study - a randomized clinical trial. Ann Surg. 2020;272(2):210–7.
93. Coffey CJ, et al. Inclusion of the mesentery in ileocolic resection for Crohn's disease is associated with reduced surgical recurrence. J Crohns Colitis. 2018;12(10):1139–50.
94. Rutgeerts P, et al. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990;99(4):956–63.
95. Fichera A, Michelassi F. Surgical treatment of Crohn's disease. J Gastrointest Surg. 2007;11(6):791–803.
96. Cameron JL, et al. Patterns of ileal recurrence in Crohn's disease. A prospective randomized study. Ann Surg. 1992;215(5):546–51; discussion 551–2.
97. D'Haens GR, et al. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. Gastroenterology. 1998;114(2):262–7.
98. De Cruz P, et al. Efficacy of thiopurines and adalimumab in preventing Crohn's disease recurrence in high-risk patients - a POCER study analysis. Aliment Pharmacol Ther. 2015;42(7):867–79.
99. Regueiro M, et al. Postoperative therapy with infliximab prevents long-term Crohn's disease recurrence. Clin Gastroenterol Hepatol. 2014;12(9):1494–502.e1.
100. Regueiro M, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology. 2009;136(2):441–50 e1; quiz 716.
101. Regueiro M, et al. Infliximab reduces endoscopic, but not clinical, recurrence of Crohn's disease after ileocolonic resection. Gastroenterology. 2016;150(7):1568–78.
102. De Cruz P, et al. Crohn's disease management after intestinal resection: a randomised trial. Lancet. 2015;385(9976):1406–17.
103. Reynolds HL Jr, Stellato TA. Crohn's disease of the foregut. Surg Clin North Am. 2001;81(1):117–35, viii.
104. Fujiya M, et al. A bamboo joint-like appearance is a characteristic finding in the upper gastrointestinal tract of Crohn's disease patients: a case-control study. Medicine (Baltimore). 2015;94(37):e1500.
105. Laube R, et al. Oral and upper gastrointestinal Crohn's disease. J Gastroenterol Hepatol. 2018;33(2):355–64.
106. Sakuraba A, et al. Endoscopic and pathologic changes of the upper gastrointestinal tract in Crohn's disease. Biomed Res Int. 2014;2014:610767.
107. Annunziata ML, et al. Upper gastrointestinal involvement of Crohn's disease: a prospective study on the role of upper endoscopy in the diagnostic work-up. Dig Dis Sci. 2012;57(6):1618–23.
108. Yamamoto T, Allan RN, Keighley MR. An audit of gastroduodenal Crohn disease: clinicopathologic features and management. Scand J Gastroenterol. 1999;34(10):1019–24.
109. Pimentel AM, Rocha R, Santana GO. Crohn's disease of esophagus, stomach and duodenum. World J Gastrointest Pharmacol Ther. 2019;10(2):35–49.
110. Lightner AL. Duodenal Crohn's disease. Inflamm Bowel Dis. 2018;24(3):546–51.
111. Tonelli F, et al. Symptomatic duodenal Crohn's disease: is strictureplasty the right choice? J Crohns Colitis. 2013;7(10):791–6.
112. Schwartzberg DM, Brandstetter S, Grucela AL. Crohn's disease of the esophagus, duodenum, and stomach. Clin Colon Rectal Surg. 2019;32(4):231–42.
113. Worsey MJ, et al. Strictureplasty is an effective option in the operative management of duodenal Crohn's disease. Dis Colon Rectum. 1999;42(5):596–600.
114. Murray JJ, et al. Surgical management of Crohn's disease involving the duodenum. Am J Surg. 1984;147(1):58–65.
115. Nugent FW, Roy MA. Duodenal Crohn's disease: an analysis of 89 cases. Am J Gastroenterol. 1989;84(3):249–54.
116. Michelassi F, et al. Primary and recurrent Crohn's disease. Experience with 1379 patients. Ann Surg. 1991;214(3):230–8; discussion 238–40.
117. Tan WC, Allan RN. Diffuse jejunoileitis of Crohn's disease. Gut. 1993;34(10):1374–8.
118. Dietz DW, et al. Strictureplasty in diffuse Crohn's jejunoileitis: safe and durable. Dis Colon Rectum. 2002;45(6):764–70.
119. Dietz DW, et al. Safety and long-term efficacy of strictureplasty in 314 patients with obstructing small bowel Crohn's disease. J Am Coll Surg. 2001;192(3):330–7; discussion 337–8.
120. Molloy JW, Kim E, Mahadevan U. Do side-by-side anastomoses decrease the risk of recurrence in Crohn's disease? Gastroenterology. 2010;138(5):2010–2.
121. Watanabe K, et al. Long-term incidence and characteristics of intestinal failure in Crohn's disease: a multicenter study. J Gastroenterol. 2014;49(2):231–8.
122. Katariya RN, et al. Stricture-plasty for tubercular strictures of the gastro-intestinal tract. Br J Surg. 1977;64(7):496–8.
123. Lee EC, Papaioannou N. Minimal surgery for chronic obstruction in patients with extensive or universal Crohn's disease. Ann R Coll Surg Engl. 1982;64(4):229–33.
124. Ambe R, Campbell L, Cagir B. A comprehensive review of strictureplasty techniques in Crohn's disease: types, indications, comparisons, and safety. J Gastrointest Surg. 2012;16(1):209–17.
125. Campbell L, et al. Comparison of conventional and nonconventional strictureplasties in Crohn's disease: a systematic review and meta-analysis. Dis Colon Rectum. 2012;55(6):714–26.
126. Michelassi F. Side-to-side isoperistaltic strictureplasty for multiple Crohn's strictures. Dis Colon Rectum. 1996;39(3):345–9.
127. Maggiori L, Michelassi F. How I do it: side-to-side isoperistaltic strictureplasty for extensive Crohn's disease. J Gastrointest Surg. 2012;16(10):1976–80.
128. Fazi M, et al. Long-term results and recurrence-related risk factors for Crohn disease in patients undergoing side-to-side isoperistaltic strictureplasty. JAMA Surg. 2016;151(5):452–60.
129. Michelassi F, et al. Side-to-side isoperistaltic strictureplasty in extensive Crohn's disease: a prospective longitudinal study. Ann Surg. 2000;232(3):401–8.
130. Michelassi F, et al. Long-term results of the side-to-side isoperistaltic strictureplasty in Crohn disease: 25-year follow-up and outcomes. Ann Surg. 2020;272(1):130–7.
131. Reese GE, et al. Strictureplasty vs resection in small bowel Crohn's disease: an evaluation of short-term outcomes and recurrence. Color Dis. 2007;9(8):686–94.
132. Rottoli M, et al. Predictors of early recurrence after strictureplasty for Crohn's disease of the small bowel during the years of biologics. Dig Liver Dis. 2019;51(5):663–8.
133. Stebbing JF, et al. Recurrence and reoperation after strictureplasty for obstructive Crohn's disease: long-term results [corrected]. Br J Surg. 1995;82(11):1471–4.
134. Jaskowiak NT, Michelassi F. Adenocarcinoma at a strictureplasty site in Crohn's disease: report of a case. Dis Colon Rectum. 2001;44(2):284–7.
135. Marchetti F, Fazio VW, Ozuner G. Adenocarcinoma arising from a strictureplasty site in Crohn's disease. Report of a case. Dis Colon Rectum. 1996;39(11):1315–21.
136. Tichansky D, et al. Strictureplasty for Crohn's disease: meta-analysis. Dis Colon Rectum. 2000;43(7):911–9.
137. Yamamoto and Keighley. Follow up of more than 10 years after strictureplasty for jejunoileal Crohn's disease: long-term results and predictive factors for outcome. Color Dis. 1999;1(2):101–6.

138. Bedrikovetski S, et al. Systematic review of rectal stump management during and after emergency total colectomy for acute severe ulcerative colitis. ANZ J Surg. 2019;89(12):1556–60.
139. Bernell O, Lapidus A, Hellers G. Recurrence after colectomy in Crohn's colitis. Dis Colon Rectum. 2001;44(5):647–54. discussion 654
140. Stocchi L. The role of segmental resection in Crohn's colitis. In: Fleshner P, Hyman N, Strong S, editors. Mastery in IBD surgery. Switzerland: Springer Nature Switzerland AG; 2019. p. 161–5.
141. Amiot A, et al. Crohn's disease recurrence after total proctocolectomy with definitive ileostomy. Dig Liver Dis. 2011;43(9):698–702.
142. Lightner AL. Segmental resection versus total proctocolectomy for Crohn's colitis: what is the best operation in the setting of medically refractory disease or dysplasia? Inflamm Bowel Dis. 2018;24(3):532–8.
143. Lopez J, et al. Natural history of Crohn's disease following total colectomy and end ileostomy. Inflamm Bowel Dis. 2014;20(7):1236–41.
144. Brown CJ, et al. Crohn's disease and indeterminate colitis and the ileal pouch-anal anastomosis: outcomes and patterns of failure. Dis Colon Rectum. 2005;48(8):1542–9.
145. Hyman NH, et al. Consequences of ileal pouch-anal anastomosis for Crohn's colitis. Dis Colon Rectum. 1991;34(8):653–7.
146. Mylonakis E, Allan RN, Keighley MR. How does pouch construction for a final diagnosis of Crohn's disease compare with ileoproctostomy for established Crohn's proctocolitis? Dis Colon Rectum. 2001;44(8):1137–42; discussion 1142–3.
147. Fazio VW, et al. Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. Ann Surg. 2013;257(4):679–85.
148. Li Y, et al. Long-term outcomes of sphincter-saving procedures for diffuse Crohn's disease of the large bowel. Dis Colon Rectum. 2016;59(12):1183–90.
149. Block GE, Schraut WH. The operative treatment of Crohn's enteritis complicated by ileosigmoid fistula. Ann Surg. 1982;196(3):356–60.
150. Fennern E, et al. Surgical techniques and differences in postoperative outcomes for patients with Crohn's disease with Ileosigmoid fistulas: a single-institution experience, 2010-2016. Dis Colon Rectum. 2019;62(10):1222–30.
151. Schraut WH, Chapman C, Abraham VS. Operative treatment of Crohn's ileocolitis complicated by ileosigmoid and ileovesical fistulae. Ann Surg. 1988;207(1):48–51.
152. Michelassi F, et al. Surgical treatment of anorectal complications in Crohn's disease. Surgery. 2000;128(4):597–603.
153. Present DH, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med. 1999;340(18):1398–405.
154. Alves A, et al. Risk factors for intra-abdominal septic complications after a first ileocecal resection for Crohn's disease: a multivariate analysis in 161 consecutive patients. Dis Colon Rectum. 2007;50(3):331–6.
155. Yamamoto T, Allan RN, Keighley MR. Risk factors for intra-abdominal sepsis after surgery in Crohn's disease. Dis Colon Rectum. 2000;43(8):1141–5.
156. Andersson P, et al. Segmental resection or subtotal colectomy in Crohn's colitis? Dis Colon Rectum. 2002;45(1):47–53.
157. Longo WE, Ballantyne GH, Cahow CE. Treatment of Crohn's colitis. Segmental or total colectomy? Arch Surg. 1988;123(5):588–90.
158. Makowiec F, et al. Long-term follow-up after resectional surgery in patients with Crohn's disease involving the colon. Z Gastroenterol. 1998;36(8):619–24.
159. Polle SW, et al. Recurrence after segmental resection for colonic Crohn's disease. Br J Surg. 2005;92(9):1143–9.
160. Martel P, et al. Crohn's colitis: experience with segmental resections; results in a series of 84 patients. J Am Coll Surg. 2002;194(4):448–53.
161. Longo WE, et al. Outcome of ileorectal anastomosis for Crohn's colitis. Dis Colon Rectum. 1992;35(11):1066–71.
162. O'Riordan JM, et al. Long-term outcome of colectomy and ileorectal anastomosis for Crohn's colitis. Dis Colon Rectum. 2011;54(11):1347–54.
163. Pastore RL, Wolff BG, Hodge D. Total abdominal colectomy and ileorectal anastomosis for inflammatory bowel disease. Dis Colon Rectum. 1997;40(12):1455–64.

Ulcerative Colitis: Surgical Management

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Karen N. Zaghiyan and Phillip R. Fleshner

Key Concepts

- Multidisciplinary management and early surgical referral are crucial in the management of ulcerative colitis patients with moderate to severe colitis. While dysplasia screening and management is changing, surgical referral remains a cornerstone in the management of multifocal and high-grade dysplasia.
- Ileal pouch-anal anastomosis is the standard surgery for medically refractory disease, cancer, or dysplasia. One, two, or three-stage surgery may be chosen and tailored to various patient factors including preoperative nutritional status, corticosteroid use, and intraoperative factors.
- Alternative approaches such as total proctocolectomy with end ileostomy, continent ileostomy, and ileorectal anastomosis are options that may be considered in select patients.
- Long-term functional outcomes of patients undergoing surgery for ulcerative colitis including bowel, sexual, and urinary function, as well as fertility preservation, are important considerations and should be discussed preoperatively and monitored closely in the postoperative setting.

Introduction

Ulcerative colitis (UC) is a diffuse inflammatory disease of the mucosal lining of the colon extending from the rectum proximally and manifests clinically as diarrhea, abdominal pain, fever, weight loss, and rectal bleeding. While medical therapy is generally first-line, surgery is often required in patients with medically refractory disease, toxic colitis, dysplasia, or malignancy. This chapter summarizes the surgical options, decision-making, and techniques surrounding these operations.

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Indications for Surgery

Approximately 30% of patients with UC will undergo surgery in their lifetime. In a majority of patients, surgery is recommended and scheduled electively, while 10% require emergent surgery due to various indications. The type of surgery is dependent on the indication for surgery and patient factors.

Elective Surgery

Elective indications for surgery include medically refractory colitis, complications, or side effects associated with medications, extraintestinal manifestations, growth retardation in children, as well as dysplasia or cancer.

Medically refractory colitis and its associated complications make up approximately 70% of the overall surgical cohort [1]. Since the United States Food and Drug Administration approval of infliximab for moderate to severe UC in 2005, several additional biologics have become available options for patients with medically refractory colitis. Medical decision-making has become more complex, and patients are frequently exposed to multiple biologics before proceeding to surgery. During this time, exposure to corticosteroids may increase surgical risk, and nutritional status may decline. An important role of the physician is to guide the patient during their medical journey while preventing them from experiencing complications that may occur as a result of prolonged intractable disease and steroid exposure. Timelines and goal setting can help patients feel in control of their health decisions when facing potential surgery. Shared decision-making may be facilitated through early surgical evaluation prior to exhaustion of all medical options. A survey of UC patients having surgery suggested that over 50% of patients felt that they should have undergone surgery at an earlier time-point [1]. Thus, it is the responsibility of physicians to provide patients with realistic expectations relating

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to their disease treatment and status to allow patients to make appropriate and timely decisions when surgery is inevitable.

Colorectal cancer (CRC), high-grade dysplasia or multifocal low-grade dysplasia are additional indications for colectomy. The overall rate of colorectal cancer in patients with UC is 3.7%. However, this risk begins to increase with the duration of disease from 2% at 10 years after the onset of UC, to 8% at 20 years after disease onset and 18% at 30 years after disease onset [2]. Patients with a young age at diagnosis, pancolitis, moderate to severe UC, family history of CRC, and presence of primary sclerosing cholangitis are also at higher risk of CRC [3]. For patients with a UC diagnosis greater than 8 years, colonoscopy surveillance every 1–2 years has been recommended using chromoendoscopy or high-definition colonoscopy with random quadrant biopsies every 10 cm [4]. During colonoscopy, targeted biopsies of any raised lesions are also performed. In the past, any high-grade dysplasia in the setting of UC was an indication for colectomy. In addition, patients with multifocal low-grade dysplasia were also referred for colectomy. However, the recently published SCENIC guidelines have changed the management of endoscopically detected dysplasia in UC. The guidelines make an important distinction between visible and invisible (random) dysplasia as well as polypoid and non-polypoid lesions. The current consensus statement, albeit based on very low-quality evidence, recommends that endoscopically resected polypoid dysplastic lesions may undergo surveillance colonoscopy rather than colectomy. The SCENIC guidelines also recommend endoscopic surveillance of non-polypoid (flat) dysplasia; however, this recommendation remains conditional and controversial with other guidelines suggesting referral to surgery [4]. The SCENIC guidelines have also challenged the routine use of random quadrant biopsies in UC cancer surveillance [5].

The management of invisible dysplasia has also been challenged. Data with low-definition endoscopes showed that 22% (18 of 81) of patients with invisible low-grade dysplasia [5, 6] and 32–42% of patients with invisible high-grade dysplasia [7] who underwent a colectomy had colorectal cancer in the pathology specimen. These rates supported the recommendation for colectomy in patients with high-grade and even low-grade dysplasia. However, the SCENIC guidelines suggest that these high rates of CRC may be irrelevant in the current high-definition endoscope era. This rationale is supported by the much lower rate of invisible dysplasia (10%) among all biopsies showing dysplasia in the current era vs 87% of biopsies with dysplasia performed prior to high-definition endoscopy or chromoendoscopy [8]. This suggests that older studies reporting a high rate of CRC with invisible dysplasia may be a result of previously unrecognizable lesions prior to the routine availability of modern endoscopic techniques. Thus, the current SCENIC recommendation for invisible dysplasia, confirmed by a gastrointestinal pathologist, is referral to an inflammatory bowel disease (IBD) center with experience in chromoendoscopy and high-definition colonoscopy. If an endoscopically resectable visible lesion is identified and in the area of the previous invisible dysplasia, then the patient may be entered into an intensive screening program. If no visible lesion is identified, patients with high-grade dysplasia are referred for colectomy, whereas patients with low-grade dysplasia are frequently offered surveillance with a greater likelihood for surgical referral in the setting of multifocal low-grade dysplasia.

Elective surgical options include total proctocolectomy with an end or continent ileostomy; ileal pouch-anal anastomosis (IPAA) performed in one, two, or three stages; or total abdominal colectomy with an ileorectal anastomosis. The choice of elective procedure is individualized based on clinical and patient factors and is discussed later in this chapter.

Emergent Surgery

Emergent indications for surgery include acute severe ulcerative colitis (ASUC) not responding to medical therapy, sepsis, toxic megacolon, perforation, or severe bleeding. Perforation and severe bleeding occur less commonly but are emergent indications for surgery. ASUC may range in severity and its response to medical therapy. ASUC can quickly progress to sepsis or toxic megacolon requiring emergency surgery.

Toxic megacolon is a life-threatening condition, combining ASUC with radiologic dilation of the colon, either total or segmental. Whereas patients with a dilated colon without signs of toxicity can be offered an initial trial of conservative management with bowel rest and serial abdominal exams, signs of sepsis including fever, tachycardia, or progressive abdominal pain are indications for urgent colectomy.

Approximately 25% of patients with UC will develop ASUC requiring hospital admission [9]. ASUC is diagnosed according to the modified Truelove and Witts criteria, combining bloody stool frequency ≥6 per day with at least one systemic toxicity such as a heart rate >90 bpm, temperature >37.8 °C, hemoglobin level of <10.5 g/dL, or an erythrocyte sedimentation rate >30 mm/hr [10]. In these patients, initial treatment includes intravenous corticosteroids, along with supportive measures such as intravenous fluids and electrolyte replacement, thromboprophylaxis, and nutritional support. Concomitant infectious etiology, most importantly from *Clostridioides difficile* or cytomegalovirus (CMV), must be ruled out. Approximately 30–40% have a partial or no response to this initial treatment approach. In the prebiologic era, patients with steroid-refractory ASUC underwent urgent colectomy [11]. While the current standard of care for patients with steroid refractory ASUC includes inpatient inf-

liximab (IFX) or cyclosporin (Cys), colectomy rates remain high, ranging from 13% to 25% in-hospital and approach 50% at 1 year [12–14]. In a recent study of 270 patients hospitalized with ASUC between 2002 and 2017, a multivariable logistic regression model identified that previous treatment with thiopurines or anti-TNFs (hazard ratio [HR], 3.86; 95% CI, 1.82–8.18), *Clostridioides difficile* infection (HR, 3.73; 95% CI, 1.11–12.55), serum level of C-reactive protein above 30 mg/L (HR, 3.06; 95% CI, 1.11–8.43), and serum level of albumin below 3.0 g/dL (HR, 2.67; 95% CI, 1.20–5.92) were associated with increased risk of colectomy. A risk prediction score was developed, with each item assigned a score of 1. The cumulative risks of colectomy within 1 year in patients with scores of 0, 1, 2, 3, or 4 were 0%, 9%, 11%, 51%, and 100%, respectively [15]. Despite these statistics, the threshold for surgery remains high, with surgery being considered only when all medical options have been exhausted. Unfortunately, this approach results in an increased risk of surgical morbidity (over 50%) and in-hospital mortality (8%) [16]. We therefore advocate for early surgical evaluation in hospitalized patients with ASUC, with surgery being considered an alternative to medical management rather than a final resort after failure of medical therapy.

In the emergent setting, the preferred surgical approach is a total abdominal colectomy with end ileostomy. The rectum, even if diseased, can generally be left as a Hartmann's stump. When there are concerns about the integrity of the rectal staple or suture line, the rectum can be delivered to the skin as a mucous fistula or as a subcutaneous rectal stump, whereby the closed rectal stump is placed subcutaneously beneath the surgical wound to minimize intraabdominal complications of a stump blowout [17, 18]. The primary consideration when performing an urgent colectomy is to avoid a pelvic dissection as this may hinder future restoration of intestinal continuity and increase the risk of autonomic nerve injury and bleeding complications both in current and future operations. Removal of the diseased colon is generally sufficient to allow the patient to come off of immunosuppressive medications and regain nutritional status and overall health. Completion proctectomy with or without IPAA can be later performed in the elective setting.

Surgical Options and Postoperative Outcomes

Preoperative Planning

Once the decision for surgery is made, several steps should be taken in the preoperative period to optimize surgical outcomes. Preoperative consultation with an enterostomal therapist should be arranged to allow for ostomy site marking and preoperative counseling [19]. Preoperative small bowel evaluation, if one has not been performed in the recent past, is important to exclude small bowel inflammation and confirm the diagnosis of ulcerative colitis. A steroid taper should be considered as tolerated to minimize perioperative steroid dose. In preparing for surgery, the surgeon should also take the lead on perioperative corticosteroid dosing. With the exception of patients with documented adrenal insufficiency, a perioperative corticosteroid stress dose is not recommended and may in fact increase infectious complications. Rather, patients with prolonged steroid exposure should be maintained on their preoperative steroid dose in the perioperative period with a steroid taper on hospital discharge [20]. Preoperative nutritional optimization, and when available, referral to a dietician is important, especially in patients with preoperative weight loss or hypoalbuminemia. Prehabilitation consisting of preoperative oral nutritional supplementation alone or combined with an exercise program has been suggested to improve postoperative recovery and reduce postoperative hospital stay in patients undergoing colorectal surgery, although data specific to surgery for inflammatory bowel disease is limited [21, 22]. An oral antibiotic combined with mechanical bowel preparation should be ordered to minimize postoperative infectious complications [23].

Ileal Pouch-Anal Anastomosis

In 1978 Parks and Nichols described the ileal pouch-anal anastomosis (IPAA) [24], which has since become the standard operation in patients desiring restoration of intestinal continuity and may be performed in one, two, or three stages. In this operation, a near complete proctocolectomy is performed, and an ileal pouch is either stapled or hand-sewn to the anal canal. While the original operation described by Sir Alan Parks included a complete stripping of the rectal mucosa and creation of a triple-loop S-pouch, a majority of centers now preserve the anal transition zone and perform a stapled anastomosis between the ileal J-pouch and anal canal. When patients are considered appropriate candidates for upfront restorative proctocolectomy with IPAA, single stage (restorative proctocolectomy, ileal pouch-anal anastomosis without diverting ileostomy) or two-stage IPAA (restorative proctocolectomy, ileal pouch-anal anastomosis with diverting ileostomy) may be considered. While some centers have advocated for a single-stage approach, a staged IPAA is a far more common and prudent approach. Creation of a diverting ileostomy at the time of IPAA prevents catastrophic septic complications in the event of an anastomotic leak. The ileostomy can later be reversed in 2–3 months. Alternatively, total abdominal colectomy with end ileostomy may be performed first, allowing the patient to recover and

regain nutritional health and later return for completion proctectomy and IPAA.

Prior to embarking on this operation, the integrity of the anal sphincter mechanism must be assessed. Patients should be motivated and willing to cope with potential postoperative complications as the surgical approach may result in impaired function, especially in patients with preexisting fecal incontinence. Ileal pouch-anal anastomosis may be performed using laparoscopic or open technique. In the elective setting, a laparoscopic approach is preferred and offers short-term benefits such as reduced minor complications and shorter hospital stay [25]. Over the long-term, a laparoscopic IPAA may reduce postoperative adhesions and offer female patients improved fertility [26]. In this chapter, a laparoscopic IPAA is described; however the nuances and key technical steps are similar irrespective of open, straight laparoscopic, hand-assisted laparoscopic or robotic approach. The surgeon is advised to use the approach that is safest in their hands, based not only on the patient's clinical condition but also surgeon experience and skill level.

Operative Technique

The patient is brought to the operating room and placed in the modified lithotomy position [27]. An orogastric tube is inserted to decompress the stomach. Trocars are placed in three positions: 11 mm umbilical port for the camera, 5 mm suprapubic port, and a 12 mm port at the future ileostomy site (Fig. 49.1). This allows adequate visualization while at the same time maximizing cosmesis in these often young patients. After creation of pneumoperitoneum, the small bowel is evaluated for Crohn's disease and the abdomen explored for any evidence of bowel perforation (purulent drainage or abscess). Abdominal colectomy is performed in a standard fashion, with close to bowel mesenteric dissection, preservation of the ileocolic artery, and avoiding injury to the duodenum, stomach, small bowel loops, spleen, and pancreas. A 10 mm laparoscopic vessel sealer is used for the majority of the dissection. Colectomy is performed from right to left. The lateral attachments are taken down, and the hepatic flexure is mobilized (Fig. 49.2a). The ileocolic pedicle is identified and preserved. The mesenteric window distal to the ileocolic artery is incised, and the transverse mesocolon and gastrocolic ligament are divided (Fig. 49.2b). The lesser sac is entered (Fig. 49.2c), small bowel loops are swept to the right, and the ligament of Treiz is identified and protected. Care is taken to avoid injury to the stomach, pancreas, and spleen as the splenic flexure is taken down (Fig. 49.2d). The remaining mesentery is divided close to the colon, and the dissection is carried down to the pelvic brim. At this point, decision must be made to proceed with or abort proctectomy and IPAA. Assessment of small bowel mesenteric length for pouch reach at this point is critical. If the mesentery is foreshortened or thick due to fat infiltration, the upper rectum should be cleared of its mesentery with superior rectal artery preservation, stapled closed with an endo-GIA stapler (Fig. 49.2e) and the ileal pouch aborted. It is our approach to extract the specimen through the future ileostomy site. The 12-mm trocar is removed, and the fascial opening is enlarged in a cruciate fashion and rectus muscle split to accommodate two fingers. A wound protector is inserted, and the rectosigmoid colon is delivered through this incision. The ileum is left attached and transected flush with the cecum extracorporeally with a GIA stapler to prevent staple line blowout during extraction. The remaining mesentery is divided with the vessel sealer, close to the bowel in order to preserve the ileocolic pedicle and future perfusion to the ileal pouch. In the event that the colon or mesentery is too thick to safely deliver the intact specimen through the ileostomy site, a small Pfannenstiel incision can be made for extraction. The end ileostomy is then matured and a transanal drain placed to decompress the rectal staple line. In severely malnourished patients when there is concern over the integrity of the rectal staple line, an alternative approach to the abdominal stump is to create a subcutaneous stump or mucous fistula.

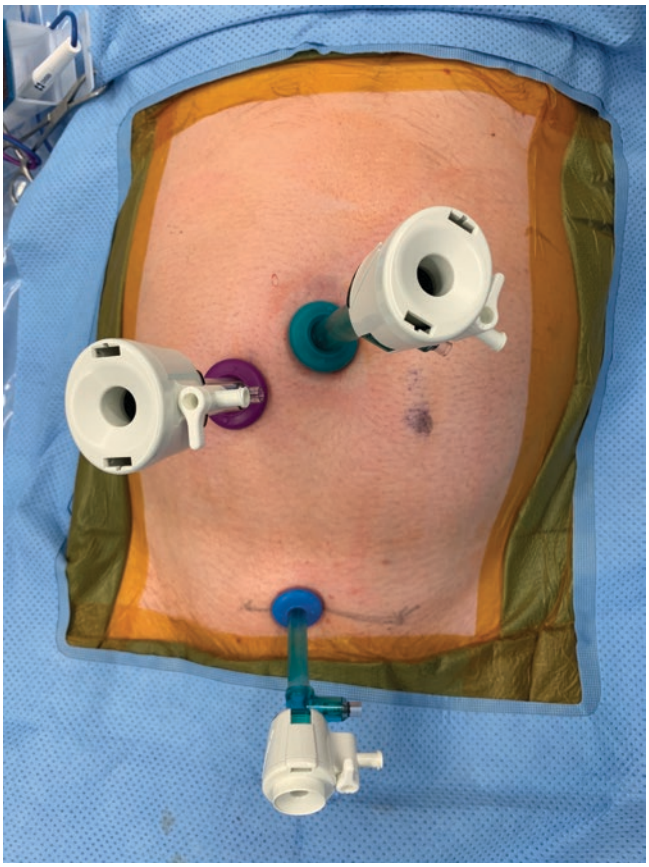

Fig. 49.1 Trocars placement for laparoscopic colectomy. A 12 mm trocar at the future ileostomy site may be used for insertion of Endo-GIA stapler. This site can be later enlarged to create the ileostomy aperture and for specimen extraction

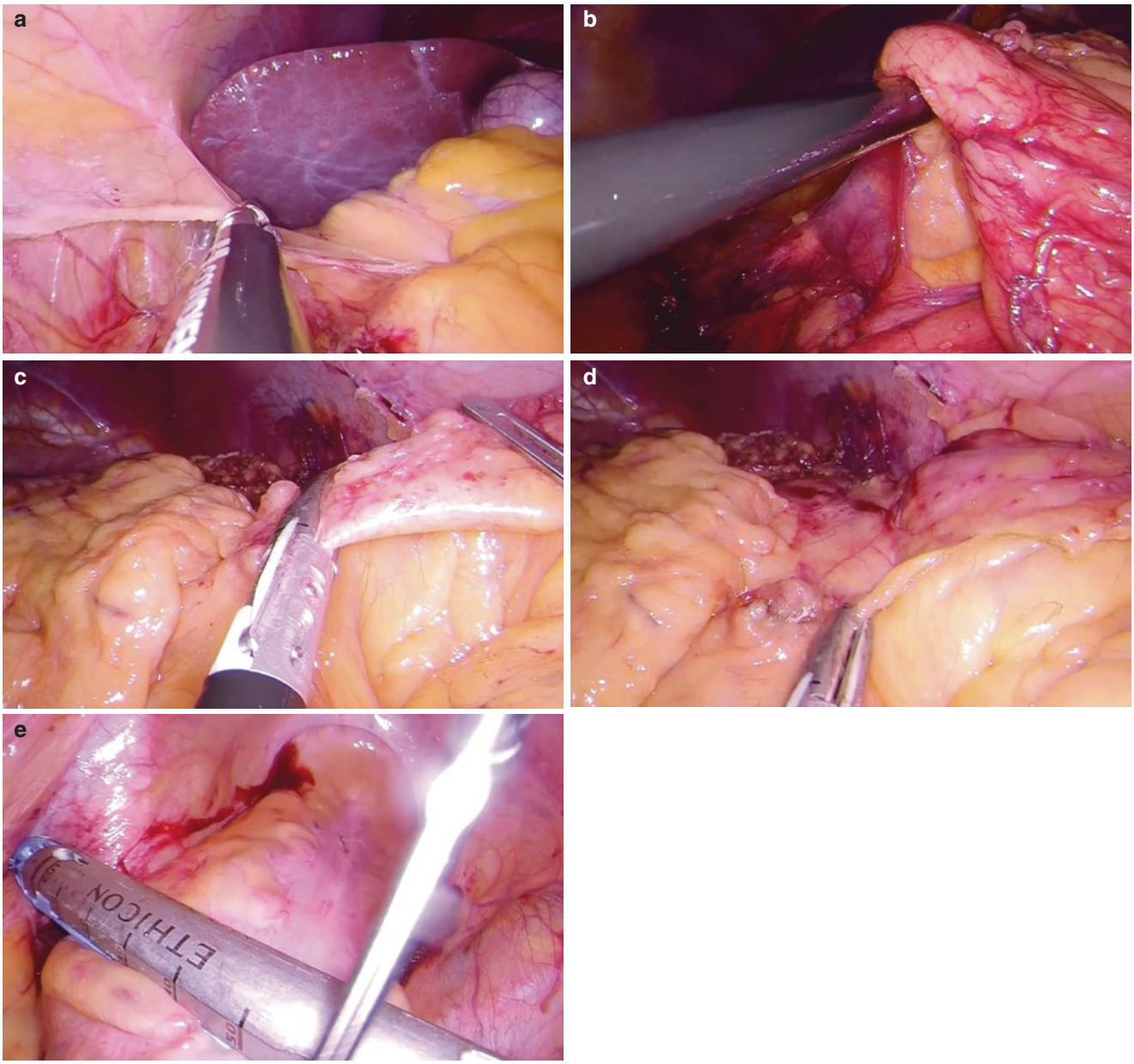

Fig. 49.2 Technical steps of laparoscopic abdominal colectomy. (**a**) The right colon is mobilized in a lateral to medial fashion toward the hepatic flexure, (**b**) the mesenteric window distal to the ileocolic artery is opened, and the mesenteric dissection is taken toward the transverse mesocolon, (**c**) the greater omentum and transverse mesocolon may be divided together or separated to gain entry into the lesser sac, (**d**) the splenic flexure is taken down working form right to left, and (**e**) the rectum is divided intracorporeally using one or two firings of a 60 mm endo-GIA stapler

If there is adequate pouch reach and the patient's clinical condition is conducive to IPAA, then the rectal dissection is carried to the pelvic floor. This dissection may be continued laparoscopically, or, alternatively, a Pfannenstiel incision can facilitate open proctectomy, while still maintaining cosmesis and minimizing incision size and associated complications. The superior rectal artery is divided with the vessel sealer, and entry is gained into the presacral space. It is our practice to perform the posterior dissection in the relatively bloodless total mesorectal excision plane. However, an alternative option, popularized by increased availability and comfort with the use of vessel sealers, is the intramesorectal or close rectal dissection to further reduce the risks of autonomic nerve injury [28]. Anterior dissection is carried close to the rectum preserving the rectoprostatic fascia in men and rectovaginal septum in women, and the lateral stalks are divided close to the rectum, again to minimize injury to autonomic nerves in the setting of benign disease. Anteriorly, the dissec-

tion is carried to the level of the prostate in men and the mid-portion of the vagina in women. Posteriorly, the dissection is carried past the end of the coccyx. When a double stapled anastomosis is planned, the rectum may be stapled closed and transected at the level of the puborectalis muscle using an articulating endo-GIA stapler or right-angle linear stapler leaving a 1–2 cm cuff of rectal mucosa.

Next the ileal reservoir is created (Fig. 49.3). The terminal ileum is aligned in a J configuration, and the pouch constructed with either a continuous absorbable suture or stapling device. Both limbs of the J should measure approximately 15–25 cm in length, the exact length guided by where the pouch reaches deepest into the pelvis. The prospective apex of the pouch must reach beyond the symphysis

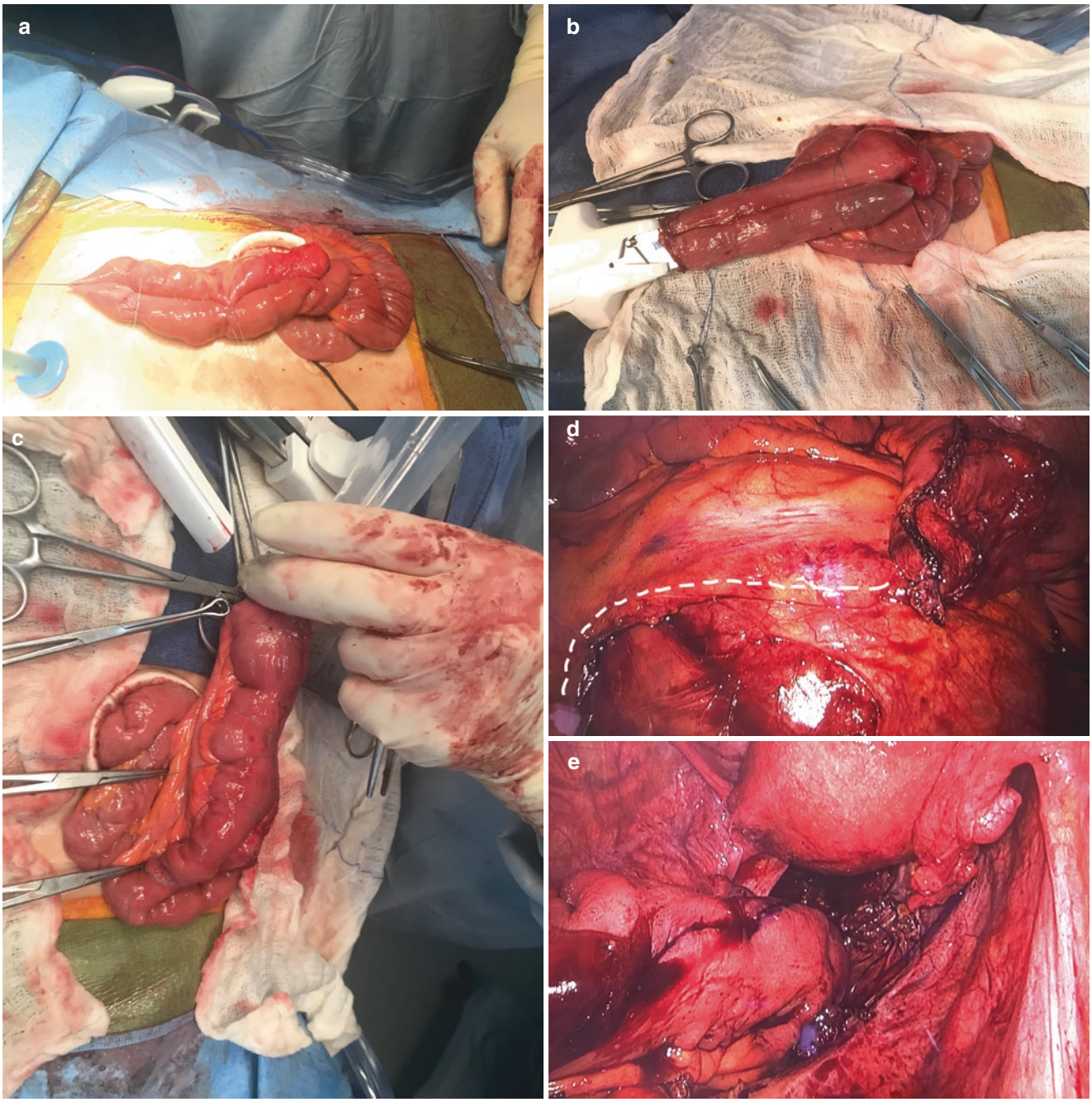

Fig. 49.3 Technical steps of ileal J pouch creation. (**a**) Pouch reach is assessed, and the apex of the pouch is chosen at the point of maximal reach beyond the pubic symphysis. An apical suture and additional aligning sutures are placed, (**b**) enterotomy is created at the apex of the pouch and linear cutting staplers are used to create the reservoir, (**c**) the pouch is air tested to assure absence of leaks, (**d**) the pouch is delivered back into the peritoneal cavity and oriented so that the mesentery is straight along the retroperitoneum (dotted line) to the duodenal sweep and proximal bowel loops are not tethered caudal to the pouch mesentery, and (**e**) the pouch is delivered to the pelvis for anastomosis

pubis in order to accomplish a tension-free ileoanal anastomosis. Selective division of mesenteric vessels to the apex of a proposed J-pouch will allow for more length. Superficial incision on the anterior and posterior aspects of the small bowel mesentery along the course of the superior mesenteric artery and mobilization of the small bowel mesentery up to and anterior to the duodenum are two additional important lengthening maneuvers.

In the case of a double-stapled anastomosis, after transection of the rectum at the level of the puborectalis muscle (Fig. 49.4a), the anvil of the midsized circular stapler device is inserted into the apex of the ileal pouch and secured in place using a running purse-string suture. Before proceeding with the anastomosis, integrity of the rectal staple line is tested using air insufflation. The stapler is placed transanally (Fig. 49.4b) and the trocar advanced through the transverse staple line and connected to the anvil (Fig. 49.4c) assisted by the abdominal operator, who ensures that no adjacent tissues are trapped within the stapling device as it is closed and fired (Fig. 49.4d). The integrity of the staple line may be checked digitally and confirmed using transanal air insufflation.

Alternatively, distal mucosal stripping may be performed with a hand-sewn ileal pouch anal anastomosis [29]. The use of a Lone Star™ retractor facilitates exposure and minimizes damage to the sphincter mechanism (Fig. 49.5a). A solution of dilute epinephrine (Fig. 49.5b) is injected into the submucosal plane to facilitate mucosectomy and minimize bleeding (Fig. 49.5c). The excised mucosa and remaining proximal rectum are removed, leaving a short cuff of denuded rectal muscle distally above the dentate line. The pouch is then pulled into the pelvis and the anastomosis carried out between the apex of the pouch and the dentate line, approximating full thickness of the pouch wall to the internal sphincter and anal mucosa (Fig. 49.5d). A proximal defunctioning loop ileostomy is created. One or two suction drains are placed in the presacral space and brought out through the lower abdominal quadrant. In the case of open proctectomy, placement of an anti-adhesion barrier around the stoma and underneath the incision should be considered to reduce the incidence and severity of postoperative abdominal adhesions [30]. Postoperative management is similar to that in patients who have had a low anterior resection. Ileostomy output can be quite high, since the stoma is more proximal than a traditional terminal ileostomy. Patients should be encouraged to keep themselves well hydrated. In some instances, antidiarrheal medication is prescribed. Enhanced recovery pathways including early diet advancement [31, 32], ambulation [33], and early urinary catheter removal [34] are safe in this patient population and have been shown to improve postoperative outcomes and hospital stay. Patients are discharged when tol-

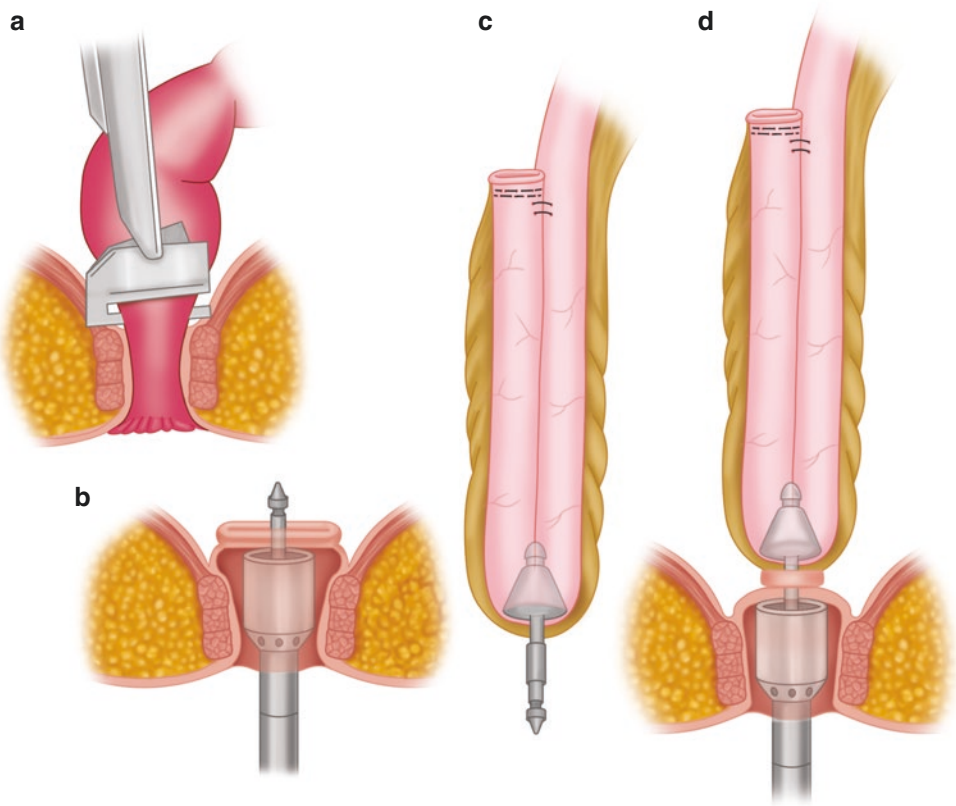

Fig. 49.4 Technical steps of double stapled ileal pouch-anal anastomosis. (**a**) The rectum is transected at the level of the puborectalis, and (**b**) the end-to-end anastomosis stapler is inserted transanally and guided by the abdominal operator through the transverse staple line; (**c**) the anvil placed in the J-pouch (**d**) and the anvil is connected to the transanal stapler and the stapler is closed and fired after assuring appropriate pouch orientation

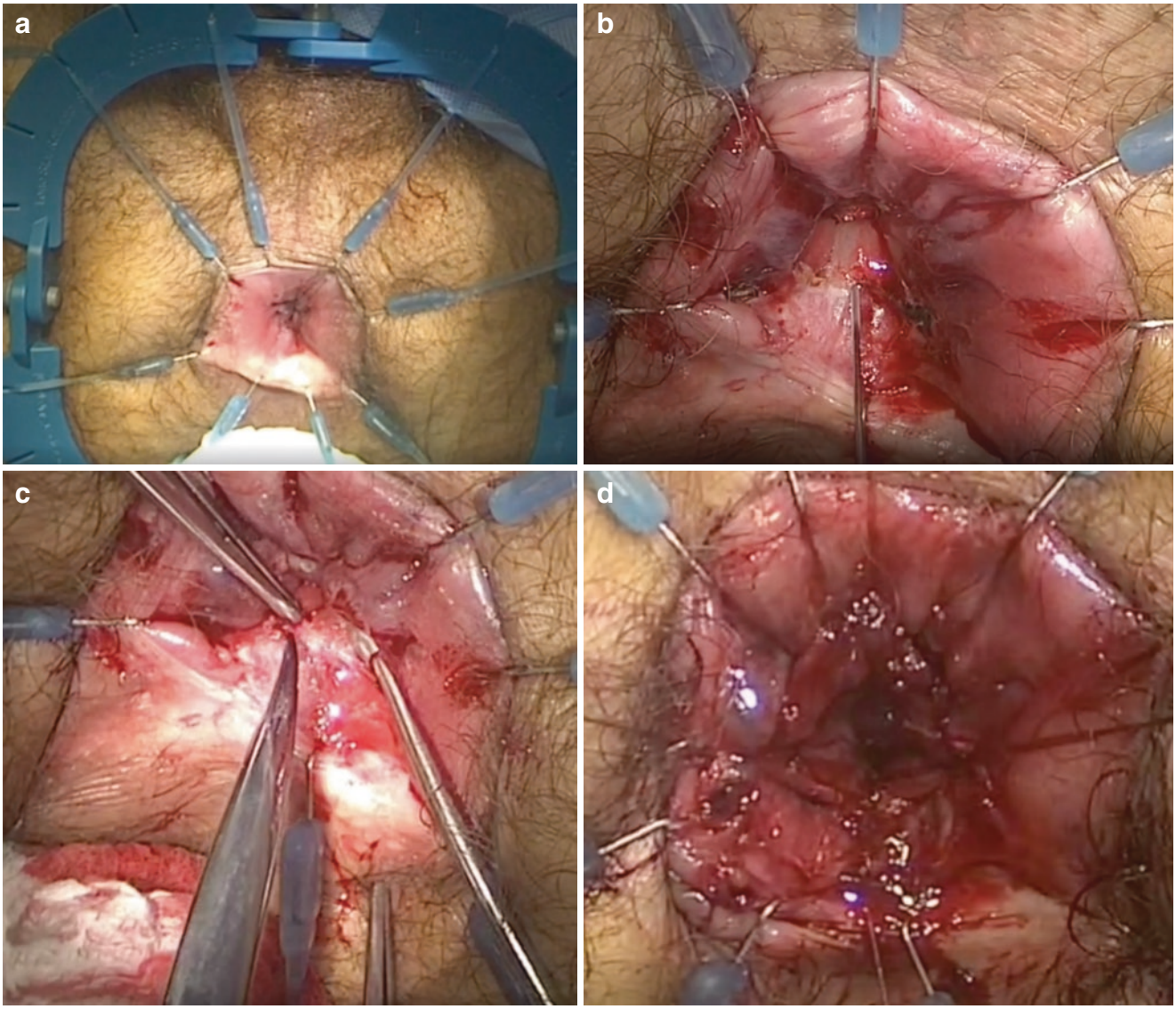

Fig. 49.5 Technical steps of mucosectomy with hand sewn ileal pouch-anal anastomosis. (**a**) Lone Star™ retractor facilitates anal retraction, (**b**) solution of dilute epinephrine is injected submucosally to help develop the dissection plane and minimize bleeding, (**c**) mucosectomy carried upward toward the distal aspect of the abdominal dissection at which point the mucosa is pushed upward and rectum transected, and (**d**) pouch is delivered to the pelvis and hand-sewn to the dentate line

erating a solid diet with adequate ileostomy output and free of signs of infection. Ileostomy may be closed approximately 6–8 weeks later. Before closure however the pouch is thoroughly investigated. Digital rectal examination is used to assess anal sphincter tone and detect anastomotic strictures or defects. The pouch is examined endoscopically to ensure that the suture lines are healed, and a contrast study is performed to detect pouch leaks, fistulas, and sinus tracts. Only after confirmation that pouch abnormalities are not present is the ileostomy closed.

Controversies

One-, Two-, or Three-Stage IPAA

In well-nourished patients undergoing an uncomplicated IPAA and tension-free anastomosis, a single-stage IPAA and omission of a diverting ileostomy have been considered. Proponents of a single-stage IPAA cite the high rate of ileostomy-related complications (43%) including obstruction (23%) and dehydration (25%) in addition to complications related to the ileostomy closure operation (29%) [35].

While level 1 evidence supporting or refuting a single-stage IPAA with omission of an ileostomy is lacking, retrospective reports of selective ileostomy omission suggest similar complication rates and overall long-term function as patients with a diverting ileostomy [36]. In a recent study of 317 diverted and 670 undiverted pouches, pouch leaks occurred in 13.7% ($n = 92$) of patients without diversion and 13.6% ($n = 43$) of patients with diversion. Five diverted patients (12%) developing a pouch leak and 41 (45%) undiverted patients with a pouch leak underwent unplanned trips to the operating room ($p < 0.01$). Ten out of 43 (27%) diverted patients with a pouch leak, and 53 of 92 (60%) of undiverted patients with a pouch leak underwent an unplanned ostomy within 200 weeks of surgery ($p < 0.01$). The rate of pouch salvage operations over total follow-up was similar between the two groups, 74% and 78% of patients with a pouch leak [37]. In another retrospective evaluation of 4031 IPAA patients, of whom 357 developed pelvic sepsis with a diverting ileostomy and 31 without, there was a higher rate of reoperation for diverting ileostomy (48%) in patients without diverting ileostomy at time of IPAA compared with patients with diverting ileostomy (12%); $p < 0.0001$. Five-year and 10-year follow-up however demonstrated no difference in pouch survival between groups, 99% vs 97%, and 88% vs 87%, respectively [38]. These studies are biased, as omission of a diverting ileostomy would only be considered in the most healthy patients having a straightforward operation. Considering the sequelae of a pelvic anastomotic leak and potential long-term effects on pouch function, it is the practice of the authors to perform routine diverting ileostomy in patients undergoing IPAA.

Many patients with UC are not appropriate candidates for upfront IPAA. In these patients, a three-stage IPAA may be offered. This approach involves initial total abdominal colectomy with end ileostomy. After several months of recovery, the patient may undergo completion proctectomy with ileal pouch-anal anastomosis and diverting loop ileostomy followed by ileostomy closure several months later. Patients best suited for a three-stage IPAA include not only hospitalized patients having urgent colectomy but also patients with preoperative malnutrition, high-dose steroids, obesity, cancer, female patients desiring pregnancy, or patients in whom there is diagnostic uncertainty (inflammatory bowel disease-unclassified).

Preoperative corticosteroids more than 20 mg/day and preoperative hypoalbuminemia (serum albumin <3 g/dL) are two factors that carry a significantly higher risk of postoperative pouch-related infectious complications [39, 40] and in the opinion of the authors are indications for initial total abdominal colectomy with staged IPAA. The implications of preoperative biologics have also been debated extensively. While several studies have suggested a higher rate of infectious complications in patients exposed to preoperative biologics, concerns over the retrospective nature of these studies and multiple confounders including concomitant treatment with corticosteroids have resulted in significant debate over this topic [41–44]. However, the recent PUCCINI study, a prospective, multicenter evaluation of 955 patients with inflammatory bowel disease undergoing abdominal surgery found that any infection (19% vs 20%) and surgical site infections (12% vs 13%) were similar in patients treated with or without anti-TNFs in the preoperative period [45]. While the effect of more recently available biologic drugs such as vedolizumab and ustekinumab are yet to be determined, there does not appear to be any robust data suggesting an independent impact on surgical morbidity in patients treated with these agents [46, 47]. Thus, preoperative treatment with biologic drugs does not appear to be an independent factor requiring initial colectomy with staged completion proctectomy and IPAA.

Obesity is an independent predictor of pouch abandonment [48] after IPAA. This is largely related to visceral fat deposition within the ileal mesentery limiting pelvic pouch reach. In addition, obese patients carry a higher risk of overall complications [49] as well as anastomotic leak [50] after IPAA. Patients having elective IPAA should therefore be counseled on preoperative weight loss when possible, and patients having a staged approach should be offered nutritional and weight loss counseling to achieve a BMI <30 kg/m^2 prior to IPAA. Patients with colon cancer in the setting of UC may be better served by a staged approach whereby the proctectomy and IPAA are performed at a later time after systemic chemotherapy in order to avoid a situation where pelvic infectious complications prohibit or delay timely chemotherapy.

Patients desiring pregnancy in the short-term after colectomy may also prefer a staged operation. In these patients, the risk of infertility related to pelvic dissection and IPAA surgery may be minimized by allowing the patient to attempt child bearing after total abdominal colectomy and end ileostomy. The patient may pursue completion proctectomy and restoration of bowel continuity when they have finished child-bearing. Lastly, in patients with inflammatory bowel disease unclassified, a staged approach can allow for pathologic evaluation of the colectomy specimen to guide surgical decision-making. Patients with Crohn's-like features may choose to delay IPAA to allow better diagnostic workup or avoid it all together.

While a three-stage IPAA is the common approach for patients initially undergoing total abdominal colectomy with end ileostomy, a modified two-stage IPAA has recently been described. In this approach, after initial total abdominal colectomy and end ileostomy, the patient returns for the second and final stage several months later (completion proctectomy, ileal pouch-anal anastomosis without diverting ileostomy). Proponents of this approach argue that patients

undergoing total abdominal colectomy and returning for surgery in overall good health and nutrition may be offered IPAA without diversion. In this approach, complications of ileostomy such as dehydration, electrolyte derangements, and the need for a third operation can be omitted. An initial report of this approach compared 23 patients who had a modified two-stage IPAA vs 31 patients who underwent a three-stage IPAA [51]. No patients having a modified two-stage IPAA had pouch-related complications requiring stoma creation. Total hospital cost and hospital stay were also lower in the modified two-stage group. In a more recent cohort comparing 223 patients who had a traditional two-stage IPAA (restorative proctocolectomy with ileal-pouch anal anastomosis and diverting loop ileostomy followed by ileostomy closure several months later) with 237 who had a modified two-stage IPAA, patients having a modified two-stage IPAA had a 4.7% rate of anastomotic leak versus 15.7% of patients having a traditional two-stage IPAA; $p < 0.01$ [52]. While these results appear promising, concerns over patient selection and the overall generalizability of this approach have limited widespread application. Prospective randomized studies may help shed more light on the overall applicability of the modified two-stage IPAA.

Optimal Pouch Design

In their initial description of the IPAA, Parks and Nichols constructed a three-limb "S" pouch with a hand-sewn pouch-anal anastomosis [24]. Several years later, Utsunomiya et al. reported on a two-limb "J" pouch, which, with the advent of the surgical stapler, became the procedure of choice due to its ease of construction [53]. As practice patterns have changed over time, a number of studies have compared both postoperative complications and functional outcomes between the different pouch designs (Fig. 49.6). The majority of these studies are limited to retrospective, single-center series of patients undergoing IPAA for either ulcerative colitis or familial adenomatous polyposis. With regard to short-term outcomes, a meta-analysis performed in 2007 of 23 studies found no difference in rates of anastomotic leak, pelvic sepsis, or pouch failure [54]. Long-term outcomes have been looked at in two large meta-analyses [54, 55] comparing pouch designs. Both studies concluded that J-pouches were subject to increased stool frequency with an average of one more bowel movement over 24 hours. All other functional outcomes however were equivalent between pouch designs.

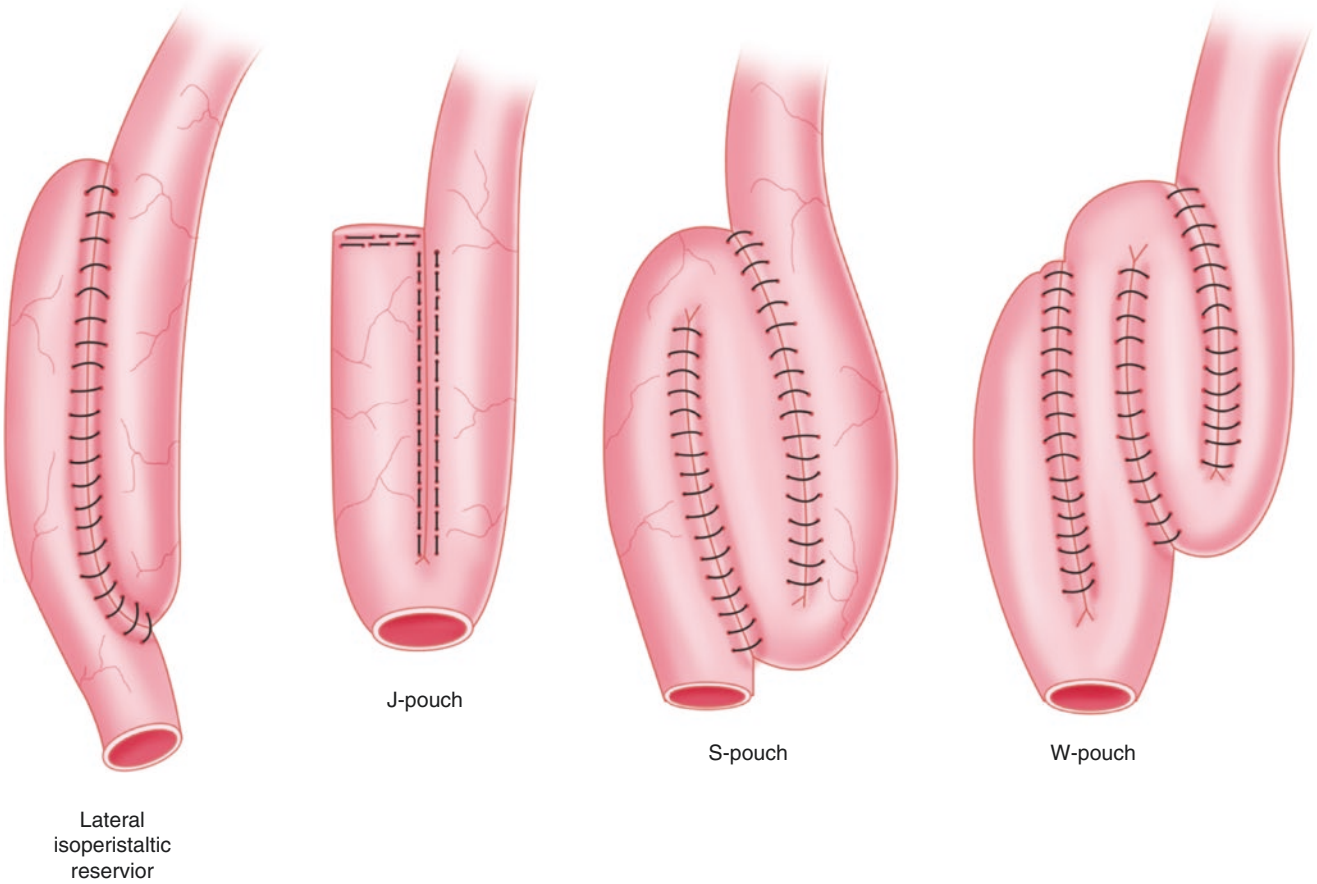

Fig. 49.6 Different ileal pouch configurations

Type of Anastomosis: Hand-Sewn or Stapled

While the original description by Parks and Nicholls in 1978 [24] suggested complete mucosectomy to the dentate line and hand-sewn anastomosis, stapling devices over the last three decades have become the default practice [56]. Several historical randomized trials [57, 58] compared mucosectomy and stapled IPAA in the 1990s, but none demonstrated the superiority of either technique. Small sample size and single institutional methods may account for such findings. Recent evidence has revealed equal long-term functional results comparing both anastomotic techniques [59], while short-term morbidity was consistently lower after stapled IPAA [60]. Regarding the risk of disease relapse or malignancy, the largest published series [61] did not find a higher rate of neoplasia in either the ATZ or pouch after a stapled procedure, while dysplasia or malignancy at the time of IPAA remain independent risk factors [62]. Thus, in patients presenting with colitis and rectal high-grade dysplasia or adenocarcinoma by the time of surgery, mucosectomy and hand-sewn IPAA should be strongly considered. Stapled anastomosis can be considered as the first choice in all other circumstances.

Transanal Pouch

An important yet technically demanding step in laparoscopic ileal pouch surgery is assuring the distal rectal transection is perpendicular to the pelvic floor. Often the angle for transection is oblique, resulting in the need for multiple stapler firings and an increased risk of anastomotic leak [63]. In addition, inadequate transection of the distal rectum may risk leaving a long rectal cuff behind resulting in an increased occurrence of cuffitis and/or pouch evacuation problems. The transanal J-pouch (ta-J-pouch) was developed in an effort to address technical shortfalls of the laparoscopic ileoanal pouch. Another advantage of this approach is the design of the ileoanal anastomosis, changing from a double staple with the potential creation of "dog ears" at the sides to a single stapled which can be easily reinforced transanally. Finally, the transanal platform allows an ergonomic dissection in a horizontal plane of the most distal and curved part of the rectum. Although short-term [64, 65] and long-term functional data [66] appear to support the role of a transanal approach to ileal pouch surgery, more robust data with increased surgical experience is eagerly awaited.

Ileorectal Anastomosis

While IPAA remains the gold standard surgical approach for ulcerative colitis, recent series of ileorectal anastomosis (IRA) for UC have suggested similar long-term functional results and quality of life. Proponents of IRA report advantages including the lower technical demand compared with IPAA, the ability to perform a single stage operation and elimination of a pelvic dissection, and the potential associated complications such as pelvic sepsis, poor function, pouchitis, sexual and urinary dysfunction, and female infertility.

Technical aspects of the operation are similar to the colectomy portion of IPAA. The ileocolic pedicle and superior rectal arteries are preserved. The ileum is transected flush with the cecum and rectum transected where the taenia coli splay. A 29 mm EEA stapler is used to provide a wide lumen and minimize stenosis. After extracorporeal transection of the ileum, the anvil is placed inside and secured with a 2–0 polypropylene purse-string suture. The bowel is re-delivered into the peritoneal cavity, pneumoperitoneum re-achieved, the ileal mesentery laid straight and flush with the retroperitoneum, and EEA anastomosis created and tested under water using flexible sigmoidoscopy. Fluorescence angiography can be used to assure perfusion to the anastomosis. In healthy, well-nourished patients with a tension-free and intact anastomosis, diverting ileostomy is generally not required.

Several studies have shown safety of IRA for UC with overall complications ranging from 24% to 28% and anastomotic leak rate of 3–4% [67–69]. Long-term failure rate is the most important concern and ranges from 18% to 49% [67, 69–71]. In a recent multicenter retrospective study of 343 patients undergoing IRA in France, multivariable analysis identified treatment with both immunosuppressants and anti-TNF before colectomy as independent predictors of IRA failure, whereas colectomy for severe acute colitis was associated with a decreased risk of IRA failure [72].

Another concern with IRA is development of dysplasia or cancer in the retained rectum. In a study published in 1981, overall cancer rate in 89 patients undergoing IRA for UC was 4.8%. This risk ranged from 0% in patients with disease less than 10 years to 13% after 25 years of disease. Patients with cancer or dysplasia in the colon at the time of colectomy had a higher risk of later developing cancer or precancer of the rectum. In patients with mild colonic dysplasia, the risk of rectal cancer or precancer was 22% (2 out of 9 patients), and in surviving patients with colon cancer or precancer, the risk of later developing rectal cancer or precancer was 71% (5 out of 7 patients) [73]. In a meta-analysis of patients with UC undergoing surgery, the risk of subsequent colorectal cancer in patients with a rectal stump, IRA or IPAA, was 2.1%, 2.4%, and 0.5%, respectively. While having an IRA or rectal stump compared with IPAA increased the risk of subsequent colorectal cancer (OR 6.4; 95% CI, 4.3–9.5), a history of colorectal cancer was the most important risk factor for development of CRC after both IRA (OR 12.8; 95% CI, 3.31–49.2) and IPAA (OR 15.0; 95% CI 6.6–34.5) [74].

While a history of colorectal cancer or high-grade dysplasia may portend an unnecessarily high risk of subsequent

dysplasia or rectal cancer after IRA, certain populations such as patients with acute severe colitis requiring urgent colectomy who are relatively naïve to biologics or immunomodulators, those with indeterminate colitis with relative rectal sparing, and patients possibly young female patients desiring to maximize fertility may be candidates for selective IRA. One important factor to consider when choosing to proceed with IRA is the functional capacity of the rectum as chronic UC may impede rectal compliance. Most importantly, the decision for IRA or IPAA should be made under the guidance of a skilled surgeon capable of performing both operations.

Continent Ileostomy

Although continent ileostomy is not primarily advised in patients needing a permanent fecal diversion, it may be a viable option in patients who have failed Brooke ileostomy or those who are candidates for an IPAA but cannot have a pouch because of rectal cancer, perianal fistulas, poor anal sphincter function, or occupations that may preclude frequent visits to the toilet. Suspicion of Crohn's disease contraindicates construction of a continent ileostomy, since the risk of recurrent disease in the pouch is increased which may necessitate resection of the entire pouch encompassing approximately 45 cm of viable small bowel and render the patient unable to maintain nutrition. Obesity and age over 40 years are associated with an increased risk of pouch dysfunction and represent relative contraindications to the continent ileostomy [75]. For patients considering continent ileostomy, an open discussion with the patient is important, stressing that although continence is likely, major complications often occur. These setbacks generally must be corrected surgically, sometimes leading to pouch excision and creation of a standard Brooke ileostomy. Only highly motivated, emotionally stable individuals should consider this procedure.

Operative Technique

After mobilization of the existing ileostomy from the abdominal wall, the reservoir is constructed. The continent ileostomy is created by using the terminal 45–50 cm of the ileum to create an aperistaltic reservoir as initially described by Kock [75] or as an S pouch. The outlet is constructed from the distal 3–5 cm of this segment, the nipple valve is created from the next 18 cm of bowel, and the remaining 30 cm is used for the pouch (Fig. 49.7a). Peritonectomy is performed overlying the mesentery supplying the nipple valve on both sides (Fig. 49.7b). This is performed to increase adhesion formation during intussusception of the nipple valve and prevent slippage. The pouch is oriented in the form of an S, and a posterior row of sutures is placed between each limb and an enterotomy made along the S-shape (Fig. 49.7b). A second posterior row of sutures is created to re-approximate the cut edges (Fig. 49.7c). The nipple valve is then created with three firings of the GIA stapler without the knife (Fig. 49.7d). A two-layer closure of the anterior portion of the pouch is then performed (Fig. 49.7e). A circumferential row of interrupted sutures are placed between the outlet and the pouch to help maintain the position of the nipple valve. The end of the ileum is then brought through the abdominal wall at the preoperatively identified site just above the escutcheon. The stoma is sutured flush with the skin and the pouch firmly anchored to the posterior rectus sheath (Fig. 49.7f). A wide plastic tube with large openings is placed into the pouch to allow gravity drainage of the pouch in the early postoperative period. This tube is occluded for progressively longer periods beginning 10 days after surgery until it can be removed for 8 hours without distress. At this point, the pouch is significantly expanded, the tube is removed, and drainage is achieved by intubating the pouch three times a day.

Postoperative Complications

Postoperative complications that occur with sufficient frequency are nipple valve slippage, pouchitis, intestinal obstruction, and fistula. Nipple valve slippage [76, 77] occurs because of the tendency of the intussuscepted segment to slide and extrude on its mesenteric aspect. Difficult pouch catheterization, chronic outflow tract obstruction, and incontinence ensue. Because of the frequency of this problem, many techniques other than simple surgical stapling have been described to stabilize the valve. Wrapping the valve with prosthetic materials does prevent valve slippage but also is accompanied by a potentially unacceptably high incidence of parastomal abscess and fistula formation [78]. Despite these technical modifications, nipple valve slippage remains the most common complication after continent ileostomy, occurring in almost 30% of patients [76–78]. Although nonoperative approaches have been attempted to correct this problem, surgical correction is virtually inevitable. The repair of the existing malfunctioning valve or creation of a new valve from the afferent ileal limb is performed.

Pouchitis is recognized in 25% of patients, making this the second most common postoperative complication after continent ileostomy [76–78]. Pouchitis refers to nonspecific inflammation that develops in the reservoir and is thought to result from stasis and overgrowth of anaerobic bacteria. Patients present with a combination of increased ileostomy output, fever, weight loss, and stomal bleeding. The diagnosis is made by history and confirmed by pouch endoscopy.

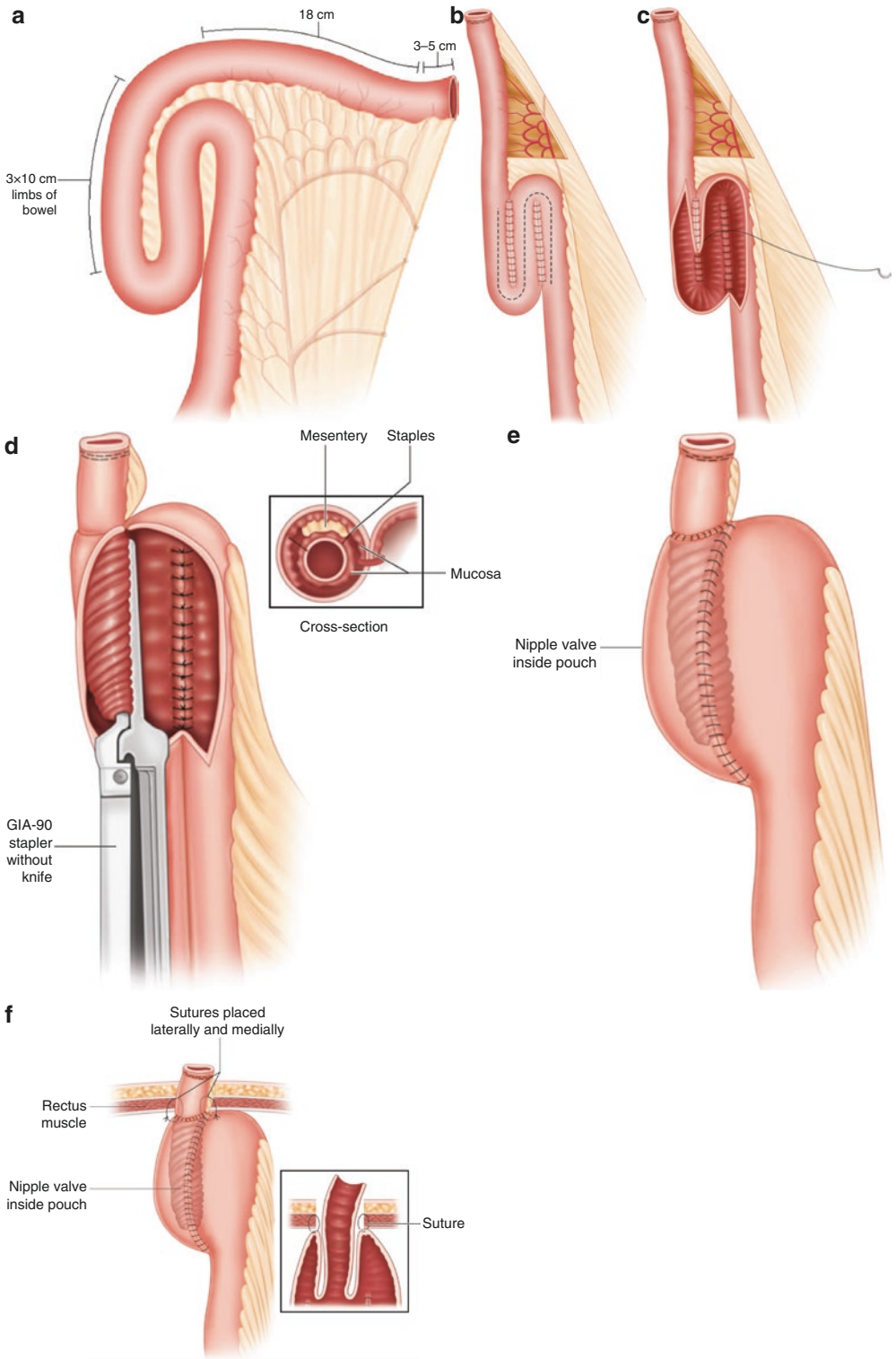

Fig. 49.7 Construction of a Kock Pouch. (**a**) About 45–50 cm of small bowel is used to create the Kock pouch. The distal 3–5 cm is used for the outlet, the middle 18 cm is used to construct the nipple valve, and the proximal 30 cm is utilized in creation of the pouch (**b**) The peritoneum overlying the mesentery to the nipple valve is excised. The S-shaped pouch is constructed by folding the proximal 30 cm of bowel into three 10 cm limbs with sutures placed between the limbs. An enterotomy is made (dotted line) starting at the distal aspect. (**c**) The posterior layer is created, (**d**) the nipple valve is created with three firings of a stapler without the knife, and (**e**) the anterior aspect of the valve is then completed with an inner and outer layer of sutures. To help maintain the nipple valve position, a row of interrupted sutures is placed between the pouch and the outlet. (**f**) After the stoma is delivered through the skin, sutures are placed between the pouch outlet and the posterior sheath of the abdominal wall on the lateral and medial aspects

Pouchitis usually responds to a course of antibiotics and continuous pouch drainage. Other complications include an incidence of intestinal obstruction after continent ileostomy of about 5%. Surgical intervention is mandatory when nonoperative therapy has been unsuccessful. The incidence of fistulas after creation of a continent ileostomy is approximately 10%. Fistulas most commonly originate in the pouch itself or at the base of the nipple valve. Pouch fistulas results from dehiscence of suture lines or rarely ileostomy tube erosion. These tracts may close with bowel rest, parenteral nutrition, and continuous pouch drainage. Fistulas from the base of the valve lead to incontinence, since ileal contents bypass the high-pressure zone of the nipple valve. These fistulas commonly arise with tearing of the sutures anchoring the pouch to the anterior abdominal wall. Valve fistulas rarely heal without operation. At laparotomy, the valve is excised, the pouch rotated, and a new continent valve constructed from the afferent tract.

Patient satisfaction with a continent ileostomy has been reported by some authors as being very high [79, 80]. Most patients note a marked improvement in their lifestyle, and almost all patients work and participate in social and recreational activities without restriction [76, 80]. These observations are understandable in that 90% of patients eventually have total continence after one or more procedures. On the other hand, their enthusiasm is surprising considering that complications are quite frequent and often require major surgical intervention [79, 80]. The often-advertised Barnett modification of the Kock pouch uses the afferent limb of small bowel to construct the nipple valve and wraps a portion of the residual efferent limb around the nipple valve [81]. Although designed to reduce the incidence of valve slippage and fistula formation, there are no controlled data to suggest that this modification is any better than the standard procedure most centers are using.

References

1. Grone J, Lorenz EM, Seifarth C, Seeliger H, Kreis ME, Mueller MH. Timing of surgery in ulcerative colitis in the biologic therapy era-the patient's perspective. Int J Color Dis. 2018;33(10):1429–35.
2. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. 2001;48(4):526–35.
3. Yashiro M. Ulcerative colitis-associated colorectal cancer. World J Gastroenterol. 2014;20(44):16389–97.
4. Van Assche G, Dignass A, Bokemeyer B, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. J Crohns Colitis. 2013;7(1):1–33.
5. Laine L, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastrointest Endosc. 2015;81(3):489–501.e426.
6. Thomas T, Abrams KA, Robinson RJ, Mayberry JF. Meta-analysis: cancer risk of low-grade dysplasia in chronic ulcerative colitis. Aliment Pharmacol Ther. 2007;25(6):657–68.
7. Bernstein CN, Shanahan F, Weinstein WM. Are we telling patients the truth about surveillance colonoscopy in ulcerative colitis? Lancet. 1994;343(8889):71–4.
8. Kiesslich R, Goetz M, Lammersdorf K, et al. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. Gastroenterology. 2007;132(3):874–82.
9. Dinesen LC, Walsh AJ, Protic MN, et al. The pattern and outcome of acute severe colitis. J Crohns Colitis. 2010;4(4):431–7.
10. Dignass A, Eliakim R, Magro F, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. J Crohns Colitis. 2012;6(10):965–90.
11. Jarnerot G, Rolny P, Sandberg-Gertzen H. Intensive intravenous treatment of ulcerative colitis. Gastroenterology. 1985;89(5):1005–13.
12. Williams JG, Alam MF, Alrubaiy L, et al. Infliximab versus ciclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomised trial. Lancet Gastroenterol Hepatol. 2016;1(1):15–24.
13. Bernardo S, Fernandes SR, Goncalves AR, et al. Predicting the course of disease in hospitalized patients with acute severe ulcerative colitis. Inflamm Bowel Dis. 2019;25(3):541–6.
14. Chang KH, Burke JP, Coffey JC. Infliximab versus cyclosporine as rescue therapy in acute severe steroid-refractory ulcerative colitis: a systematic review and meta-analysis. Int J Color Dis. 2013;28(3):287–93.
15. Le Baut G, Kirchgesner J, Amiot A, et al. A scoring system to determine patients' risk of colectomy within 1 y after hospital admission for acute severe ulcerative colitis. Clin Gastroenterol Hepatol. 2020;10:S1542-3565(20)30029-X. https://doi.org/10.1016/j.cgh.2019.12.036. Epub ahead of print. PMID: 31927106.
16. Teeuwen PH, Stommel MW, Bremers AJ, van der Wilt GJ, de Jong DJ, Bleichrodt RP. Colectomy in patients with acute colitis: a systematic review. J Gastrointest Surg. 2009;13(4):676–86.
17. Carter FM, McLeod RS, Cohen Z. Subtotal colectomy for ulcerative colitis: complications related to the rectal remnant. Dis Colon Rectum. 1991;34(11):1005–9.
18. Gu J, Stocchi L, Remzi F, Kiran RP. Intraperitoneal or subcutaneous: does location of the (colo)rectal stump influence outcomes after laparoscopic total abdominal colectomy for ulcerative colitis? Dis Colon Rectum. 2013;56(5):615–21.
19. Bass EM, Del Pino A, Tan A, Pearl RK, Orsay CP, Abcarian H. Does preoperative stoma marking and education by the enterostomal therapist affect outcome? Dis Colon Rectum. 1997;40(4):440–2.
20. Zaghiyan K, Melmed GY, Berel D, Ovsepyan G, Murrell Z, Fleshner P. A prospective, randomized, noninferiority trial of steroid dosing after major colorectal surgery. Ann Surg. 2014;259(1):32–7.
21. Achilli P, Mazzola M, Bertoglio CL, et al. Preoperative immunonutrition in frail patients with colorectal cancer: an intervention to improve postoperative outcomes. Int J Color Dis. 2020;35(1):19–27.
22. Gillis C, Buhler K, Bresee L, et al. Effects of nutritional prehabilitation, with and without exercise, on outcomes of patients who undergo colorectal surgery: a systematic review and meta-analysis. Gastroenterology. 2018;155(2):391–410.e394.
23. Carmichael JC, Keller DS, Baldini G, et al. Clinical practice guidelines for enhanced recovery after colon and rectal surgery from the American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal and Endoscopic Surgeons. Dis Colon Rectum. 2017;60(8):761–84.
24. Parks AG, Nicholls RJ. Proctocolectomy without ileostomy for ulcerative colitis. Br Med J. 1978;2(6130):85–8.
25. McKenna NP, Potter DD, Bews KA, Glasgow AE, Mathis KL, Habermann EB. Ileal-pouch anal anastomosis in pediatric NSQIP: does a laparoscopic approach reduce complications and length of stay? J Pediatr Surg. 2019;54(1):112–7.

26. Gorgun E, Cengiz TB, Aytac E, et al. Does laparoscopic ileal pouch-anal anastomosis reduce infertility compared with open approach? Surgery. 2019;166(4):670–7.
27. Yao L, Fleshner P, Zaghiyan K. Modified technique for laparoscopic total abdominal colectomy with stoma site specimen extraction - stage one of a three-stage ileal pouch anal anastomosis. Presented at Society of American Gastrointestinal and Endoscopic Surgeons Annual Meeting 1–4 April 2020, Cleveland: V201.2020.
28. de Zeeuw S, Ahmed Ali U, van der Kolk MB, van Laarhoven KC. Ileal pouch anal anastomosis with close rectal dissection using automated vessel sealers for ulcerative colitis: a promising alternative. Dig Surg. 2011;28(5–6):345–51.
29. Kaminski JP, Zaghiyan K, Fleshner P. Transanal mucosectomy revisited. Dis Colon Rectum. 2016;59(10):998–9.
30. Salum M, Wexner SD, Nogueras JJ, et al. Does sodium hyaluronate- and carboxymethylcellulose-based bioresorbable membrane (Seprafilm) decrease operative time for loop ileostomy closure? Tech Coloproctol. 2006;10(3):187–90; discussion 190-181.
31. Chough I, Zaghiyan K, Ovsepyan G, Fleshner P. Practice changes in postoperative feeding after elective colorectal surgery: from prospective randomized study to everyday practice. Am Surg. 2018;84(10):1675–8.
32. Lau C, Phillips E, Bresee C, Fleshner P. Early use of low residue diet is superior to clear liquid diet after elective colorectal surgery: a randomized controlled trial. Ann Surg. 2014;260(4):641–7; discussion 647–649.
33. Daskivich TJ, Houman J, Lopez M, et al. Association of wearable activity monitors with assessment of daily ambulation and length of stay among patients undergoing major surgery. JAMA Netw Open. 2019;2(2):e187673.
34. Patel DN, Felder SI, Luu M, Daskivich TJ, Zaghiyan KN, Fleshner P. Early urinary catheter removal following pelvic colorectal surgery: a prospective, randomized, noninferiority trial. Dis Colon Rectum. 2018;61(10):1180–6.
35. Karjalainen EK, Renkonen-Sinisalo L, Mustonen HK, Farkkila M, Lepisto AH. Restorative proctocolectomy in ulcerative colitis: effect of preoperative immunomodulatory therapy on postoperative complications and pouch failure. Scand J Surg. 2021;110(1):51–58.
36. Hainsworth PJ, Bartolo DC. Selective omission of loop ileostomy in restorative proctocolectomy. Int J Color Dis. 1998;13(3):119–23.
37. Widmar M, Munger JA, Mui A, et al. Diverted versus undiverted restorative proctocolectomy for chronic ulcerative colitis: an analysis of long-term outcomes after pouch leak short title: outcomes after pouch leak. Int J Color Dis. 2019;34(4):691–7.
38. Lavryk OA, Hull TL, Duraes LC, et al. Outcomes of ileal pouch-anal anastomosis without primary diverting loop ileostomy if postoperative sepsis develops. Tech Coloproctol. 2018;22(1):37–44.
39. Markel TA, Lou DC, Pfefferkorn M, et al. Steroids and poor nutrition are associated with infectious wound complications in children undergoing first stage procedures for ulcerative colitis. Surgery. 2008;144(4):540–5; discussion 545–547.
40. Okita Y, Araki T, Okugawa Y, et al. The prognostic nutritional index for postoperative infectious complication in patients with ulcerative colitis undergoing proctectomy with ileal pouch-anal anastomosis following subtotal colectomy. J Anus Rectum Colon. 2019;3(2):91–7.
41. Selvaggi F, Pellino G, Canonico S, Sciaudone G. Effect of preoperative biologic drugs on complications and function after restorative proctocolectomy with primary ileal pouch formation: systematic review and meta-analysis. Inflamm Bowel Dis. 2015;21(1):79–92.
42. Ferrante M, D'Hoore A, Vermeire S, et al. Corticosteroids but not infliximab increase short-term postoperative infectious complications in patients with ulcerative colitis. Inflamm Bowel Dis. 2009;15(7):1062–70.
43. Ferrante M, de Buck van Overstraeten A, Schils N, et al. Perioperative use of vedolizumab is not associated with postoperative infectious complications in patients with ulcerative colitis undergoing colectomy. J Crohns Colitis. 2017;11(11):1353–61.
44. Zittan E, Milgrom R, Ma GW, et al. Preoperative anti-tumor necrosis factor therapy in patients with ulcerative colitis is not associated with an increased risk of infectious and noninfectious complications after ileal pouch-anal anastomosis. Inflamm Bowel Dis. 2016;22(10):2442–7.
45. Cohen BL, Fleshner P, Kane SV, Herfarth HH, Palekar N, Farraye FA, JAL, Katz J, Cohen RD, Gerich ME, Cross RK, PDH, Tinsley A, Glover SC, Siegel CA, Bohl JL, HI, Raymond S, Huang R, Suarez-Farinas M, Sands BE. 415a – Anti-tumor necrosis factor therapy is not associated with post-operative infection: results from prospective Cohort of ulcerative colitis and Crohn's disease patients undergoing surgery to identify risk factors for postoperative infection I (Puccini). Gastroenterology. 2019;156:S-80.
46. Novello M, Stocchi L, Holubar S, et al. Surgical outcomes of patients treated with ustekinumab vs. vedolizumab in inflammatory bowel disease: a matched case analysis. Int J Color Dis. 2019;34(3):451–7.
47. Lightner AL, McKenna NP, Alsughayer A, et al. Biologics and 30-day postoperative complications after abdominal operations for Crohn's disease: are there differences in the safety profiles? Dis Colon Rectum. 2019;62(11):1352–62.
48. Poh KS, Qureshi S, Hong YK, et al. Multivariate prediction of intraoperative abandonment of ileal pouch anal anastomosis. Dis Colon Rectum. 2020;63(5):639–45.
49. McKenna NP, Mathis KL, Khasawneh MA, et al. Obese patients undergoing ileal pouch-anal anastomosis: short-and long-term surgical outcomes. Inflamm Bowel Dis. 2017;23(12):2142–6.
50. Sahami S, Bartels SA, D'Hoore A, et al. A multicentre evaluation of risk factors for anastomotic leakage after restorative proctocolectomy with ileal pouch-anal anastomosis for inflammatory bowel disease. J Crohns Colitis. 2016;10(7):773–8.
51. Swenson BR, Hollenbeak CS, Poritz LS, Koltun WA. Modified two-stage ileal pouch-anal anastomosis: equivalent outcomes with less resource utilization. Dis Colon Rectum. 2005;48(2):256–61.
52. Zittan E, Wong-Chong N, Ma GW, McLeod RS, Silverberg MS, Cohen Z. Modified two-stage ileal pouch-anal anastomosis results in lower rate of anastomotic leak compared with traditional two-stage surgery for ulcerative colitis. J Crohns Colitis. 2016;10(7):766–72.
53. Utsunomiya J, Iwama T, Imajo M, et al. Total colectomy, mucosal proctectomy, and ileoanal anastomosis. Dis Colon Rectum. 1980;23(7):459–66.
54. Lovegrove RE, Heriot AG, Constantinides V, et al. Meta-analysis of short-term and long-term outcomes of J, W and S ileal reservoirs for restorative proctocolectomy. Color Dis. 2007;9(4):310–20.
55. Simillis C, Afxentiou T, Pellino G, et al. A systematic review and meta-analysis comparing adverse events and functional outcomes of different pouch designs after restorative proctocolectomy. Color Dis. 2018;20(8):664–75.
56. Larson DW, Cima RR, Dozois EJ, et al. Safety, feasibility, and short-term outcomes of laparoscopic ileal-pouch-anal anastomosis: a single institutional case-matched experience. Ann Surg. 2006;243(5):667–70; discussion 670-662.
57. Reilly WT, Pemberton JH, Wolff BG, et al. Randomized prospective trial comparing ileal pouch-anal anastomosis performed by excising the anal mucosa to ileal pouch-anal anastomosis performed by preserving the anal mucosa. Ann Surg. 1997;225(6):666–76; discussion 676-667.
58. Hallgren TA, Fasth SB, Oresland TO, Hulten LA. Ileal pouch anal function after endoanal mucosectomy and handsewn ileoanal anastomosis compared with stapled anastomosis without mucosectomy. Eur J Surg. 1995;161(12):915–21.

59. Schluender SJ, Mei L, Yang H, Fleshner PR. Can a meta-analysis answer the question: is mucosectomy and handsewn or double-stapled anastomosis better in ileal pouch-anal anastomosis? Am Surg. 2006;72(10):912–6.
60. Kirat HT, Remzi FH, Kiran RP, Fazio VW. Comparison of outcomes after hand-sewn versus stapled ileal pouch-anal anastomosis in 3,109 patients. Surgery. 2009;146(4):723–9; discussion 729–730.
61. Kariv R, Remzi FH, Lian L, et al. Preoperative colorectal neoplasia increases risk for pouch neoplasia in patients with restorative proctocolectomy. Gastroenterology. 2010;139(3):806–12, 812. e801–802.
62. Lightner AL, Pemberton JH, Dozois EJ, et al. The surgical management of inflammatory bowel disease. Curr Probl Surg. 2017;54(4):172–250.
63. Lee S, Ahn B. The relationship between the number of intersections of staple lines and anastomotic leakage after the use of a double stapling technique in laparoscopic colorectal surgery. Surg Laparosc Endosc Percutan Tech. 2017;27(4):273–81.
64. de Buck van Overstraeten A, Mark-Christensen A, Wasmann KA, et al. Transanal versus transabdominal minimally invasive (completion) proctectomy with ileal pouch-anal anastomosis in ulcerative colitis: a comparative study. Ann Surg. 2017;266(5):878–83.
65. Zaghiyan K, Warusavitarne J, Spinelli A, Chandrasinghe P, Di Candido F, Fleshner P. Technical variations and feasibility of transanal ileal pouch-anal anastomosis for ulcerative colitis and inflammatory bowel disease unclassified across continents. Tech Coloproctol. 2018;22(11):867–73.
66. Chandrasinghe P, Carvello M, Wasmann K, et al. Transanal ileal pouch-anal anastomosis for ulcerative colitis has comparable long-term functional outcomes to transabdominal approach: a multicentre comparative study. J Crohns Colitis. 2020;14(6):726–33.
67. Andersson P, Norblad R, Soderholm JD, Myrelid P. Ileorectal anastomosis in comparison with ileal pouch anal anastomosis in reconstructive surgery for ulcerative colitis – a single institution experience. J Crohns Colitis. 2014;8(7):582–9.
68. Borjesson L, Lundstam U, Oresland T, Brevinge H, Hulten L. The place for colectomy and ileorectal anastomosis: a valid surgical option for ulcerative colitis? Tech Coloproctol. 2006;10(3):237–41; discussion 241.
69. Pastore RL, Wolff BG, Hodge D. Total abdominal colectomy and ileorectal anastomosis for inflammatory bowel disease. Dis Colon Rectum. 1997;40(12):1455–64.
70. Leijonmarck CE, Lofberg R, Ost A, Hellers G. Long-term results of ileorectal anastomosis in ulcerative colitis in Stockholm County. Dis Colon Rectum. 1990;33(3):195–200.
71. Uzzan M, Kirchgesner J, Oubaya N, et al. Risk of rectal neoplasia after colectomy and ileorectal anastomosis for ulcerative colitis. J Crohns Colitis. 2017;11(8):930–5.
72. Uzzan M, Cosnes J, Amiot A, et al. Long-term follow-up after Ileorectal anastomosis for ulcerative colitis: a GETAID/GETAID Chirurgie multicenter retrospective cohort of 343 patients. Ann Surg. 2017;266(6):1029–34.
73. Grundfest SF, Fazio V, Weiss RA, et al. The risk of cancer following colectomy and ileorectal anastomosis for extensive mucosal ulcerative colitis. Ann Surg. 1981;193(1):9–14.
74. Derikx L, Nissen LHC, Smits LJT, Shen B, Hoentjen F. Risk of neoplasia after colectomy in patients with inflammatory bowel disease: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2016;14(6):798–806.e720.
75. Kock NG, Darle N, Hultén L, Kewenter J, Myrvold H, Philipson B. Ileostomy. Curr Probl Surg. 1977;14(8):1–52.
76. Litle VR, Barbour S, Schrock TR, Welton ML. The continent ileostomy: long-term durability and patient satisfaction. J Gastrointest Surg. 1999;3(6):625–32.
77. Lepistö AH, Järvinen HJ. Durability of Kock continent ileostomy. Dis Colon Rectum. 2003;46(7):925–8.
78. Fazio VW, Church JM. Complications and function of the continent ileostomy at the Cleveland Clinic. World J Surg. 1988;12(2):148–54.
79. Beck DE. Clinical aspects of continent ileostomies. Clin Colon Rectal Surg. 2004;17:57–63.
80. Nessar G, Fazio VW, Tekkis P, et al. Long-term outcome and quality of life after continent ileostomy. Dis Colon Rectum. 2006;49(3):336–44.
81. Mullen P, Behrens D, Chalmers T, et al. Barnett continent intestinal reservoir. Multicenter experience with an alternative to the Brooke ileostomy. Dis Colon Rectum. 1995;38(6):573–82.

Complications of the Pelvic Pouch

50

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Key Concepts

- Pelvic sepsis is the most common cause of pouch loss.
- Patients with IPAA dysfunction should undergo a structured assessment.
- Pouch dysfunction is often inappropriately ascribed to a diagnosis of Crohn's disease.
- Fecal diversion may palliate disabling symptoms from pouch dysfunction.
- Pouchitis is the most common complication of IPAA.

Introduction

The ileoanal pouch reservoir (IPAA) made stoma-free living a reality in patients, who desire to maintain bowel continuity, requiring the removal of the colorectum [1, 2]. This operation was specifically created with a vision to achieve a higher quality of life after proctocolectomy, providing the patient with an alternative to a permanent lifelong stoma and restoring the natural route of defecation. Contemporary improvements have enhanced the operation since its popularization in the 1980s, but the goals of surgery remain the same: to cure disease while providing the highest possible quality of life (QOL) for the patient.

Failure of the IPAA is an uncommon but devastating situation for patients undergoing restorative proctocolectomy [3]. Patients with IPAA dysfunction, in whom local corrective measures fail, have traditionally been managed with permanent fecal diversion, with or without excision of the failed pelvic pouch [4]. However, advancements in the understanding of pouch failure have opened the door for surgical revision; selected patients who are decidedly motivated to avoid permanent conventional ileostomy may be considered for surgical pouch salvage with a reasonable expectation of good results [5–8]. Critical to the success of pouch revision is the understanding of why pouches fail, which is an evolving topic, as the treatment of pouch complications varies greatly depending on etiology. The management of pouch-related complications, including pouch salvage surgery, is challenging and is best approached in a multidisciplinary, patient-centered fashion with input from both the patient and experienced IPAA clinicians for best results.

Risk Factors for Pouch Dysfunction

The success of an IPAA procedure and its long-term functional outcomes are very much dependent upon adequate healing and maintenance of integrity of the many staple or suture lines required. Anastomotic disruption, with the resultant development of peri-pouch sepsis, is a dreaded complication of staple or suture line failure and typically has marked detrimental effects on long-term functional outcomes [9, 10]. Pelvic sepsis is reported to occur in up to 25% of IPAA patients and is due primarily to the disruption of the pouch-anal anastomosis or, less frequently, the staple line at the tip of the J-pouch [11]. Thirty percent of these patients will experience pouch failure, making it the most common cause of pouch loss [1, 12].

Much emphasis has been placed on avoidance of anastomotic complications by identification of adverse risk factors. Strategies of avoiding or delaying pouch creation in patients taking higher doses of corticosteroid and/or biologic therapy and performing this restorative procedure using a staged approach have been recommended for this reason [13]. Despite patient optimization and technical perfection, anastomotic leak is a known consequence of IPAA surgery, and strategies for management are necessary. The ramifications

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of a leak are great in terms of long-term function; equally concerning and burdensome are the associated financial strains on the patient and healthcare system as these complications often lead to a delay in ileostomy closure and a need for additional radiographic intervention, pouch revision or excision, and prolonged hospital convalescence [14, 15].

Pouch failure due to structural non-septic complications or functional issues is a less studied cause of IPAA dysfunction. One source of these complications may be due to technical missteps performed at the index pouch surgery. Examples include inappropriate rotation or twisting of the small bowel mesentery as it runs into the pelvis (180° or 360° rotation) that causes obstruction or ischemia or an elongated rectal cuff (or S-pouch outlet) causing outlet obstruction and pouch emptying issues. An emphasis on proper technique of IPAA surgery and a vigilance during these challenging cases can prevent these complications from occurring or identify them early so they may be corrected.

Finally, patient selection is crucial to achieving success after pouch surgery. Those patients who have pelvic floor or anal sphincter compromise may not fare well in terms of pouch function and quality of life, and one should be realistic when discussing outcomes when these issues are present. Additionally, a diagnosis of Crohn's disease should generate a thoughtful, individualized assessment of the risk prior to pouch surgery.

Approach to the Patient with a Dysfunctional Pouch

Initial Evaluation

First and foremost, patients referred with a diagnosis of IPAA dysfunction should undergo a comprehensive and standardized evaluation, understanding that the previous diagnosis may be incorrect. Commonly, a patient with non-specific pouch issues is labelled as having chronic pouchitis or Crohn's disease and undergoes a long-term treatment on this basis, without significant improvement in symptoms. Other causes of pouch dysfunction such as chronic pelvic sepsis may be easily missed.

A complete history should be obtained including a full review of the patient's symptoms, treatments that have been attempted prior to the present evaluation, and response to each treatment. Operative reports should be obtained and reviewed, with specifics of surgery and convalescence noted. Any indication of technical difficulty must be thoroughly explored, as a technical complication of the initial pouch surgery may be mistaken for pouchitis. One should pay particular attention to the condition of the patient at the time of pouch creation and the use of covering ileostomy, as large doses of immunosuppression negatively affect pouch healing; anastomotic complications may result in occult sinus tracts or chronic anastomotic leaks with symptoms mimicking pouchitis.

It is not unusual for an empiric diagnosis of "Crohn's disease" or "chronic pouchitis" to be given to patients with symptoms of pouch dysfunction, with limited or no support from endoscopy or other imaging studies. One drawback of this approach is that patients may be given a presumptive diagnosis of Crohn's disease that is never confirmed and medical therapy considered unsuccessful. Therefore, it is important to establish the etiology of compromised pouch function when it begins, even if the symptoms have been longstanding. The correct diagnosis accounting for pouch dysfunction is crucial as treatment options are at times vastly different for each complication [16].

Endoscopic evaluation is performed to look for key identifiers of pouch dysfunction. One must approach pouchoscopy in a standardized fashion, so as to carefully examine the rectal cuff, pouch body, and afferent limb to identify both mucosal changes as well as clues to structural abnormalities such as an elongated rectal cuff, a strictured or twisted afferent limb, or a prolapsing anterior body wall. Pouch endoscopy is very helpful when done in conjunction with an anoperineal exam under anesthesia to identify fistulae, abscesses, or other anal pathology not as easily seen in the endoscopy suite. Contrast enemas and pelvic MRI may reveal or rule out anastomotic complications, fistulae, sinuses, or chronic leaks that may be the source of symptoms.

Next, the surgeon must assess the patient's health status and quality of life during the initial patient encounter, even if the etiology of pouch dysfunction is still unclear. Patients are often referred to the surgeon after years of medical treatments that have left the patient malnourished, decompensated, and mentally exhausted. These individuals may benefit from surgical intervention such as fecal diversion sooner rather than later.

Finally, it is important to have an honest and straightforward discussion with the patient regarding expectations. It must be emphasized that surgical outcomes depend on many factors, especially the etiology of pouch failure. Expectations must be discussed and agreed upon prior to embarking on surgical correction.

Multidisciplinary Approach to Diagnosis

When a patient presents with IPAA dysfunction and the etiology of failure is in question, a multidisciplinary approach is in order. After preoperative evaluation with history, physical, and radiographic testing as outlined above, an evaluation with an anoperineal exam under anesthesia and pouchoscopy

is performed as a team including a colorectal surgeon and gastroenterologist. The anoperineum, pouch-anal anastomosis, pouch body, and afferent limb (complete to the ileostomy closure site) may be examined with members of both specialties in the operating room, enabling both perspectives and respective expertise to be utilized. Any clinical signs of pouchitis or any other IPAA complications are noted (anastomotic sinus or fistula, stricture, pouch prolapse, Crohn's disease, etc.), many of which may cause similar symptoms. Biopsies are obtained for pathologic review. At the completion of the exam, the findings are discussed with the patient and family member, and a patient-centered treatment strategy begins to develop. This multidisciplinary team approach is ideal for the patient as he/she is often presented an immediate plan for treatment, with opportunity for discussion with members of both specialties. The strategy can always be tailored at a later time as pathology results and/or recommendations from a multidisciplinary case conference are made.

The Case for the "Thoughtful" Ileostomy

Fecal diversion is an effective way of alleviating symptoms in patients suffering from a failing IPAA and buying time while investigation continues and decisions are made regarding pouch salvage. Any patient suffering significant health consequences or with poor quality of life is a candidate for ileostomy during any part of the pouch dysfunction evaluation. This approach may provide symptomatic relief as mucosal inflammation is lessened by diversion of the fecal stream and anoperineal excoriation as a result of frequency of bowel motions that may be controlled. The pouch is left in place, allowing for relief of symptoms without committing to a major pelvic operation. This approach can also be useful in patients with little chance of pouch salvage who are not initially accepting of a permanent stoma. A loop ileostomy without "burning the bridge" may convince the patient that fecal diversion will dramatically improve their life as compared to a dysfunctional IPAA and ease the psychological transition to ultimate pouch excision [17].

Loop ileostomy provides many benefits. First, it allows for relief of symptoms related to a dysfunctional pouch in a manner that can be temporary and somewhat easily reversed if the patient is not pleased. In many cases, it may be completed with a laparoscopic approach, even if open IPAA had previously been performed; this will usually shorten convalescence and minimize adhesion formation in case repeat laparotomy for pouch revision or excision is desired. Second, patients are able to experience or have a reminder of what life is like with an ileostomy and may choose to keep the ileostomy on a more permanent basis.

Exploration at the time of ileostomy allows for a thorough exam of the abdomen and small bowel to identify any pathology missed on prior imaging that may be the source of the patient's symptoms. Possible sources are mesenteric twists, afferent limb adhesions, abdominal wall or pelvic mesh adherent to the ileal pouch, or large ovarian cysts thought to be part of the ileal pouch on preoperative imaging. In each of these situations, the pathology can be operatively addressed.

When creating an ileostomy in this setting, it is important to consider the next potential surgical steps in the patient's future. The site of the ileostomy should be made with the most dependent portion of the small bowel and at least 15 cm proximal to the pouch, such that this enterotomy could be used for a new pouch-anal anastomosis in those who may be candidates for pouch revision or recreation in the future.

Etiology and Management of Pouch Complications

Structural Complications of the Pouch

Afferent Limb (AF) Complications

Complications involving the pre-pouch ileum, or the afferent limb (AL) of the pouch, have historically been termed afferent limb syndrome (ALS). ALS is becoming a more recognized and diverse group of findings after pouch surgery in which patients present with symptoms of bowel obstruction, abdominal pain and cramping, and dyschezia but have an otherwise normal pouch body and outlet on endoscopy or distal contrast study. The causes of ALS were initially thought to include only a displacement of the pre-pouch ileum posterior to the pouch causing obstructive symptoms; but a more contemporary understanding of ALS has shown a growing number of potential abnormalities of this portion of the bowel, many of which can be difficult to identify on initial evaluation. For example, a fibrotic stricture causing ALS may be easily seen during pouchoscopy, but angulation of the afferent limb due to adhesions or an inappropriate rotation of the small bowel mesentery is sometimes only identified at laparotomy with findings of partial or complete obstruction [18].

There are several important discussion points regarding ALS that should be highlighted. First, although CD occurring in the pre-pouch ileum can cause fibrostenotic or inflammatory changes of the AL, many of these changes may NOT be due to CD. Chronic nonsteroidal anti-inflammatory medications and Crohn's disease-like conditions (CDLC) can cause similar radiographic and endoscopic findings; clinicians should be careful not to label a patient as having CD of the pouch unless there is reasonable certainty in the diagnosis (Fig. 50.1). Many patients given a label of "CD of the pouch" are branded with this negative stigma and are only offered pouch excision, when in actuality, they may be candidates for salvage procedures.

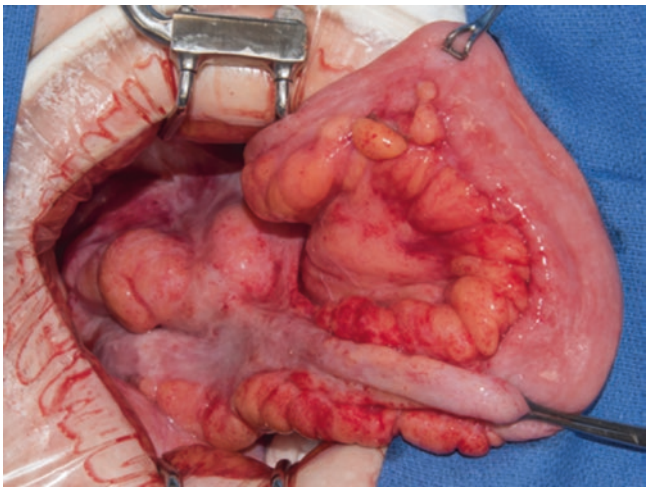

Fig. 50.1 Chronic inflammation of the afferent limb of the ileal pouch forming a strictured segment and causing obstructive symptoms

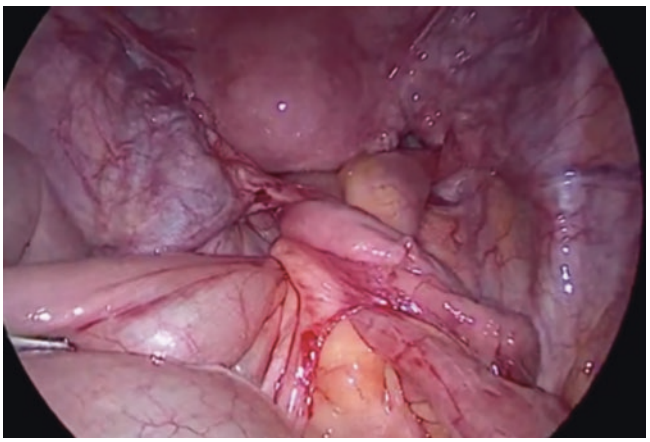

Fig. 50.2 Adhesive bands causing volvulus of the afferent limb of the J-pouch. Note the dilated upstream small bowel (left) due to obstruction of the distal small bowel. A laparoscopic lysis of adhesions with reduction of volvulus was successfully performed

Dysfunction of the AL may also be caused by factors external to the bowel wall (Fig. 50.2). Volvulus or trapping of a redundant AL underneath the small bowel mesentery may result in acute ischemia of the limb or a more chronic intermittent obstructive pattern; patients may be intolerant of large meals, but the pouch is typically normal on radiographic imaging and/or pouchoscopy [19].

Another variant of this is a 180° or 360° rotation of the small bowel mesentery at the time of pouch creation. This incorrect rotation can cause external compression of the mesenteric edge of the AL, often in an intermittent fashion, which makes diagnosis difficult unless the patient is having overt obstructive symptoms. At endoscopy, insufflation of the AL may overcome the external compression and a patent; otherwise normal appearance is suggested. Acute angulation of the AL without mesenteric rotation, "accordioning" of a floppy or redundant pouch, or a rotation of the anterior wall of the pouch can cause obstructive symptoms. Pouch-pexy with creation of a temporary diverting ileostomy to pull the pouch upright "on stretch" helps to secure the pouch in a proper orientation [20–22].

Many patients who suffer from ALS are candidates for endoscopic and/or surgical correction and will not require pouch excision. AL strictures may be assessed for endoscopic balloon dilation, although many strictures persist and require surgical correction. Such strictures are amenable to either surgical resection with primary anastomosis of the pre-pouch ileum, stricture plasty, or a bypass to the pouch inlet. Those with a diagnosis of CD may benefit from ongoing, postoperative medical therapy to prevent inflammatory recurrence. In this way, pre-pouch strictures are dealt with similarly to fibrostenotic CD in other locations [23, 24].

Issues of the Pouch Body

Pouch-Anal Anastomotic (PAA) Defect

One of the most common and devastating complications of IPAA surgery is a leak of the pouch-anal anastomosis. When this occurs in the acute setting (immediate postoperative period), patients may present with fever, leukocytosis, pelvic pain, or other signs/symptoms of sepsis (chills/night sweats), often prompting CT imaging which reveals a pelvic abscess and/or staple line leak. Soluble contrast enema of the pouch, pelvic magnetic resonance imaging (MRI), or examination under anesthesia (EUA) are also helpful to better characterize an anastomotic leak if one is suspected in the early postoperative period [25]. The presentation may be more indolent in some cases, with patients exhibiting indirect symptoms of pelvic sepsis, such as prolonged ileus or urinary retention. Upper pelvic or abdominal abscesses may be percutaneously drained with a CT or ultrasound-guided percutaneous technique; surgical drainage may be required for those not amenable to image-guided measures.

For lower pelvic abscesses or collections obviously associated with an anastomotic disruption, EUA with gentle anoscopy and placement of a flexible mushroom drain through the anastomotic defect is strongly recommended. Care must be taken to avoid drainage approaches that would lead to complex fistula formation; the transanal approach is preferred over percutaneous measures for lower pelvic abscesses for this reason. In patients exhibiting peritonitis or hemodynamic instability, exploration in the operating room with pelvic washout and wide drainage is indicated. This approach, when necessary, is associated with poor pouch outcomes; the rate of pouch excision exceeds 40% with an associated low likelihood of ileostomy reversal [26].

Swift recognition and treatment of anastomotic disruption are paramount to preserve optimal IPAA function and avoid the known long-term sequelae of pelvic sepsis. In cases

where local sepsis is quickly controlled, pouch function is typically preserved, whereas a delay in management risks chronic inflammation with peri-pouch fibrosis and poor compliance of the pouch [11].

When an anastomotic disruption does not heal with the conservative measures described above, patients may develop pouch sinuses, fistulae, strictures, or a number of other pouch-related complications that require further management. Anoperineal fistulae may present as chronic pelvic or anoperineal sepsis which usually require source control with mushroom or draining setons. This presentation is often very similar to CD, but there are subtle and critically important differences. In a patient with AL, sepsis originates from the pouch-anal anastomosis, with the majority of the fibrosis or chronic inflammation at the anastomosis itself; the distal pouch and anal canal are otherwise soft and supple. The anoperineum may be excoriated similar to CD, but without a bluish hue, and there is lack of other CD findings such as waxy skin tags. There is typically (but not always) more fixed fibrosis of the distal pelvis in patients with complications truly attributable to CD.

These subtle clues may help distinguish between CD and sepsis due to AL; but in many cases, these two conditions are indistinguishable, leading to management conundrums. Patients are best evaluated and managed using a multidisciplinary approach involving experienced pouch surgeons and gastroenterologists. Studies have shown that up the three quarters of IPAA patients diagnosed as CD of the pouch were reclassified as having AL after secondary evaluation at a specialty IPAA center and underwent pouch salvage with good results.

Less commonly described, but equally challenging to manage, is the anastomotic sinus-a blind-ending track resulting from an anastomotic dehiscence (Fig. 50.3). It typically presents months to years after IPAA surgery that was complicated by an anastomotic leak, even if the initial leak was not appreciated or documented. It is reported to occur in 2.8–8% of patients undergoing a pelvic pouch procedure, may threaten the integrity of the pouch-anal anastomosis, and is an important predictor of pouch failure [14, 27]. The most common location of a pouch sinus is the posterior portion of the pouch-anal anastomosis and is often associated with presacral inflammation or fibrosis. Pouch sinuses may present as asymptomatic findings on imaging obtained for other indications (e.g., routine evaluation prior to stoma closure) or may exhibit a wide range of symptoms including pelvic or tailbone pain, fecal urgency, night fevers, and other symptoms of pouch dysfunction or failure.

Asymptomatic sinuses require differing management strategies depending on the circumstances of the patient. Sinuses detected in patients without symptoms may be left alone without any intervention, assuming they are not diverted. Those discovered during preoperative evaluation prior to closure of a covering ileostomy will likely heal with a conservative approach; a delay in ileostomy closure of 3–6 months and a repeat pouchogram prior to closure are advised [14, 27, 28].

Sinuses that persist despite these measures can be very difficult to manage for the surgeon and both morbid and frustrating for the patient. Contrast studies of the pouch, pelvic MRI, and EUA are helpful for further delineation of the tract [29]. Treatment begins with periodic incision and drainage of the sinus with healing by secondary intention over a course of usually 6–9 months. Some sinuses may be amenable to endoscopic debridement with sinusotomy (needle-knife therapy) with or without fecal diversion [27, 30]. Revisional or redo pouch surgery via a transabdominal/transanal approach may be considered for refractory cases.

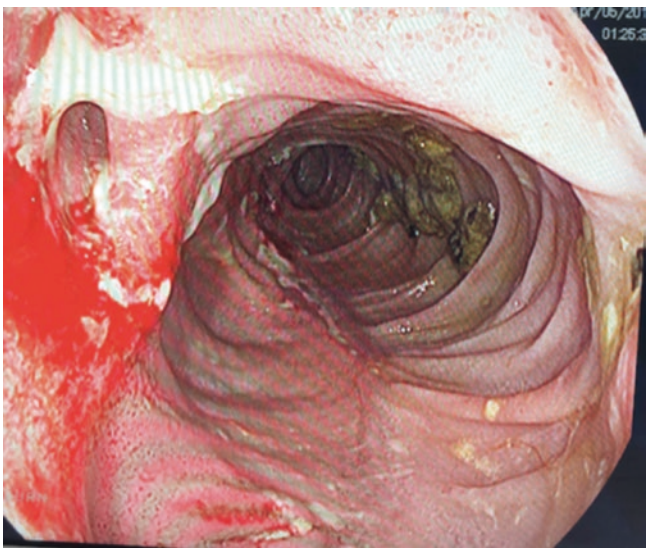

Fig. 50.3 A sinus tract of the pouch-anal anastomosis

"Tip of J" Pouch Leak

The tip of the J-pouch is the anatomic end of the small bowel and may be at risk for ischemic injury or staple line dehiscence, which can lead to sinus formation or persistent staple link leak. If these occur, patients often present with an abscess in the upper pelvis adjacent to the tip of J or with a persistently draining lower midline abdominal wound associated with a low-volume enterocutaneous fistula. These leaks typically do not heal without intervention; although there are reports of endoscopic repair, most will require surgical revision and (much less commonly) full recreation of the pelvic pouch [31, 32].

Incomplete healing of the anterior (or common channel) suture or staple line is a less commonly noted complication of the pelvic pouch. These present as a pelvic abscess, often in the mid-pelvis, that persists despite drainage and without an obvious defect at the pouch-anal anastomosis. Imaging studies may show a connection to the midportion of the

pouch body or even, more rarely, a fistulous connection to other staple lines of the pouch including the tip of J. A full surgical repair of the pouch is usually required, as these also typically do not resolve without intervention. One must be prepared to fully revise or redo the pouch body when embarking on corrective surgery for this complication.

Failure of Pouch "Scaffolding"

The anterior portion of the pouch will usually have more redundancy than the posterior portion, as the shorter, "limiting" axis is typically the posterior aspect of the pouch/small bowel mesentery. Because of this, the anterior portion of the pouch is "floppier" and may become tethered to the presacral fascia, which can limit capacity, or produce internal anterior wall prolapse and cause outlet obstruction. The pouch may also exhibit full thickness external prolapse and protrude from the anus similar to that observed in rectal prolapse [33, 34].

Patients may present with a wide range of symptoms including inability to fill or empty the pouch, pelvic pain, and obstructive symptoms. These patients are often diagnosed with chronic pouchitis. A comprehensive evaluation as described above may identify the abnormal configuration, but sometimes the clues are limited, and this is found only on abdominal exploration. Pouch-pexy techniques (sometimes with an "ileostomy on tension" as described above) is helpful to maintain the appropriate pouch "scaffold." Reports describing mesh or other matrix fixation of the pouch have been published; larger studies with longer follow-up are needed to assess the success and safety of this corrective approach [33, 35].

180°/360° Mesenteric Rotation

Incorrect orientation of the pouch and small bowel mesentery as it descends into the pelvis may cause external compression of the AL or compression/limitation of the volume of the pouch body, resulting in either frequent pouch emptying and/or obstructive symptoms with difficult filling of the pouch. This complication is thought to occur at the time of pouch-anal anastomotic creation, if the pouch inadvertently is allowed to rotate posteriorly (180° defect) or with complete revolution (360°). Patients may be at increased risk for pouch ischemia if the mesenteric blood flow is compromised and may have undue tension on the posterior portion of the anastomosis, a location already prone to anastomotic dehiscence [36, 37].

This complication, as is the case with most others, is better prevented than remediated; appropriate orientation of the mesentery should be assured at the time of anastomotic creation, especially during a laparoscopic or robotic approach, since the abdominal portion of the mesentery is often out of view. To correct this complication, a complete detachment and recreation of the pouch-anal anastomosis is required.

Efferent Limb (EL) Problems

Complications involving the pouch outlet, or efferent limb complications (EL), are likely to present as inability or difficulty emptying the pelvic pouch, with obstructive symptoms, straining with bowel motions, and feelings of incomplete emptying.

Efferent Stricture

Pouch-anal anastomotic strictures usually develop within the first 9 months after surgery. They are more commonly noted after mucosectomy with creation of hand-sewn pouch-anal anastomosis but can be seen in up to 17% of all pouch patients [38, 39]. Development of stricture after IPAA is similar among the commonly used stapler sizes (28/29 mm vs 31/33 mm) used to create the pouch-anal anastomosis [40]. Soft, weblike strictures are often seen after a diverted stapled anastomosis and are amenable to gentle digital dilation. They generally do not recur after restoration of intestinal continuity or are responsive to daily self-dilation [41]. Long, fibrotic strictures commonly result from perioperative pelvic sepsis or pouch ischemia. These generally do not respond to repetitive dilation in the long term, and surgical options are often considered and include (transanal or transabdominal) pouch advancement or pouch revision. Pouch excision with permanent ileostomy may be considered if patient factors are not favorable or if the patient desires this option [42].

Elongated S-Pouch Outlet/Elongated Rectal Cuff (Pouch-Rectal Anastomosis)

At times, efferent limb issues may be caused by technical errors made at the time of pouch creation. These are most commonly in the form of an S-pouch outlet that is made too long or a rectal cuff that is left too long (pouch-rectal anastomosis; Fig. 50.4). Again, meticulous surgical technique dur-

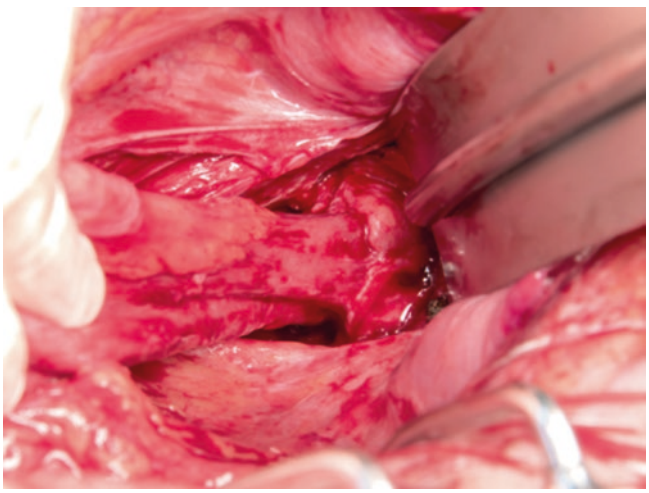

Fig. 50.4 Efferent limb syndrome caused by an elongated rectal cuff (pouch-rectal anastomosis)

ing the de novo pouch operation is critical and can help to avoid these difficult to manage complications. When they do occur, nonoperative maneuvers such as transanal intubation to evacuate the pouch may be offered for amelioration of symptoms but are not likely acceptable as a long-term option to patients and can cause tissue trauma with repetitive use over the years.

Transabdominal/transanal pouch revision is typically employed to shorten the elongated segment. In the setting of an elongated rectal cuff, the surgeon may have the option to restaple a very long cuff with a 30 mm linear stapler and maintain the anal transition zone. If so, a redo double-stapled pouch-anal anastomosis is achievable, and a transanal approach (and mucosectomy) avoided [43].

A situation becoming more commonly seen (and debated) is creation of a pelvic pouch after a proctectomy that preserves the mesorectum and leaves it in place. Although some surgeons argue that this serve as a space filler so that the pouch does not rotate and is "protective" of the retroperitoneal or presacral structures, in actual practice, the residual mesorectum may act as a "collar" around the distal pouch and can contribute to evacuation issues. The correction of this requires transabdominal completion mesorectal excision with a recreation of a new pouch-anal anastomosis.

Inflammatory Complications of the Pouch

Pouchitis

Pouchitis is the most common long-term complication of IPAA surgery. Despite the absence of a surgical "cure" for refractory or chronic pouchitis, the surgeon's role in the multidisciplinary management of pouchitis is crucial to aid with diagnosis and offer options for symptom management.

Although the etiology and pathogenesis of pouchitis are not entirely clear, pouch creation may provide an "inflammation-prone" environment as the distal ileum is converted to storage reservoir. About half of patients who undergo IPAA surgery for UC will develop at least one episode of pouchitis in their lifetime. Approximately 40% of patients experience a single episode (increased frequency of loose bowel movements, tenesmus, rectal bleeding, lower abdominal cramping, and malaise) and respond to a 2–4-week course of oral antibiotics. The remaining 60% will follow a relapsing course; half of these patients will suffer from refractory pouchitis and require treatment with second-line therapies such as chronic antibiotics, steroids, or biologic agents.

A small minority of patients with treatment-resistant pouchitis does not find relief with medical therapy and may desire surgical options for treatment and alleviation of symptoms. These patients should undergo a comprehensive pouch failure evaluation to rule out diseases with similar presentations as outlines earlier in the chapter and be offered the appropriate treatment options depending on the most likely etiology of failure. If refractory pouchitis is suspected, patients may be considered for fecal diversion as a means of alleviating symptoms from mucosal inflammation and perianal excoriation from frequent bowel motions. These patients may also be considered for pouch excision or a loop ileostomy with the pouch left in situ, depending on individualized risk factors for either pouch neoplasia (pouch in situ) and wound healing (pouch excision) [44]. One should be hesitant to offer a redo pouch surgery in this setting without a clear reason to hope for a different outcome with a second pouch.

Pouchitis may be divided into three categories that consider the presumed etiological and pathogenic factors of the condition. Classic pouchitis occurs from dysbiosis of commensal bacteria or infection from bacterial, viral, or fungal pathogens. Patients in this category present with homogeneous, diffuse inflammation of the pouch with or without ulcers. Immune-mediated pouchitis is typically found in the setting of primary sclerosing cholangitis or concomitantly with other autoimmune conditions. Inflammation in this category is found both within the pouch body and afferent limb, with some cases exhibiting concurrent cuffitis [45, 46]. Ischemia-associated pouchitis is thought to occur when undue mesenteric tension on the pouch causes a chronically ischemic environment in the pouch and is characterized by inflammatory changes of only one limb of the pouch in a vascular distribution. Alternatively, one may note ulcerations along the common channel staple line. The typical patient in this category is an obese male with excessive visceral adiposity [47].

A helpful algorithm to treat patients suffering from pouchitis is to initiate a 2-week course of oral ciprofloxacin and Flagyl. Those who are antibiotic-responsive and have resolution of symptoms may undergo additional antibiotic treatment as symptoms recur. Those who respond but are dependent on medications for remission should continue a monitored maintenance antibiotic/probiotic regimen. Patients who continue to have symptoms despite antibiotic therapy should be evaluated for pathogen-induced pouchitis (CMV/C difficile infection) or immune-mediated pouchitis and undergo the appropriate treatment depending on presumed etiology [45]. When ischemic pouchitis is suspected, the patient should be encouraged to pursue loss of visceral adiposity [48].

Cuffitis

Cuffitis is the symptomatic inflammation of the remnant rectal cuff that remains in UC patients after they undergo stapled IPAA. Symptoms can occur in up to 6% of patients with a double-stapled anastomosis and are at times confused with those caused by pouchitis. In these cases, patients may be inappropriately diagnosed and treated for refractory pou-

chitis, when better medical and surgical treatments are available for cuffitis. Medical options of topical steroid enemas, suppositories, or aminosalicylate (5-ASA) drugs are effective. In rare cases when symptoms are not responsive, surgical intervention is warranted. The residual rectal mucosa can be removed with a transanal mucosectomy, followed by ileal pouch advancement with pouch-anal handsewn anastomosis or by transabdominal/transanal pouch redo with anal canal mucosectomy. The success of surgery is increased if the initial stapled anastomosis is no more than 3–4 cm above the dentate line [27] and a tension free anastomosis is fashioned [49].

Crohn's Disease of the Pouch

A diagnosis of CD of the pouch does not necessarily require one to pursue pouch removal with permanent conventional ileostomy as a first step. Disease phenotype heavily influences degree of pouch retention. A study of 65 patients with de novo CD of the pouch reported that 57% were able to maintain their pouch with acceptable function despite this diagnosis. However, the presence of fistulae at the time of diagnosis of CD of the pouch and early diagnosis of Crohn's disease after initial pouch surgery were independent risk factors for pouch failure [50].

Surgical therapies for CD of the pouch may be employed independently or in combination with medical and endoscopic treatments. Regardless of approach, it is most important to consider the desires of the patient and his or her individualized definition of quality of life, as this should be the ultimate measure of treatment success. Many patients diagnosed with CD of the pouch desire pouch preservation and should be offered an evaluation in an IBD center with surgeons experienced in treating this challenging scenario. Those who are not interested in pouch preservation and choose to pursue a permanent conventional ileostomy should be equally supported in this endeavor as well. In either case, the majority of patients with CD of the pouch benefit from both medical and surgical therapy in parallel.

Diagnosis with Exam Under Anesthesia

Making an accurate diagnosis of CD of the pelvic pouch is the cornerstone of success in these challenging patients. An examination under anesthesia (EUA) is often the best first operative option in these patients, allowing the surgeon to establish the correct diagnosis, control sepsis control, and obtain biopsies. Fistulae from a CD pouch are easily confused with pelvic sepsis from a chronic pouch-anal anastomotic leak, and distinguishing between these is critical as the treatment and prognosis are vastly different. It is generally accepted that pelvic sepsis within 3–6 months following ileostomy closure after IPAA is likely a postoperative complication rather than a sequela of CD of the pouch, which is more likely to manifest more than 12 months after IPAA [16, 51].

Control of Sepsis

An initial EUA allows the surgeon to carry out the next critical step of managing CD-related pouch fistulae, which is the control of sepsis. This can be performed using carefully placed mushroom drains in abscess cavities and non-cutting silastic setons to manage fistula tracts (Fig. 50.5). Indiscriminate injury or division of the anal sphincter complex should be avoided, as the risk for fecal incontinence is high. Cautious and gentle completion of these local procedures may control symptoms, improve quality of life, and help to maintain the best chance for pouch preservation for the future [51].

Fecal Diversion

As mentioned previously, a diverting loop ileostomy with pouch in situ is an effective method of controlling symptoms

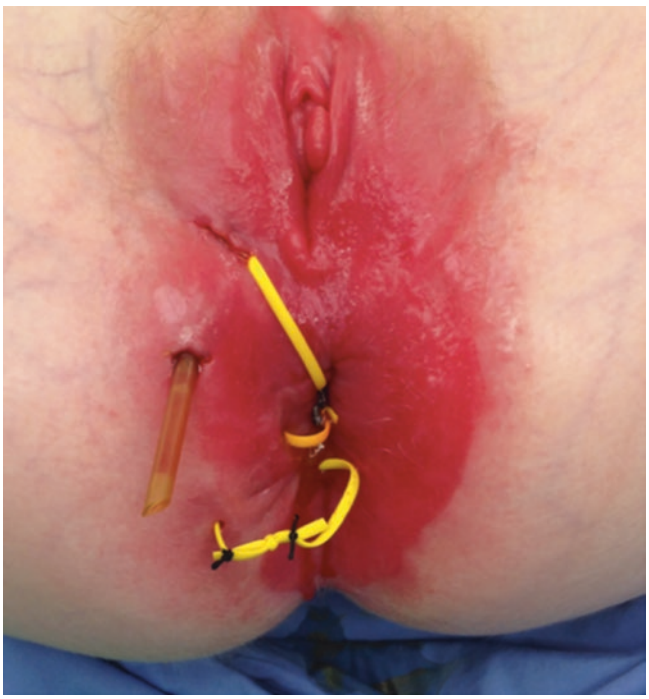

Fig. 50.5 Anoperineal sepsis in a patient with Crohn's disease of the pouch. Control of sepsis is achieved with thoughtfully placed drains and setons

from fistulizing CD of the pouch when the patient has failed medical/endoscopic therapy and/or is not ready to commit to pouch excision or pouch revision (if an option). It is important to emphasize that fecal diversion *improves* but does not necessarily *resolves* anorectal symptoms, as patients may experience ongoing mucous drainage and untoward symptoms from diversion pouchitis [52].

Pouch Excision

Pouch excision is, at times, a necessary surgical option when medical, endoscopic, and local surgical therapies fail but comes with a high morbidity rate. Pathologic confirmation of CD of the pouch is not always confirmed after pouch excision, as shown in a series of 35 such patients, with only 7 cases achieving pathologic diagnosis of CD [53]. A morbid complication of pouch excision is the nonhealing perineal wound and subsequent development of perineal sinus, which can be more difficult to manage than a pouch left in situ. This occurs in up to 40% of patients, and the risk for this troublesome complication should be considered when developing a surgical strategy (Fig. 50.6) [54]. Fecal diversion with staged pouch excision may help reduce the risk for nonhealing.

Pouch Revision in the Setting of CD

Carefully selected patients suffering from fistulizing CD of the pouch may be candidates for pouch revision, either with perineal/perianal repair of the existing pouch or major corrective surgery with recreation of a new pouch-anal anastomosis and/or new pouch.

Any surgical repair of a pouch fistula first requires control of sepsis to normalize tissue quality, followed by medical therapy to reduce inflammation and promote healing. During this time, response to therapy is monitored and assessed, and discussions regarding the next steps must establish reasonable patient expectations and the goals of surgery in these very challenging cases.

Local procedures such as seton placement, mucosal advancement, and fistulotomy have been studied as a means to mitigate symptoms of CD-related pouch fistulas. Although there is evidence to support the use of local procedures for CD-related complications of the pouch, the presence of a fistula at the time of CD diagnosis was an independent risk factor associated with pouch failure [50].

Data regarding pouch revision for CD pathology of the pouch are very limited. Unpublished data regarding patients undergoing redo IPAA for CD revealed pouch retention rates were lower than index pouches (<60% vs 79% at 5 years) but perioperative complications and functional outcomes were comparable. This highlights the critical importance of proper patient selection for this process. Additionally, acceptable outcomes of revisional IPAA surgery for CD of the pouch can be achieved in very carefully selected patients who present for surgery with no active anoperineal disease, limited small bowel disease, and an uncompromised anal sphincter.

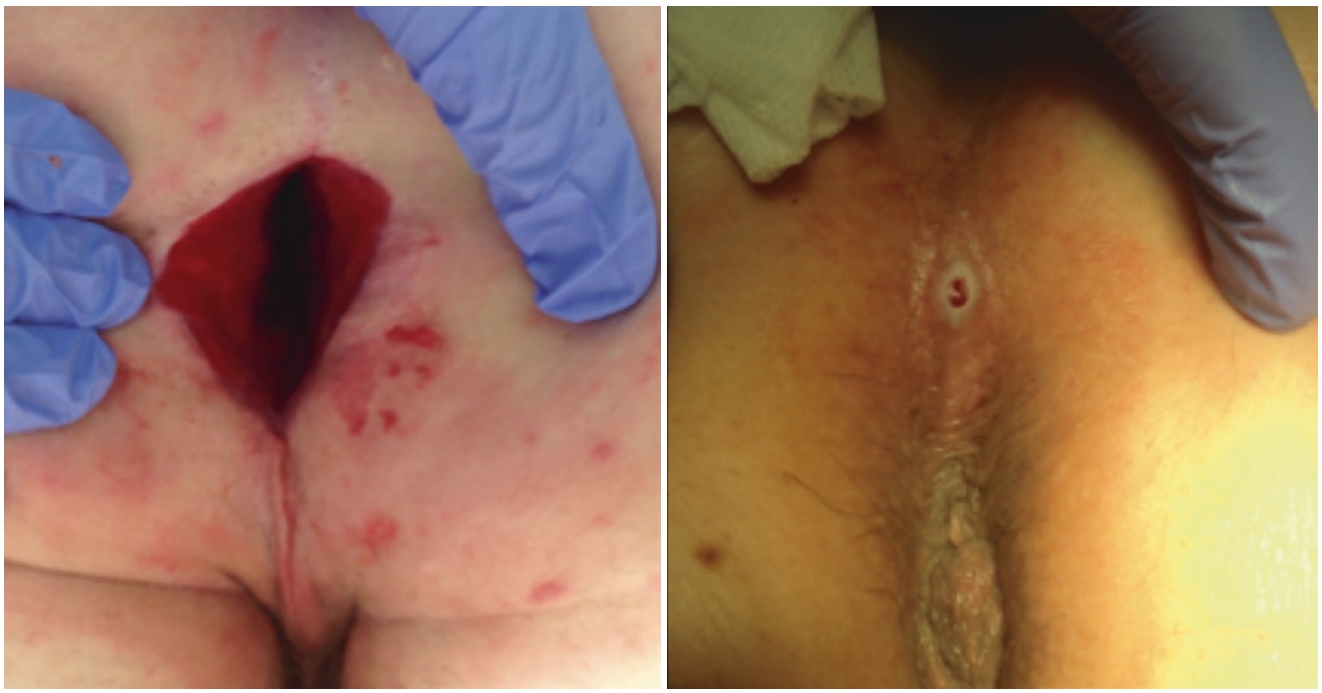

Fig. 50.6 A nonhealing perineal wound (left) and persistent sinus tract (right) after pouch excision for Crohn's disease

Above all, any patient undergoing pouch revision for fistulizing CD must have insight as to the complexity and limitations of redo surgery in this setting and accept the increased risk for postoperative complications, eventual pouch loss, or need for long-term medical therapy.

When considering surgical options for CD of the pouch, it is important to re-emphasize that many patients are misdiagnosed with CD, when failure is actually due to technical complications at the pouch-anal anastomosis. These patients are commonly good candidates for a redo pouch but were not considered owing to an incorrect diagnosis of CD.

Functional Complications of the Pouch

Irritable pouch syndrome is a clinical scenario in which a pouch patient suffers from symptoms of diarrhea, urgency, pelvic pain, and cramping in the absence of endoscopic or histologic findings of mucosal inflammation. It is thought to be related to visceral hypersensitivity and hypermotility of the pouch, but the true etiology is poorly understood. In one study of 61 patients after RP IPAA, 43% exhibited the clinical symptoms described above, with postoperative complications, pouchitis, and CD ruled out. Although an effective treatment strategy is still being elucidated, patients often benefit from a combination of systemic and topical antidiarrheal, antispasmodic, and anticholinergic therapies, in addition to cognitive behavioral therapy [55, 56].

Dyssynergic defecation (DD) or nonrelaxing pelvic floor dysfunction, in which the puborectalis muscle fails to relax during defecation, can cause dyschezia and straining in pouch patients. DD can occur as a primary disorder (idiopathic) or secondary disorder (associated with inflammatory pouch conditions like pouchitis or cuffitis). Anal manometry commonly shows paradoxical contractions of the muscle and failure of the balloon expulsion test. Pelvic floor physical therapy (biofeedback) is helpful in many cases of both primary and secondary DD, along with the treatment of underlying inflammatory conditions that may coexist [57–59].

Neoplasia of the Pouch

Cancers of the pelvic pouch are poorly understood, difficult to detect even with routine endoscopic surveillance, and have a poor prognosis. Studies on the topic are sparse and primarily consist of case reports and small series. One of the largest studies of over 3000 pouch patients reported a cumulative incidence for pouch dysplasia of 0.8% at 5 years and 2.2% at 20 years after pouch construction [60]. Pouch dysplasia is primarily noted at the anal transition zone or rectal cuff and is more likely to occur in IBD patients whose original indication for proctocolectomy was dysplasia or cancer.

Less than 50 cases of pouch cancer have been reported in the literature, with the majority being adenocarcinoma located in the ATZ (64%) or pouch body (19%). Cumulative incidence for pouch cancer has been reported as 0.2%, 0.4%, and 2.4% at 5, 10, and 20 years in one large study of over 3000 UC patients [60], with similar results in other studies [61].

Outcomes of Surgical Management of Pouch Complications

The decision regarding what surgical options to offer a patient with a failed IPAA is extremely complex with life-altering consequences for the patient. On the one hand, pouch excision offers the hope of a better quality of life (QOL) but requires the acceptance of a permanent conventional ileostomy and risk for wound healing issues. Conversely, pouch repair and revision maintain continuity of the intestine but sometimes require a commitment to undergo multiple major operations over an extended period of time. The literature informing the optimal approach to pouch failure with regard to pouch excision vs pouch redo is limited. There are no randomized trials available or studies that directly compare the two approaches. The large majority of available studies are retrospective and descriptive experiences of specialized, high-volume IPAA centers.

The traditional approach to pouch failure has been to offer the patient pouch excision with a permanent conventional ileostomy, often in one operative setting. However, several studies on the topic have reported significant postoperative morbidity after this operation. A retrospective review from the Mayo clinic of 147 patients undergoing pouch excision reported short- and long-term complication rates of 57% and 37%, respectively, with 11% requiring a return to the operating room due to complications within the immediate postoperative period [4]. This is consistent with a prior study from St Mark's Hospital reporting a 25% and 53.7% early and late postoperative complication rate, respectively. Over half of the patients required readmission, with greater than 50% of

these patients requiring reoperation. Persistent perineal wounds were reported in 40% and 10% at 6 and 12 months, respectively [54]. Another retrospective report highlighted the difficult challenge of postoperative perineal wound healing in their study of 47 patients undergoing pouch excision. Of these, nearly 30% suffered from perineal wound complications, including perineal wound infections (100%), perineal sinus tracts (28%), and perineal hernia (7%) [62].

The significant morbidity and need for permanent conventional ileostomy are major drawbacks of pouch excision for pouch failure [63], thus making pouch redo an attractive alternative in highly selected patients. Remzi reported the largest experience describing outcomes of redo pouch surgery performed in over 500 patients spanning three decades. The large majority suffered from sepsis-related pouch dysfunction. Postoperative complications occurred in 53%, with pelvic sepsis the most common. Ileus/bowel obstruction (16%), anastomotic leak (8%), and wound infection (8%) were the most common short-term complications (along with pelvic sepsis). A total of 20% of patients had redo IPAA failure, but 83% of patients had a functional IPAA at most recent follow-up, with 5- and 10-year pouch survival noted to be 90% and 82%, respectively. This report is one of few that examined QOL and functional outcomes and reported that more than 90% of patients recommended surgery to others and would undergo the surgery again if needed [5]. Overall, these results support the important role of pouch revision surgery in carefully selected patients. Many patients with IPAA failure may have a second chance to achieve stoma-free living with acceptable bowel function and quality of life with the redo pouch.

Other series report similar positive results, albeit with smaller number of patients and more limited follow-up. One recent study of 81 patients undergoing pouch revision reported a predicted 5- and 10-year pouch survival of 85% and 65%, respectively, and pouch loss of 23%. The overall (early and late) complication rate was 35.6%, with most the common complications being ileus/bowel obstruction and recurrent fistula [6]. Another study described the outcomes of 51 patients undergoing pouch salvage, 23 of these undergoing transabdominal redo. Of these, 69% were reported to have acceptable functional results, with septic events described as the most notable and morbid postoperative complication [8]. Others have also reported successful redo IPAA with good functional outcomes and patient satisfaction with acceptable rates of complications [64–67].

Patients with IPAA dysfunction should be offered the opportunity to undergo comprehensive evaluation in an IPAA center (experienced in revisionary pouch surgery), with discussion of multidisciplinary management options. A patient's decision to pursue an improved QOL by accepting pouch excision with a permanent lifelong ileostomy should be honored without exception and without persuasion otherwise. For appropriately selected patients desiring an attempt at pouch salvage, pouch revision and redo are good options with a high likelihood of success and require a thoughtful and honest discussion between patient and clinicians to set shared goals and expectations for care.

One additional tool in the toolbox of the reoperative pouch surgeon is the continent ileostomy (CI). CI is an intra-abdominal ileal reservoir made with a continent nipple valve that allows for patient control of stool evacuation (Fig. 50.7a–c). A catheter is inserted into the pouch several times daily by the patient to empty the pouch, at private and convenient times. In this way, patients are able to maintain continence with improved lifestyle and body image as compared to a permanent ileostomy [68–71]. Although less commonly created in contemporary times than the J-pouch, it remains a good option for selected patients desiring a control of bowel habits but who are not candidates for a pelvic pouch.

Despite its many benefits over conventional ileostomy, CI is a complex procedure that carries significant risk of postoperative complications as well as a long-term need for reoperation to repair nipple valve slippage, the commonest complication and indication for reoperation in these patients [70–72]. Patients must undergo extensive preoperative counseling to confer understanding of the associated risks and accept a realistic vision of life with CI. In carefully selected and motivated patients, CI continues to be a durable option, with long-term pouch survival rates approaching 80% [73]. CI patients enjoy greater QOL than others with a conventional ileostomy and that 95% would choose to undergo the procedure again and recommend it to others [74, 75].

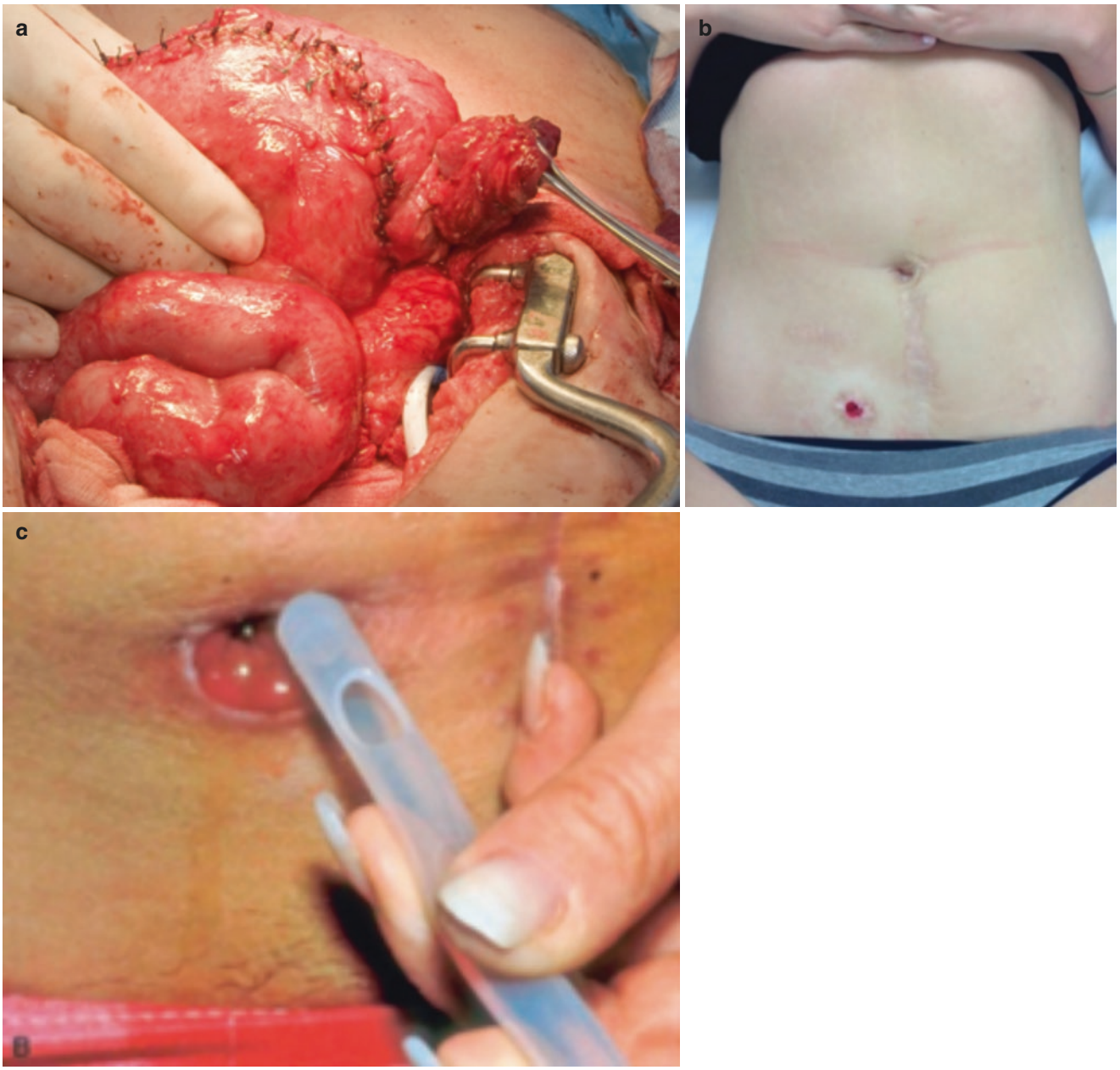

Fig. 50.7 A continent ileostomy created in a patient not suitable for a pelvic pouch (**a**). The inconspicuous stoma (**b**) gives patient control of continence with intermittent intubation and improved quality of life (**c**)

Conclusion

The debate as to how best to approach IPAA failure is multifaceted and ongoing, with limited comparative studies on which to base important decisions. One of the major barriers to mastering this topic is the remarkable uniqueness of every IPAA failure patient. Each patient is different with a distinctive etiology of pouch dysfunction coupled with personal desires and QOL aspirations. Further studies are necessary to continue to learn how to approach the patient with a failed or failing pouch; an individualized plan of care is necessary to achieve the best outcomes.

References

1. Fazio VW, Kiran RP, Remzi FH, Coffey JC, Heneghan HM, Kirat HT, Manlich E, Shen B, Martin ST. Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. Ann Surg. 2013;257:679–85.

2. Meagher AP, Farouk R, Dozois RR, Kelly KA, Pemberton JH. J ileal pouch-anal anastomosis for chronic ulcerative colitis: complications and long-term outcome in 1310 patients. Br J Surg. 1998;85(6):800–3.
3. Remzi FH, Lavryk OA, Ashburn JH, Hull TL, Lavery IC, Dietz DW, Kessler H, Church JM. Restorative proctocolectomy: an example of how surgery evolves in response to paradigm shifts in care. Color Dis. 2017;19(11):1003–12.
4. Lightner AL, Dattani S, Dozois EJ, Moncrief SB, Pemberton JH, Mathis KL. Pouch excision: indications and outcomes. Color Dis. 2017;19(10):912–6.
5. Remzi FH, Aytac E, Ashburn J, Gu J, Hull TL, Dietz DW, Stocchi L, Church JM, Shen B. Transabdominal redo ileal pouch surgery for failed restorative proctocolectomy: lessons learned over 500 patients. Ann Surg. 2015;262(4):675–8.
6. Lightner AL, Shogan BD, Mathis KL, Larson DW, Duchalais E, Pemberton JH, Dozois EJ. Revisional and reconstructive surgery for failing IPAA is associated with good function and pouch salvage in highly selected patients. Dis Colon Rectum. 2018;61(8):920–30.
7. Tekkis PP, Heriot AG, Smith JJ, Das P, Canero A, Nicholls RJ. Long-term results of abdominal salvage surgery following restorative proctocolectomy. Br J Surg. 2006;93(2):231–7.
8. Shawki S, Belizon A, Person B, Weiss EG, Sands DR, Wexner SD. What are the outcomes of reoperative restorative proctocolectomy and ileal pouch-anal anastomosis surgery? Dis Colon Rectum. 2009;52(5):884–90.
9. Nisar PJ, Kiran RP, Shen B, Remzi FH, Fazio VW. Factors associated with ileoanal pouch failure in patients developing early or late pouch-related fistula. Dis Colon Rectum. 2011;54:446–53.
10. Forbes SS, O'Connor BI, Victor JC, Cohen Z, McLeod RS. Sepsis is a major predictor of failure after ileal pouch-anal anastomosis. Dis Colon Rectum. 2009;52:1975–81.
11. Kirat HT, Remzi FH, Shen B, Kiran RP. Pelvic abscess associated with anastomotic leak in patients with ileal pouch-anal anastomosis (IPAA): transanastomotic or CT-guided drainage? Int J Color Dis. 2011;26:1469–74.
12. Sagap I, Remzi FH, Hammel JP, Fazio VW. Factors associated with failure in managing pelvic sepsis after ileal pouch-anal anastomosis (IPAA) - a multivariate analysis. Surgery. 2006;140:691–703.
13. Ross H, Steele SR, Varma M, Dykes S, Cima R, Buie WD, Rafferty J. Practice parameters for the surgical treatment of ulcerative colitis. Dis Colon Rectum. 2014;57:5–22.
14. Akbari RP, Madoff RD, Parker SC, et al. Anastomotic sinuses after ileoanal pouch construction: incidence, management, and outcome. Dis Colon Rectum. 2009;52:452–5.
15. Nyam DC, Wolff BG, Dozois RR, Pemberton JH, Mathison SM. Does the presence of a pre-ileostomy closure asymptomatic pouch-anal anastomotic sinus tract affect the success of ileal pouch-anal anastomosis? J Gastrointest Surg. 1997;1:274–7.
16. Garrett KA, Remzi FH, Kirat HT, Fazio VW, Shen B, Kiran RP. Outcome of salvage surgery for ileal pouches referred with a diagnosis of Crohn's disease. Dis Colon Rectum. 2009;52(12):1967–74.
17. Schwartzberg DM, Esen E, Remzi FH. Thoughtful ileostomy creation in patients undergoing redo IPAA. Dis Colon Rectum. 2020;63(1):117–20.
18. Sellers MM, Elnekaveh BM, Hahn SJ, Hirten RP, Greenstein AJ. Surgical solutions for refractory J-pouch inlet obstruction. Color Dis. 2019;21(6):679–83.
19. Geers J, Bislenghi G, D'Hoore A, Wolthuis AM. Surgical management of an ileal J-pouch-anal anastomosis volvulus. Dis Colon Rectum. 2019;62(8):1014–9.
20. Okita Y, Araki T, Kawamura M, et al. Clinical features and management of afferent limb syndrome after ileal pouch-anal anastomosis for ulcerative colitis. Surg Today. 2016;46(10):1159–65. https://doi.org/10.1007/s00595-016-1307-7.
21. Kirat HT, Kiran RP, Remzi FH, Fazio VW, Shen B. Diagnosis and management of afferent limb syndrome in patients with ileal pouch-anal anastomosis. Inflamm Bowel Dis. 2011;17(6):1287–90.
22. Kayal M, Plietz M, Rizvi A, et al. Inflammatory pouch conditions are common after ileal pouch anal anastomosis in ulcerative colitis patients [published online ahead of print, 2019 Oct 6]. Inflamm Bowel Dis. 2019;izz227.
23. Okita Y, Araki T, Hiro J, et al. Laparoscopic ileopexy for afferent limb syndrome after ileal pouch-anal anastomosis. Asian J Endosc Surg. 2017;10(4):424–6.
24. Rottoli M, Vallicelli C, Bigonzi E, et al. Prepouch ileitis after ileal pouch-anal anastomosis: patterns of presentation and risk factors for failure of treatment. J Crohns Colitis. 2018;12(3):273–9.
25. Hedrick TL, Sawyer RG, Foley EF, Friel CM. Anastomotic leak and the loop ileostomy: friend or foe? Dis Colon Rectum. 2006;49:1167–76.
26. Scott NA, Dozois RR, Beart RW Jr, Pemberton JH, Wolff BG, Ilstrup DM. Postoperative intra-abdominal and pelvic sepsis complicating ileal-pouch anal anastomosis. Int J Color Dis. 1988;3:149–52.
27. Ahmed Ali U, Shen B, Remzi FH, Kiran RP. The management of the anastomotic pouch sinus after IPAA. Dis Colon Rectum. 2012;55:541–8.
28. Whitlow CB, Opelka FG, Gathright JB Jr, Beck DE. Treatment of colorectal and ileoanal anastomotic sinuses. Dis Colon Rectum. 1997;40:760–3.
29. Tang L, Cai H, Moore L, Shen B. Evaluation of endoscopic and imaging modalities in the diagnosis of structural disorders of the ileal pouch. Inflamm Bowel Dis. 2010;16:1526–31.
30. Lian L, Geisler D, Shen B. Endoscopic needle knife treatment of chronic presacral sinus at the anastomosis at an ileal pouch-anal anastomosis. Endoscopy. 2010;42 Suppl 2:E14.
31. Kochhar GS, Shen B. Endoscopic treatment of leak at the tip of the "J" ileal pouch. Endosc Int Open. 2017;5(1):E64–6.
32. Kirat HT, Kiran RP, Oncel M, Shen B, Fazio VW, Remzi FH. Management of leak from the tip of the "J" in ileal pouch-anal anastomosis. Dis Colon Rectum. 2011;54(4):454–9.
33. Joyce MR, Fazio VW, Hull TT, et al. Ileal pouch prolapse: prevalence, management, and outcomes. J Gastrointest Surg. 2010;14(6):993–7.
34. Freeha K, Gao XH, Hull TL, Shen B. Characterization of risk factors for floppy pouch complex in ulcerative colitis. Int J Color Dis. 2019;34(6):1061–7.
35. Hardt J, Kienle P. Laparoscopic ventral pouch pexy with acellular dermal matrix (ADM)-a novel technique for the treatment of full-thickness pouch prolapse after restorative proctocolectomy and j-pouch. Int J Color Dis. 2018;33(11):1643–6.
36. Ullah MZ, Fajobi OA, Bhargava AM. Long-axis rotational volvulus in a W ileoanal pouch: an unusual but potentially preventable problem. Report of a case. Dis Colon Rectum. 2007;50(4):540–3.
37. Landisch RM, Knechtges PM, Otterson MF, Ludwig KA, Ridolfi TJ. Pouch volvulus in patients having undergone restorative proctocolectomy for ulcerative colitis: a case series. Dis Colon Rectum. 2018;61(6):713–8.
38. Lewis WG, Kuzu A, Sagar PM, Holdsworth PJ, Johnston D. Stricture at the pouch-anal anastomosis after restorative proctocolectomy. Dis Colon Rectum. 1994;37(2):120–5.
39. Prudhomme M, Dozois RR, Godlewski G, Mathison S, Fabbro-Peray P. Anal canal strictures after ileal pouch-anal anastomosis. Dis Colon Rectum. 2003;46(1):20–3.
40. Kirat HT, Kiran RP, Lian L, Remzi FH, Fazio VW. Influence of stapler size used at ileal pouch-anal anastomosis on anastomotic leak, stricture, long-term functional outcomes, and quality of life. Am J Surg. 2010;200(1):68–72.

41. Shen B, Fazio VW, Remzi FH, et al. Endoscopic balloon dilation of ileal pouch strictures. Am J Gastroenterol. 2004;99(12):2340–7.
42. Fazio VW, Tjandra JJ. Pouch advancement and neoileoanal anastomosis for anastomotic stricture and anovaginal fistula complicating restorative proctocolectomy. Br J Surg. 1992;79(7):694–6.
43. Wu XR, Kiran RP, Mukewar S, Remzi FH, Shen B. Diagnosis and management of pouch outlet obstruction caused by common anatomical problems after restorative proctocolectomy. J Crohns Colitis. 2014;8(4):270–5.
44. Kiran RP, Kirat HT, Rottoli M, Xhaja X, Remzi FH, Fazio VW. Permanent ostomy after ileoanal pouch failure: pouch in situ or pouch excision? Dis Colon Rectum. 2012;55(1):4–9.
45. Shen B. Pouchitis: what every gastroenterologist needs to know. Clin Gastroenterol Hepatol. 2013;11(12):1538–49.
46. Shen B. Acute and chronic pouchitis--pathogenesis, diagnosis and treatment. Nat Rev Gastroenterol Hepatol. 2012;9(6):323–33.
47. Shen B, Plesec TP, Remer E, et al. Asymmetric endoscopic inflammation of the ileal pouch: a sign of ischemic pouchitis? Inflamm Bowel Dis. 2010;16(5):836–46.
48. Wu XR, Ashburn J, Remzi FH, Li Y, Fass H, Shen B. Male gender is associated with a high risk for chronic antibiotic-refractory pouchitis and ileal pouch anastomotic sinus. J Gastrointest Surg. 2016;20(3):631–9.
49. Fazio VW, Tjandra JJ. Transanal mucosectomy Ileal pouch advancement for anorectal dysplasia or inflammation after restorative proctocolectomy. Dis Colon Rectum. 1994;37(10):1008–11.
50. Gu J, Stocchi L, Kiran RP, Shen B, Remzi FH. Do clinical characteristics of de novo pouch Crohn's disease after restorative proctocolectomy affect ileal pouch retention? Dis Colon Rectum. 2014;57(1):76–82.
51. Shen B, Fazio VW, Remzi FH, Lashner BA. Clinical approach to diseases of ileal pouch-anal anastomosis. Am J Gastroenterol. 2005;100(12):2796–807.
52. Wu XR, Kiran RP, Remzi FH, Katz S, Mukewar S, Shen B. Preoperative pelvic radiation increases the risk for ileal pouch failure in patients with colitis-associated colorectal cancer. J Crohns Colitis. 2013;7(10):e419–26.
53. Lightner AL, Fletcher JG, Pemberton JH, Mathis KL, Raffals LE, Smyrk T. Crohn's disease of the pouch: a true diagnosis or an oversubscribed diagnosis of exclusion? Dis Colon Rectum. 2017;60(11):1201–8.
54. Karoui M, Cohen R, Nicholls J. Results of surgical removal of the pouch after failed restorative proctocolectomy. Dis Colon Rectum. 2004;47(6):869–75.
55. Shen B, Sanmiguel C, Bennett AE, et al. Irritable pouch syndrome is characterized by visceral hypersensitivity. Inflamm Bowel Dis. 2011;17(4):994–1002.
56. Shen B, Achkar JP, Lashner BA, et al. Irritable pouch syndrome: a new category of diagnosis for symptomatic patients with ileal pouch-anal anastomosis. Am J Gastroenterol. 2002;97(4):972–7.
57. Quinn KP, Tse CS, Lightner AL, Pendegraft RS, Enders FT, Raffals LE. Nonrelaxing pelvic floor dysfunction is an underestimated complication of ileal pouch-anal anastomosis. Clin Gastroenterol Hepatol. 2017;15(8):1242–7.
58. Khanna R, Li Y, Schroeder T, et al. Manometric evaluation of evacuatory difficulty (dyschezia) in ileal pouch patients. Inflamm Bowel Dis. 2013;19(3):569–75.
59. Silva-Velazco J, Hull TL, Stocchi L, Gorgun E. Is it really small-bowel obstruction in patients with paradox after IPAA? Dis Colon Rectum. 2015;58(3):328–32.
60. Kariv R, Remzi FH, Lian L, et al. Preoperative colorectal neoplasia increases risk for pouch neoplasia in patients with restorative proctocolectomy. Gastroenterology. 2010;139(3):806–12.
61. Derikx LA, Kievit W, Drenth JP, et al. Prior colorectal neoplasia is associated with increased risk of ileoanal pouch neoplasia in patients with inflammatory bowel disease. Gastroenterology. 2014;146(1):119–28.
62. Maya AM, Boutros M, DaSilva G, Wexner SD. IPAA-related sepsis significantly increases morbidity of ileoanal pouch excision. Dis Colon Rectum. 2015;58(5):488–93.
63. Tekkis PP, Lovegrove RE, Tilney HS, Smith JJ, Sagar PM, Shorthouse AJ, Mortensen NJ, Nicholls RJ. Long-term failure and function after restorative proctocolectomy - a multi-centre study of patients from the UK National Ileal Pouch Registry. Color Dis. 2010;12(5):433–41.
64. Dehni N, Remacle G, Dozois RR, Banchini F, Tiret E, Parc R. Salvage reoperation for complications after ileal pouch-anal anastomosis. Br J Surg. 2005;92(6):748–53.
65. Pellino G, Selvaggi F. Outcomes of salvage surgery for ileal pouch complications and dysfunctions. The experience of a referral centre and review of literature. J Crohns Colitis. 2015;9(7):548–57.
66. Theodoropoulos GE, Choman EN, Wexner SD. Salvage procedures after restorative proctocolectomy: a systematic review and meta-analysis. J Am Coll Surg. 2015;220(2):225–42.
67. Fonkalsrud EW, Bustorff-Silva J. Reconstruction for chronic dysfunction of ileoanal pouches. Ann Surg. 1999;229(2):197–204.
68. Kock NG. Intra-abdominal "reservoir" in patients with permanent ileostomy. Preliminary observations on a procedure resulting in fecal "continence" in five ileostomy patients. Arch Surg. 1969;99(2):223–31.
69. McLeod RS, Fazio VW. The continent ileostomy: an acceptable alternative. J Enterostomal Ther. 1984;11(4):140–6.
70. Fazio VW, Church JM. Complications and function of the continent ileostomy at the Cleveland Clinic. World J Surg. 1988;12(2):148–54.
71. Fazio VW, Tjandra JJ. Technique for nipple valve fixation to prevent valve slippage in continent ileostomy. Dis Colon Rectum. 1992;35(12):1177–9.
72. Nessar G, Wu JS. Evolution of continent ileostomy. World J Gastroenterol. 2012;18(27):3479–82.
73. Nessar G, Fazio VW, Tekkis P, Connor J, Wu J, Bast J, Borkowski A, Delaney CP, Remzi FH. Long-term outcome and quality of life after continent ileostomy. Dis Colon Rectum. 2006;49(3):336–44.
74. Aytac E, Ashburn J, Dietz DW. Is there still a role for continent ileostomy in the surgical treatment of inflammatory bowel disease? Inflamm Bowel Dis. 2014;20(12):2519–25.
75. Lian L, Fazio VW, Remzi FH, Shen B, Dietz D, Kiran RP. Outcomes for patients undergoing continent ileostomy after a failed ileal pouch-anal anastomosis. Dis Colon Rectum. 2009;52(8):1409–14; discussion 4414–6.

Infectious Colitis

51

Craig A. Reickert and Maher A. Abbas

Key Concepts

- Campylobacter is the most common cause of bacterial colitis worldwide.
- Yersinia may cause a mesenteric adenitis and ileitis resembling Crohn's disease.
- Amebic colitis causes flask-like ulcers.
- The diagnosis of CMV may be made by identification of viral inclusion bodies on mucosal biopsies.

Bacterial Colitidies

Campylobacter

The symptoms of campylobacter infection are usually diarrhea (often bloody diarrhea), fever, and abdominal pain. In the United States (US), the Centers for Disease Control and Prevention (CDC) has identified an incidence of 19.6 cases per 100,000 people making campylobacter the most common bacterial colitis. Worldwide, the incidence is 25–30 cases per 100,000 population [1]. Most cases are related to ingestion of contaminated food or water. Poultry is a common, but not exclusive, source of infection. Definitive diagnosis is confirmed by stool culture or polymerase chain reaction (PCR) testing of the stool in the setting of symptoms of infectious diarrhea. Endoscopic findings may reveal mild inflammatory changes but without pathognomonic findings.

Campylobacter infection is usually self-limited and does not require specific treatment other than supportive care for the diarrhea. Campylobacter infection has a median incubation period of 2–4 days. The bacteria multiply in the bile and invade the gastrointestinal mucosa to the depth of the lamina propria. The infection causes edematous enteritis with bloody diarrhea. The infection can inflame the terminal ileum and cecum and create a clinical picture similar to appendicitis. Campylobacter infection usually resolves in 7 days without significant sequelae. However, up to 16% may have persistent colonization for up to 10 weeks. In addition, severe complications from campylobacter include clinically significant lower gastrointestinal (GI) bleeding, toxic colitis, pancreatitis, Reiter's syndrome, and Guillain-Barre syndrome [2].

Treatment with antibiotics is not usually required, but may be indicated for severe disease. Drug-resistant forms of the bacteria are common in some areas with high disease incidence [3]. Fluoroquinolone antibiotics are highly effective but have a high rate of drug resistance (>25% in the USA and up to 80% in some areas of the world). Treatment with azithromycin is almost as effective as a fluoroquinolone with lower rates of drug resistance [4]. Most studies advise up to 3 days of antibiotic therapy, but severely compromised patients may benefit from longer courses, parenteral medications, and/or multi-drug treatment [5]. Patients with campylobacter infection do not require specific isolation precautions.

Salmonella

Infection with salmonella has two types of clinical presentations. Non-typhoid salmonella infections are characterized with diarrhea (usually self-limited) with gastrointestinal symptoms such as nausea, vomiting, and cramping. The incubation period is between 8 and 48 hours after the ingestion of contaminated food. Typhoid fever describes the presence of salmonella infection with symptoms of fever, delirium, pain, and skin rash. Typhoid fever is related to bacteremia from the GI tract infection. The typhoid fever presentation is associated with salmonella typhi and salmonella

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paratyphi. Salmonella enteritidis and salmonella typhimurium are most common in the US population [1]. Routes of transmission include food, feces, fingers, fomites, and flies (the 5 Fs). Many infections are related to contaminated meat and poultry products [2].

Diagnosis with stool culture or PCR or a positive blood culture with the organism is confirmatory. Endoscopic findings are non-specific and do not confirm the diagnosis. Most infections do not require treatment and are self-limited. Treatment with antibiotics for patients with bacteremia is reasonable and should be considered in immunocompromised or frail patients. Fluoroquinolones are the treatment of choice, although azithromycin is a reasonable alternative, particularly in developing nations or in patients with exposure during travel to those endemic areas [5].

Shigella

Infection with shigella is more common in young children but can affect all individuals. In the USA, *Shigella sonnei* is the most common [1]. Transmission via contaminated water and from contaminated or infected individuals is the most common routes of spread. Infection is associated with diarrhea, usually non-bloody, but colitis, tenesmus, and bloody stools may develop 3–5 days after onset of symptoms. Children frequently recover in 3–4 days, while adults may need 3–4 weeks to fully recover from the infection. Complications include perforation, toxic colitis, hemolytic-uremic syndrome, and dehydration/electrolytes abnormalities [2].

Diagnosis requires stool culture or PCR for confirmation. Endoscopic findings are non-specific and non-diagnostic. Symptoms usually resolve without antibiotic therapy, but patients may continue to shed the organism for up to 6 weeks without symptoms. Antibiotic resistance is becoming more common and empiric/universal treatment for patients is not advisable. In patients with more systemic signs of infection, complications, or immunosuppression, as well as patients who have public health consequences due to the prolonged shedding (such as food handlers, child-care providers, nursing home residents), treatment based on culture/sensitivity results is recommended, with fluoroquinolones, azithromycin, or a third-generation cephalosporin [6]. Treatment should be limited to between 3 and 5 days for most patients.

Escherichia coli

Escherichia coli (*E. coli*) bacteria are among the most populous species of bacteria in the normal human colon. Most are harmless and even beneficial. There are five pathotypes or groups of *E. coli* conclusively associated with diarrhea: shiga toxin-producing *E. coli* (STEC) (also known as verocytotoxin-producing *E. coli* (VTEC) or enterohemorrhagic *E. coli* (EHEC)), enterotoxigenic *E. coli* (ETEC), enteropathogenic *E. coli* (EPEC), enteroaggregative *E. coli* (EAEC), and enteroinvasive *E. coli* (EIEC). Both EPEC and EIEC are non-toxin producers. An additional pathotype, diffusely adherent *E. coli* (DAEC), has been described but has not been conclusively linked to pathologic manifestations and diarrheal illness [2].

Infections from EPEC frequently affect infants, while EAEC affects children with more persistent diarrhea. ETEC and EAEC are often associated with traveler's diarrhea. EIEC is endemic in South America and parts of Europe, and it is associated with dysentery in these areas. All pathotypes have caused disease in the USA and around the world. Collectively non-STEC infections have lower incidence in the USA, Canada, Australia, New Zealand, Japan, and countries in Northern and Western Europe. Non-STEC infections have highest incidence in most of Asia, the Middle East, Africa, Mexico, and Central and South America.

STEC (including groups known as VTEC and EHEC) is associated with a hemorrhagic colitis presenting with diarrhea that may be bloody. It is often implicated in food-borne outbreaks in the USA and globally more common in industrialized nations. A well-described strain of *E. coli* O157:H7 was identified in 1982 [7]. The reservoir for this bacterium is cows, and transmission of this strain is associated with food transmission (undercooked beef or milk). Both EHEC serotypes O157:H7 and non-O157:H7 produce shiga-like toxins similar to *Shigella dysenteriae*. Outbreaks have been associated more often with the *E. coli* O157:H7 subtype. Most infections are not severe and are self-limited. However, some patients progress to bloody diarrhea, and a subgroup of these patients may develop hemolytic uremic syndrome (HUS) and life-threatening complications. STEC infections with non-O157 strains are important causes of diarrheal outbreaks, accounting for 75% of STEC infections [8]. Stool analysis for pathogens and shiga toxin can help confirm non-O157 STEC [9].

Stool cultures or the rapid multiplex GI panel PCR test for STEC should be considered for all patients with bloody diarrhea. Endoscopic findings of colitis and focal ulcerations may be seen but are not diagnostic [10]. Clinical treatment of most patients with diarrhea from *E. coli* is supportive with early hydration and correction of electrolytes. Avoidance of anti-motility agents is critical in STEC infection as increased toxin production and exposure can exacerbate the risk of HUS.

There are no antibiotic regimens for *E. coli* infection, and treatment with antibiotics is not recommended in most cases. Several antibiotics have actually been found to increase the risk of HUS in STEC. EAEC in children may be treated with rifaximin for protracted cases. There are no current vaccines or prophylactic regimens to reduce the risk of traveler's diarrhea associated with *E. coli*.

Yersinia

Transmission of yersinia occurs via the handling of contaminated animals as well as ingestion of contaminated food (often infection is related to undercooked pork or contaminated milk products). Diarrhea with fever and abdominal pain may last up to 21 days. The clinical findings of mesenteric adenitis or ileitis could be confused with Crohn's disease. Further systemic complications of a migratory arthritis, Reiter's syndrome, and findings of erythema nodosum are sometimes noted and further complicate the diagnostic dilemma. Colonoscopy findings can also mimic Crohn's disease with erosions in the right colon [10].

Diagnostic testing with stool culture may not be able to identify yersinia by isolation methods. Hemagglutinin testing for titers in a ratio of 1:128 is indirect confirmation of infection. More recently PCR-based assays were developed for the detection of plasmid- and chromosome-borne virulence genes in *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* [11]. In most cases the disease resolves without treatment. Supportive care for the diarrhea may be required. In patients with systemic manifestations, antibiotic coverage with aminoglycosides, trimethoprim/sulfamethoxazole (TMP-SMX), doxycycline, and fluoroquinolones have all been effective [2].

Vibrio

Vibrio infection is associated with both non-cholerae and cholerae presentations. Vibrio contaminates shellfish, so consumption of raw and undercooked shellfish is the main route of transmission. The development of diarrhea and abdominal cramping within 48 hours of ingesting raw shellfish is consistent with acute vibrio infection. Routine stool cultures do not often include vibrio species, so a special request may be made based on history of exposure [12]. PCR stool testing can be helpful. *Vibrio parahaemolyticus* causes diarrhea and cramping but is self-limited and not associated with massive diarrhea. Tetracycline, fluoroquinolones, aminoglycosides, and third-generation cephalosporins for treatment of severe infection are all effective. Vibrio cholerae species are associated with invasive infection with severe, voluminous (up to 1 liter per hour) diarrhea which can lead to dehydration, hypovolemic shock, and death within hours of the development of symptoms [13]. Vibrio cholerae strains O1 and O319 are the most commonly associated with outbreaks [14]. Treatment of cholerae symptoms requires high-volume crystalloids resuscitation with the addition of ciprofloxacin or doxycycline (treatment is a single dose) to control the active bacteria.

Other Bacterial Colitidies

Infection with other bacteria associated with colitis includes *Mycobacterium tuberculosis*, *Aeromonas* species, *Bacteroides*, *Listeria*, as well as *Clostridium difficile* (covered in a separate chapter). Bacterial sexually transmitted diseases (STDs) such as gonorrhea, chlamydia, or syphilis predominantly affect the anorectal region through direct transmission (covered under a separate chapter).

Tuberculosis infection is carried from the primary pulmonary site via swallowed sputum. *Mycobacterium tuberculosis* infection of the GI tract is associated with abdominal pain, fever, and weight loss. Inflammation of the ileocolic region can be mistaken for new-onset Crohn's disease or complicated appendicitis [15]. Endoscopic findings and biopsy are not pathognomonic and radiology findings are variable in reliability. Computer tomography findings are non-specific in most cases (Fig. 51.1). Surgical intervention is reserved for diagnostic purposes in undiagnosed cases or in the setting of an established diagnosis when there is perforation or obstruction [16].

Aeromonas colitis is most often associated with diarrhea. Symptoms can persist for 2 weeks or longer and must be suspected in cases of exposure based on travel to endemic areas. Stool cultures can be diagnostic but require specific request in non-endemic areas. While symptoms may persist, they are often self-limited. Treatment in immunocompromised patients includes fluoroquinolones or azithromycin [17].

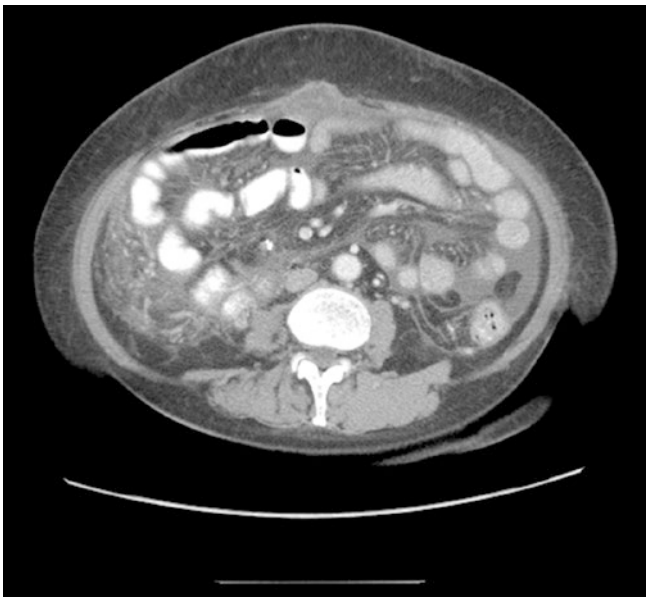

Fig. 51.1 Computed tomography of tuberculous colitis with dissemination into the peritoneal cavity with ascites and omental infiltration (axial view)

Bacteroides fragilis colitis is associated with infection by a subclass of organisms with a secreted toxin [18]. The symptoms of acute diarrhea are self-limited. *Listeria monocytogenes* is associated with acute colitis in immunocompromised individuals [19]. Treatment in immune compromised patients would include TMP-SMX but is not required in most otherwise healthy patients.

Parasitic Colitidies

Amebic Colitis

Amebiasis is caused by *Entamoeba histolytica*. It is prevalent in areas of the world with limited sanitation capabilities such as tropical central/southern America, Africa, and Asia [20, 21]. Travel exposure is the most common finding in patients diagnosed in the USA. Transmission between humans is most often via fecal/oral contamination. The amebic cysts can persevere in the soil for up to a month. The cycle of transmission includes ingestion of mature cysts which replicate inside the gastrointestinal tract through a process of excystation, resulting in active trophozoites (non-encysted amebae) which can invade the colonic wall. Incubation times after exposure can be from 2 to 4 weeks before the development of symptoms. While the majority of patients are asymptomatic or have mild symptoms, individuals can develop a wide spectrum of symptoms including poor appetite, weight loss, fever, nausea, vomiting, lower abdominal pain, diarrhea (including bloody diarrhea in some cases), and anemia due to colonic inflammation and ulceration [20, 21]. The parasite can cause deep ulcerations in the colon leading to full-thickness perforation [22, 23]. Extraintestinal complications of amebiasis due to bloodstream infection can involve the liver, brain, and lung [24–26]. Hepatic abscess can develop in absence of colonic symptoms and can rupture into the abdomen or the chest cavity leading to lung abscess or empyema [21, 27, 28]. Amebiasis can lead to death when there is colonic perforation or systemic extraintestinal disease with a reported mortality rate up to 50% [29]. Approximately 55,000 amebiasis-related deaths were reported globally in 2010 [30].

The diagnosis of amebiasis can be confirmed by stool tests including microscopy, increased white blood cell (non-specific), and PCR antigen testing which is highly sensitive and specific [31, 32]. More than one stool sample (up to three on different days) is needed in some patients to make the diagnosis. Serologic testing to detect antibodies can be helpful and usually becomes positive after a period of 2 weeks. Higher level of antibodies is noted in patients with extraintestinal disease such as hepatic abscess. The antibody level can remain positive for a long period of time after treatment. Therefore, a positive test may not necessarily represent active disease. Endoscopic findings usually include ulcerations of various depths and widths from a few millimeters to centimeters (Fig. 51.2). While the right colon is most often affected, ulcerations can occur on the left side as well.

Histopathologic assessment of the specimen usually demonstrates flask-shaped ulcers (Fig. 51.3). In some cases, the trophozoites are noted at the periphery of the ulcer using

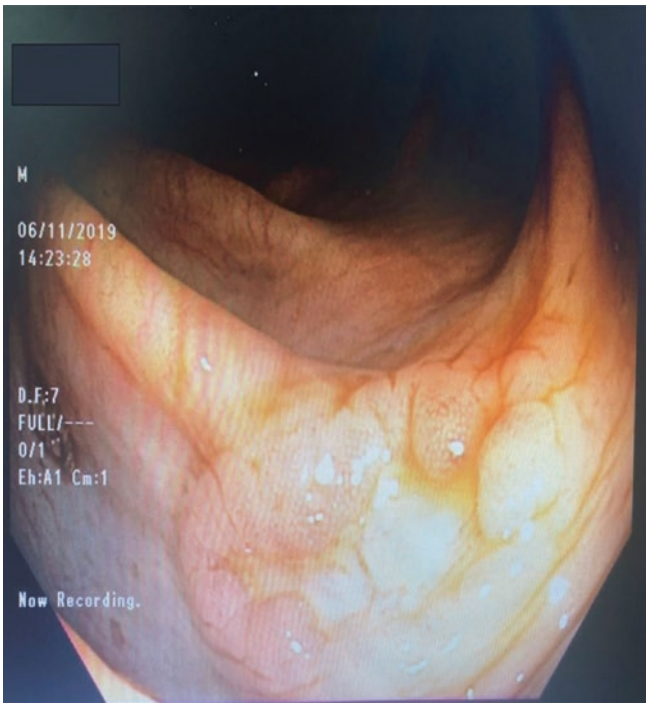

Fig. 51.2 Colonoscopy findings of amebic ulcer

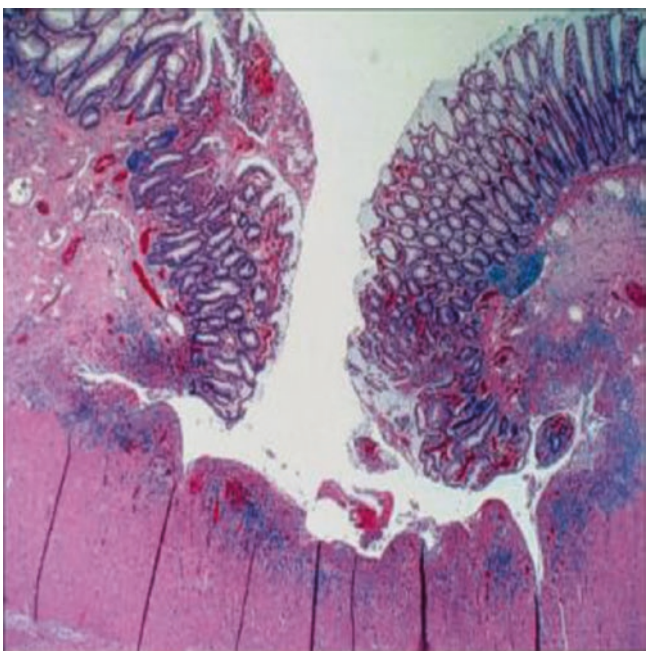

Fig. 51.3 Histopathologic examination of an amebic ulcer. Note the flask-shaped ulcer

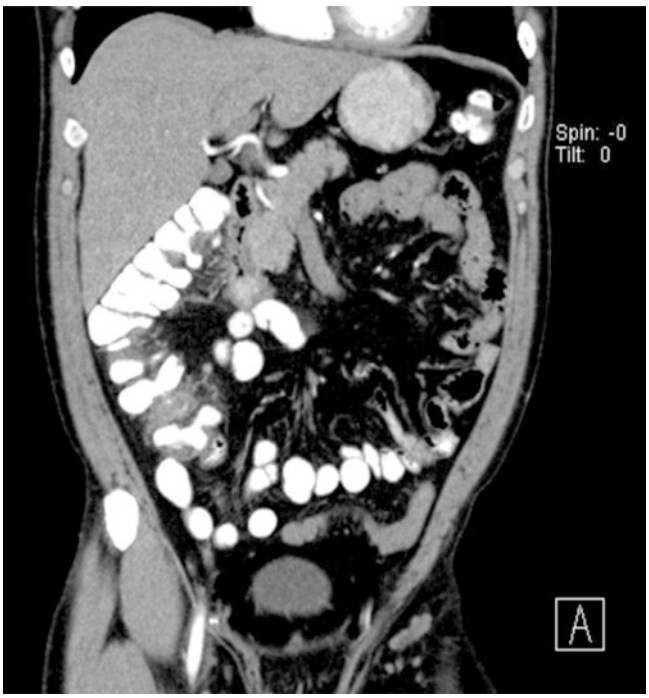

Fig. 51.4 Computed tomography of amebic colitis involving the ascending colon (coronal view)

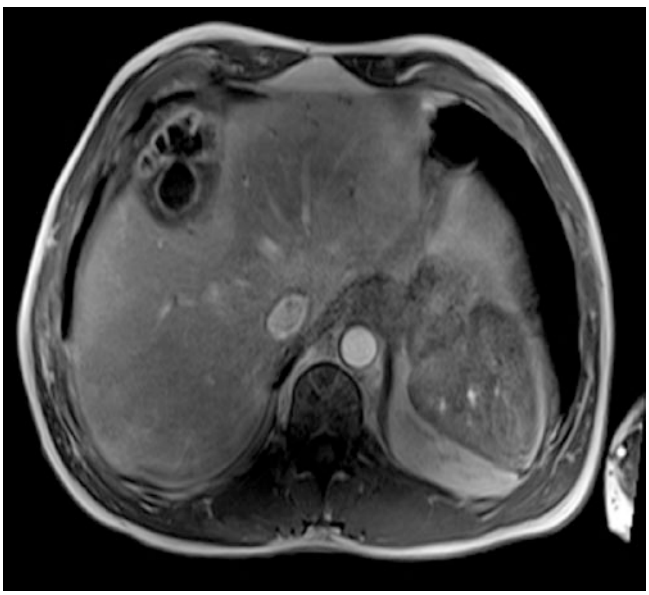

Fig. 51.5 Magnetic resonance scan of amebic hepatic abscess (axial view, T1 sequence post-contrast)

immunohistochemical stains specific to antibodies against the *Entamoeba histolytica*. While computed tomography can be helpful in delineating areas of inflammation, the presence of hepatic abscess or perforation is not specific for amebic colitis (Fig. 51.4). Hepatic abscess can be assessed by ultrasound examination, computed tomography, or magnetic resonance imaging (Fig. 51.5). An uncommon presentation of amebiasis is ameboma which is a granulomatous mass in the wall of the colon. It can present with obstructive symptoms and can be confused for a malignancy [33, 34].

Asymptomatic patients can be treated with a luminal agent directed at the cysts to prevent transmission to other humans. Luminal agents include paromomycin, diloxanide furoate, or iodoquinoline. Management of confirmed active disease of amebic colitis needs a combination therapy initially with amebicidal agent followed by a luminal medication. A 10-day course of metronidazole is considered as first-line therapy for patients with active colitis [35, 36]. Other medication options include tinidazole, nitazoxanide, dehydroemetine, and chloroquine. Amebic hepatic abscess is treated with medical therapy; patients with a large abscess or those who fail to respond to medical therapy can benefit from imaging-guided aspiration or drainage [25, 26, 37]. Surgical intervention is reserved for the rare complications of perforation or toxic colitis.

A group from Mexico City reported their 30-year experience with patients who suffered perforations from amebic colitis [23]. During the study period, 112 cases of colonic perforation related to amebiasis were identified (0.6% of all emergency abdominal operations). The right colon was the most common location of disease (90.5%), and multiple colon perforations were noted in 74% of patients. A segmental colectomy was performed in 53.3% of the patients, subtotal colectomy with end ileostomy in 35.3%, exteriorization of the colon in 10.7%, and primary repair in 0.8%. A mortality rate of 40% was noted.

Anisakidosis

Infections caused by *Anisakis simplex* and *Pseudoterranova decipiens* are associated with gastritis; >90% of the infections have been reported from Japan. Consumption of contaminated raw fish allows the larvae to attach to the GI tract (4% involving colon). Symptoms of lower abdominal pain, fever, and diarrhea are common [38]. The larvae burrow into the muscular wall and cause a hypersensitivity reaction with granulomas and eosinophils. Symptoms and signs can be confused with appendicitis, ileitis, diverticulitis, and acute abdomen [39]. Surgery for complications of perforation and obstruction can be required and is often the means of diagnosis. Treatment with albendazole for 7–21 days can be effective [40].

Ascaris

Ascaris lumbricoides infection is prevalent in tropical and subtropical climates. It is a major world health issue with up to 1.2 billion infected persons at this time. A human host

consumes ascaris eggs; the larvae hatch in the small intestine and migrate via venous return to the lungs. The larvae are able to enter the airway and can be returned to the GI tract by being swallowed in the sputum from the airway. Larvae in the intestine grow into adults and begin to produce eggs. Adult ascaris worms can live for up to 2 years and can produce thousands of eggs each day. Eggs are passed in the stool and can live for years in the environment [41].

Most patients with infection are asymptomatic. Patients with very high worm burden may have symptoms of abdominal pain or bowel obstruction. Treatment of obstructing worm masses can include milking the mass into the more distal bowel; resection may be required even in the absence of bowel compromise from the obstructive process [42].

Diagnosis can be confirmed with stool microscopy. The eggs and larvae are well described and easy to identify. Retrograde GI contrast studies can identify the curvilinear densities or obstruction from the parasites. Treatment with mebendazole or albendazole is highly effective [43].

Infection with *Ascaris suum*, a similar infection in pigs, has also been found in humans and can be an important alternate source of infection in areas where the use of pig manure as fertilizer is common [44].

Strongyloides

The intestinal nematode *Strongyloides stercoralis* is prevalent in tropical climates but also has a notable incidence in the Appalachian areas of the USA. Larvae shed from infected hosts can penetrate the skin of a new host to cause infection. The larvae travel to the lungs and are swallowed in sputum to allow adults to grow in the GI tract. Strongyloides can autoinfect their host [45].

Patients demonstrate acute infection with skin changes from the burrowing larvae – larvae currens. Chronic states with auto-infection can present with diarrhea, pain, and wasting [46]. The infection can sometimes present with findings of pancolitis, potentially mimicking ulcerative colitis. Endoscopy cannot easily distinguish it from other forms of colitis [47]. Stool detection of larvae confirms the diagnosis. However, repeated testing, duodenal biopsy, enzyme-linked immunosorbent assay (ELISA) testing, or bronchial washings may be required for confirmation.

Ivermectin for 2 days is the first-line treatment. Albendazole and mebendazole are alternate medications for treatment [48].

Trichuris

Trichuris trichiura, or whipworm, infection affects almost 800 million people around the world, mostly in tropical and subtropical climates. Ingestion of contaminated soil/food allows the larvae to grow in the colon. Adult worms can secrete thousands of eggs per day. Most infected humans have minimal or no symptoms. Advanced infection can create symptoms of diarrhea, bleeding, and tenesmus with stool having a characteristic odor [49].

Symptomatic rectal prolapse can occur with the ability to observe the worms on the mucosa. Additional symptoms of anemia from bleeding and growth retardation in children are noted. Confirmation of the diagnosis with stool microscopy, the barrel-shaped eggs and worms are easily identified. Colonoscopy can visually identify the worms. Treatment with mebendazole or albendazole is effective [50]. Surgical repair of prolapse can be required but is otherwise not typically part of the treatment of trichuris infection.

Enterobius

Pinworm infection by *Enterobius vermicularis* is common in all areas of the world. Most of the infected humans are children. Spread is by ingestion of eggs. The adult worms grow in the cecum for 10–12 weeks. Female pinworms migrate to the perianal skin and deposit up to 10,000 eggs in the perianal skin folds. The larvae hatch and create an intense pruritus. Scratching of the skin can allow larvae to travel on the fingers to auto-infect or infect others through oral ingestion [51]. Diagnostic testing with the tape test – pressing a strip of adhesive tape against the perianal skin to pull eggs onto the tape and allow microscopic detection – is easy and diagnostic. Treatment with mebendazole or albendazole is effective. Care is taken to treat all family members; environmental cleaning to prevent reinfection is usually required for proper eradication.

Cryptosporidium

Infection by cryptosporidium, an intracellular protozoan parasite, was first described in humans in 1976 [52]. Ingestion of oocysts from contaminated food or water allows growth in the small bowel and shedding of oocysts in the stool. The oocysts are small, making filtration challenging, and are resistant to chlorination. Heating, freezing, and ozonation can destroy the oocysts. The oocysts are able to create infection with exposure to only a few oocysts.

Cryptosporidiosis typically presents in one of four clinical scenarios: pediatric diarrhea in developing areas, traveler's diarrhea, diarrhea in immunocompromised conditions, and water-borne outbreaks in developed areas. Diarrhea in immunocompetent patients is usually self-limited. The explosive diarrhea can present with fever, abdominal pain, and nausea. In immunocompromised patients, the symptoms are pro-

tracted, and biliary symptoms of acalculous cholecystitis and cholangitis have been described. Cholecystectomy can be helpful in these severe cases along with supportive care. Detection of the oocysts in the stool by PCR or ELISA test is diagnostic. No medication has been found effective to control infection with cryptosporidium. In patients with the human immunodeficiency virus (HIV), treatment with highly active antiretroviral therapy (HAART) can help shorten the disease course [53]. Nitazoxanide is shown to help shorten disease in immunocompetent patients. Cure rates of 60–75% are described [54]. Avoiding swimming for 2 weeks after resolution of symptoms is advisable to reduce spread of the disease.

Balantidium

The major source for *Balantidium coli* infection is pigs [55]. Ingestion of contaminated food and water allows spread of the only ciliated protozoan that infects humans. The ingested parasite cysts lodge in the colon and create ulceration and inflammation with both bloody and non-bloody diarrhea. Stool study can identify the trophozoites. Treatment with tetracycline is effective. Alternate treatment with metronidazole and doxycycline are also effective.

Giardia

Giardia lamblia is a common parasitic infection in the USA and around the world. Transmission is through water, fecal contamination, and fecal-oral spread. Consumption of untreated water in rural areas or fecal contamination of water and swimming pools leads to disease transmission. Ingestion of oocysts allows the giardia trophozoites to attach to the small bowel mucosa. The development of diarrhea usually occurs within 1–2 weeks of infection. The stool appears greasy and has a foul odor. Stool examination is able to confirm the diagnosis. ELISA or immunofluorescence antigen detection or PCR stool test is useful. Metronidazole is the first line of therapy [56].

Schistosomiasis

Trematode infection by *Schistosoma haematobium*, *S. mansoni*, and *S. japonicum* affects around 250 million people each year around the world. Most infections occur in tropical regions. It is most common in Africa. The parasite eggs are shed in urine and stool from infected hosts. Snails are intermediate hosts and the mobile cercariae are released into water. The cercariae can attach and invade the skin of a new host. They migrate to the heart and lungs, and then the liver, while continuing to mature. *S. haematobium* affects the urinary bladder, while *S. mansoni* and *S. japonicum* affect the mesentery of the small bowel and colon. The eggs are deposited in the tissues and the immune response creates significant damage to the local organs [57]. Symptoms of pain and diarrhea are common. Additional organ damage with urinary obstruction, mass, enteric fistulas, and hepatic, pulmonary, and neurologic impairment are all described. Stool evaluation commonly identifies the eggs and confirms the diagnosis. Treatment with praziquantel is effective [58]. Surgical intervention for complications of perforation and obstruction may be required but is uncommon.

Tapeworms

Parasitic flatworm infections from *Taenia solium*, *T. saginata*, *Diphyllobothrium latum*, *Hymenolepis nana*, and *Dipylidium caninum* allow growth of the worm in the GI tract of the host. Most infections are asymptomatic. *T. solium* is spread by consumption of contaminated pork. *T. saginata* is associated with contaminated beef. *T. solium* ingestion can be associated with the development of cysticercosis, associated with progressive neurologic symptoms. *D. latum* is associated with consumption of raw fish; the adult worm attaches to the terminal ileum and may be associated with megaloblastic anemia. The actual worm may be identified in the feces; ELISA and PCR stool test can help make the diagnosis. All infections respond to treatment with praziquantel. In some cases, a bowel preparation to clear the GI tract shortly after treatment can be helpful [59].

Trypanosoma

Chagas disease is caused by infection with *Trypanosoma cruzi*. Infection is endemic in Central and South America. Clinical findings are grouped into acute and chronic phases. Immediately after an acute infection, patients may manifest fever, malaise, edema, lymphadenopathy, and hepatosplenomegaly. These symptoms resolve and are followed by a latent period. Up to 30% of patients may develop chronic symptoms, while the remainder may stay asymptomatic for life. Chronic symptoms relate to end-organ damage, cardiomyopathy, megaesophagus, and megacolon [60]. The parasite is associated with damage to the GI neurons resulting in dilation and impaired function. Symptoms are related to the organ dysfunction and may include constipation, abdominal pain, dysphagia, and volvulus. Surgical intervention for complications from symptoms may be required, but is not curative. All patients with diagnosed trypanosome infection benefit from treatment [61]. Benznidazole and nifurtimox are indicated but can have significant GI and neurological side effects.

Fungal Colidities

Histoplasma

Infection with *Histoplasma capsulatum* can be associated with GI involvement. The fungal disease is endemic in the USA in the Ohio and Mississippi river valley regions. Pulmonary infection may be commonly seen. A subgroup of patients can develop progressive disseminated histoplasmosis (PDH). Patients with PDH can develop GI ulcerations, sometimes severe, deep ulcers, and pseudopolyps which can be confused with inflammatory bowel disease (IBD) or malignancy. Confirmation of the diagnosis is made with tissue culture [62]. Surgical intervention for cases of perforation or obstruction may be required. Treatment is intravenous (IV) amphotericin B. Itraconazole is an alternative but not first-line therapy.

Candida

Candida is a common organism in humans. Candida colitis is rare and it presents with diarrhea and abdominal pain. It is associated with severe systemic illness and immune compromise. Diagnosis by microscopic confirmation of budding yeast with hyphae or culture can be confirmatory. Endoscopic examination reveals white plaque-like lesions [63]. Treatment with fluconazole, with dosage based on severity of illness, can be helpful. Mortality is high in immunocompromised patients. Colectomy may be performed for perforation or peritonitis but is associated with a very high risk of death.

Other Fungal Colitidies

Colitis associated with advanced disseminated *Aspergillus* presents with fever, pain, GI bleeding, and tenderness. Complications of perforation or ischemia may require surgery. Pathology evaluation can confirm the presence of the characteristic hyphae, and culture can confirm the diagnosis. Treatment of disseminated aspergillosis is voriconazole. Amphotericin B is a second-line medication [64].

Cryptococcal infection by *C. neoformans* and *C. gattii* can affect the GI tract in severe cases. Patients are usually immunocompromised or immunosuppressed. Colitis with spontaneous perforation has been described in these patients [65]. Surgical intervention can be required to control the abdominal emergency. GI nodules from disseminated infection can mimic IBD. Biopsy with histology or culture may confirm the diagnosis. Treatment for disseminated cryptococcal infection is IV amphotericin B [66].

Viral Colitidies

Cytomegalovirus

Cytomegalovirus (CMV), a double-stranded DNA virus, is a member of the herpesvirus family. It is an extremely common pathogen with an estimated prevalence between 31% and 70% in children of various ethnicities in the USA [67]. At a global level, the seroprevalence of CMV has been estimated as high as 83% in the general population [68]. Transmission of CMV occurs through various routes including perinatal, breast milk, viral shedding in close-contact settings including sexual transmission, and blood products during transfusion and/or organ transplantation. In the immunocompetent patient, primary CMV infection is often asymptomatic. Patients at highest risk for symptomatic CMV infection are immunocompromised and immunosuppressed individuals such as those with HIV or IBD or transplant recipients. However, symptomatic CMV infection can occur in immunocompetent individuals and has been reported in elderly patients with significant medical comorbidities or critically ill individuals [69, 70].

CMV can affect various parts of the body including the brain and central nervous system, the eyes, the lungs, the heart, the kidneys, the esophagus, the liver, the pancreas, the small bowel, and the colon. It is speculated that when CMV colitis occurs, it is due to a reactivation of a latent infection secondary to an alteration in immune competence of the patient's T lymphocytes. This secondary infection is believed to be the most common cause of CMV colitis. Primary infection can occur in immunocompromised patient if not previously exposed to CMV. Symptoms of CMV colitis include fever, malaise, abdominal pain, diarrhea, rectal bleeding, and weight loss.

Endoscopic findings typically consist of mucosal friability and ulcerations of the colon. CMV can present as an ischemic-like colitis or a polypoid mass suspicious for colon cancer [71–73]. Biopsies of the colon taken during colonoscopy are critical in establishing the diagnosis as seropositivity for CMV is very common in the general population and cannot provide a definitive answer regarding active infection. It is important to take representative biopsies from various parts of the colonic lesions including the edges. The identification on hematoxylin and eosin (H&E) stains of CMV inclusion bodies surrounded by a clear halo ("owl's eye"), surrounded by inflamed cells, is indicative of active CMV colitis. Inclusion bodies surrounded by normal-appearing cells may represent colonization. Due to the low sensitivity of the H&E stains, PCR tests or CMV-specific immunohistochemistry is advisable if the diagnosis is not confirmed initially by H&E stains.

Active CMV colitis should be treated. Treatment is initiated via the intravenous route in severely ill patients and followed by oral treatment. Ganciclovir and foscarnet are the anti-viral medications of choice [74]. Surgical intervention is undertaken in patients who fail medical management or those with persistent bleeding and/or perforation. While perforation can occur in various parts of the digestive tract, most perforations are noted between the ileum and the splenic flexure [75]. Multiple areas of perforations can be encountered, especially in immunocompromised patients. Resection without primary anastomosis and fecal diversion is advisable. The morbidity and mortality of CMV colitis with perforation is significant. Galiatsatos reported a 31% mortality in immunocompetent patients [76]. In immunosuppressed and immunocompromised patients, the mortality can be significantly higher [75].

Other Viral Colitidies

While CMV colitis is the most relevant for a colorectal surgeon's practice, it is important to note that several other viruses can cause inflammation and gastrointestinal infections and are worthy of brief mention in this chapter. Such viruses include rotavirus, Norwalk virus, astrovirus, picobirnavirus, calicivirus, herpes simplex virus (HSV), norovirus, sapovirus, and adenovirus. Most of these viruses cause gastroenteritis with predominant symptoms associated with upper gastrointestinal disease (such as nausea, vomiting, diarrhea); but some can cause colitis as well. HSV-2 is associated with sexually transmitted proctitis. Due to the symptom overlap between gastroenteritis and colitis, i.e., abdominal pain, cramping, and diarrhea, the proper diagnosis requires careful assessment of the patient. These viruses have been implicated in outbreaks but can also affect immunosuppressed and immunocompromised patients such as those with inflammatory bowel disease [77, 78].

Infectious Colitis in Immunocompromised Patients

Inflammatory Bowel Disease

Patients with inflammatory bowel disease (ulcerative colitis and Crohn's disease) and infectious colitis pose specific challenges for the treating clinician for two main reasons: delay in diagnosis and the overall health status of the patient in terms of malnutrition, anemia, and immunosuppression. The clinical presentation and endoscopic findings of inflammatory bowel disease may be indistinguishable from infectious colitis. Furthermore, initial investigative studies including stool analysis and endoscopic biopsies may not demonstrate superimposed infection. Patients with inflammatory bowel disease are susceptible to infectious colitis; but unless promptly diagnosed with a superimposed infection, they are often treated for exacerbation of their inflammatory bowel disease by escalating their immunosuppression therapy which can lead to disastrous complications with sepsis and perforation. Thus, patients with inflammatory bowel disease with progressive symptoms should be evaluated carefully with suspicion for an infectious element entertained. A multidisciplinary evaluation with repeat testing and assessment should be considered in order to optimize the patient's outcome.

All types of infectious colitidies have been reported in inflammatory bowel disease patients including bacterial, mycobacterial, fungal, viral, and parasitic [74, 79–83]. Some patients with infectious colitidies may present with extraintestinal organ involvement such as the liver, lungs, or brain. The incidence of parasitic-related infections can vary depending on endemic areas. Soylu from Turkey reported regional variations in the incidence of amebiasis in patients with ulcerative colitis within the same country [81]. Of particular interest in the setting of inflammatory bowel disease is *Clostridium difficile*-superimposed infection. This entity has been well described and is now routinely tested for in patients with worsening inflammatory bowel disease symptoms [84–89]. Inflammatory bowel disease is associated with a higher rate of treatment failure and recurrence. *Clostridium difficile* infection is addressed in another chapter of this textbook.

CMV infection is prevalent in patients with inflammatory bowel disease, with a reported incidence of 10–33% [80, 90–92]. While CMV infection can occur in both ulcerative colitis and Crohn's disease, it is more common in ulcerative colitis [74]. The multiplex PCR assay of stool is one of the best methods to test for CMV and other causes of infectious colitis [93, 94]. While CMV presence may not be the cause of symptoms, treatment should be strongly considered in patients with severe symptoms or those who are steroid-resistant. Furthermore, the use of anti-viral therapy for CMV may yield a beneficial long-term effect on the management of patients with inflammatory bowel disease [95].

Immunosuppression for inflammatory bowel disease and/or other autoimmune disorders can hinder the immune system's capability to limit the extent or progression of infectious colitis. Steroids and other immune-modulating drugs including biologic therapy, such as anti-TNF inhibitors, may have a profound effect on the immune system. Infectious colitis in patients on steroids therapy can lead to progression of disease and perforation whether there is underlying inflammatory bowel disease or not [22, 96]. Abbas reported a case of perforation in a patient presumed initially to have ulcerative colitis exacerbation and treated with prolonged steroids therapy [22]. Surgical resection revealed severe amebic colitis without evidence of inflammatory bowel disease.

Human Immunodeficiency Virus

The description of the human immunodeficiency virus (HIV) in the 1980s led to significant advances in our understanding of the immune system, its complex cascades of reactions, and interactions with environmental factors such as infections. HIV targets T lymphocytes of the CD4+ type leading to impairment of the immune system and its ability to fight certain infections. In the early days of the HIV epidemic, most patients succumbed to cachexia and overwhelming opportunistic infections affecting the various organs including the lungs and the digestive tract. The digestive tract is a major site for viral replication leading to depletion of CD4+ T cells.

Patients with HIV are susceptible to all the various types of infectious colitidies described earlier in this chapter including bacterial, fungal, parasitic, and viral [74]. Patients with CD4+ T cell count less than 200/mm^3 are at significant risk for developing opportunistic infections. Gastrointestinal symptoms are common in patients with HIV with diarrhea being the most frequent [97–99]. The most common type of opportunistic colitis in HIV patients is CMV [100, 101]. A thorough investigation is necessary especially in patients with low CD4+ count and those who do not respond promptly to conservative medical management. Stool studies and endoscopic evaluation with biopsies can be helpful [97, 102]. A new generation of stool tests such as the multiplex PCR assay can detect many various types of viral as well as bacterial and parasitic infections [94, 103]. The use of highly active antiretroviral therapy (HAART) for HIV improves the immune system response by increasing the CD4+ count [104, 105].

Transplant Patients

Transplantation has revolutionized the world of medicine and provided the opportunity for a cure or long-term survival for previously fatal conditions. However solid organ transplantations are not without risks when it comes to long-term immunosuppression. Despite significant advances in the management of immunosuppression and the introduction of a newer generation of less toxic medications, the risk of infectious complications remains significant. Gastrointestinal infections and diarrhea are common in the solid organ transplant population with some series reporting the incidence of diarrhea between 22% and 52% [106–108]. It is important to differentiate infectious diarrhea in transplant patients from diarrhea associated with immunosuppression medications. A retrospective review of 422 admissions of transplant patients with diarrhea over 18-month period reported that the majority of cases had no identifiable etiology and were often self-limited. The most common identifiable infectious were *Clostridium difficile*, norovirus, and cytomegalovirus [109]. The clinical history especially in respect to any associated symptoms and medication usage, coupled with diagnostic investigation, is of paramount importance. Workup includes blood tests inclusive of complete blood count, renal and liver function tests, blood cultures (if warranted), and stool studies including the PCR-based multiplex GI pathogens testing. Colonoscopy is considered in patients with persistent severe symptoms and negative preliminary workup.

References

1. Tack DM, Marder EP, Griffin PM, et al. Preliminary incidence and trends of infections with pathogens transmitted commonly through food - foodborne diseases active surveillance network, 10 U.S. Sites, 2015-2018 [published correction appears in MMWR Morb Mortal Wkly Rep. 2019;68(20):465]. MMWR Morb Mortal Wkly Rep. 2019;68(16):369–73.
2. Papaconstantinou HT, Thomas JS. Bacterial colitis. Clin Colon Rectal Surg. 2007;20:18–27.
3. Peterson MC. Clinical aspects of campylobacter jejuni infections in adults. West J Med. 1994;161(2):148–52.
4. Wieczorek K, Osek J. Antimicrobial resistance mechanisms among campylobacter. Biomed Res Int. 2013;2013:340605.
5. Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. Clin Infect Dis. 2017;65(12):e45–80.
6. Pons MJ, Gomes C, Martinez-Puchol S, Ruiz L, Mensa L, Vila J, Gascon J, Ruiz J. Antimicrobial resistance in Shigella spp. causing traveler's diarrhoea (1995-2010): a retrospective analysis. Travel Med Infect Dis. 2013;11(5):315–9.
7. Riley LW, Remis RS, Helgerson SD, McGee HB, Wells JG, Davis BR, Hebert RJ, Olcott ES, Johnson LM, Hargrett NT, Blake PA, Cohen ML. Hemorrhagic colitis associated with a rare Escherichia coli serotype. N Engl J Med. 1983;308(12):681–5.
8. Kuehne A, Bouwknegt M, Havelaar A, et al. Estimating true incidence of O157 and non-O157 Shiga toxin-producing Escherichia coli illness in Germany based on notification data of haemolytic uraemic syndrome. Epidemiol Infect. 2016;144(15):3305–15.
9. Frank C, Faber MS, Askar M, Bernard H, Fruth A, Gilsdorf A, Hohle M, Karch H, Krause G, Prager R, Spode A, Stark K, Werber D. Large and ongoing outbreak of haemolytic uraemic syndrome, Germany, May 2011. Euro Surveill. 2011;16(21):19878.
10. Mantzaris GJ. Endoscopic diagnosis of infectious colitis. Ann Gastroenterol. 2007;20(1):71–4.
11. Thoerner P, Kingombe CI, Bögli-Stuber K, Bissig-Choisat B, Wassenaar TM, Frey J, Jemmi T. PCR detection of virulence genes in *Yersinia enterocolitica and Yersinia pseudotuberculosis* and investigation of virulence gene distribution. Appl Environ Microbiol. 2003;69(3):1810–6.
12. Newton A, Kendall M, Vugia DJ, Henao OL, Mahon BE. Increasing rates of vibriosis in the United States, 1996–2010: review of surveillance data from 2 systems. Clin Infect Dis. 2012;54(S5):S391–5.
13. Ali M, Lopez AL, You YA, Kim YE, Sah B, Maskery B, Clemens J. The global burden of cholerae. Bull World Health Organ. 2012;90:209–218A.
14. Daniels NA, Shafaie A. A review of pathogenic Vibrio infections for clinicians. Inf Med. 2000;17(10):665–85.
15. Breiter JR, Hajjar JJ. Segmental tuberculosis of the colon diagnosed by colonoscopy. Am J Gastroenterol. 1981;76(4):369–73.

16. Sharma MP, Bhatia V. Abdominal tuberculosis. Indian J Med Res. 2004;120(4):305–15.
17. Igbinosa IH, Igumbor EU, Aghdasi F, Tom M, Okoh AI. Emerging Aeromonas species and their significance in public health. Sci World J. 2012;2012:625023.
18. Jiang Z, DuPont HL, Brown EL, Nandy RK, Ramamurthy T, Sinha A, Ghosh S, Guin S, Gurleen K, Rodrigues S, Chen JJ, McKenzie R, Steffen R. Microbial etiology of travelers' diarrhea in Mexico, Guatemala, and India: importance of enterotoxigenic Bacteroides fragilis and Arcobacter species. J Clin Microbiol. 2010;48(4):1417–9.
19. Lorber B. Listeria monocytogenes. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. 6th ed. Philadelphia: Elsevier; 2005.
20. Haque R, Huston CD, Hughes M, Houpt E, Petri WA. Amebiasis. N Engl J Med. 2003;348(16):1565–73.
21. Farrar J, Hotez P, Junghanss T, Kang G, Lalloo D, White NJ. Manson's tropical diseases: Elsevier Health Sciences; The Netherlands. 2013. p. 664–71.
22. Abbas MA, Mulligan DC, Ramzan NN, Blair JE, Smilack JD, Shapiro MS, Lidner TK, Olden KW. Colonic perforation in unsuspected amebic colitis. Dig Dis Sci. 2000;45:1836–41.
23. Athié-Gutiérrez C, Rodea-Rosas H, Guízar-Bermúdez C, Alcántara A, Montalvo-Javé EE. Evolution of surgical treatment of amebiasis-associated colon perforation. J Gastrointest Surg. 2010;14(1):82–7.
24. Lardière-Deguelte S, Ragot E, Amroun K, Piardi T, Dokmak S, Bruno O, Appere F, Sibert A, Hoeffel C, Sommacale D, Kianmanesh R. Hepatic abscess: diagnosis and management. J Visc Surg. 2015;152(4):231–43.
25. Kumar R, Ranjan A, Narayan R, Priyadarshi RN, Anand U, Shalimar. Evidence-based therapeutic dilemma in the management of uncomplicated amebic liver abscess: a systematic review and meta-analysis. Indian J Gastroenterol. 2020; https://doi.org/10.1007/s12664-019-01004-. [Epub ahead of print].
26. Vakamacawai E, McCaig E, Waqainabete I, Cox MR. Amoebic liver abscesses in Fiji: epidemiology, clinical presentation and comparison of percutaneous aspiration and percutaneous catheter drainage. World J Surg. 2020;44(3):665–72.
27. Shamsuzzaman SM, Hashiguchi Y. Thoracic amebiasis. Clin Chest Med. 2002;23(2):479–92.
28. Zakaria A, Al-Share B, Al AK. Primary pulmonary amebiasis complicated with multicystic empyema. Case Rep Pulmonol. 2016; https://doi.org/10.1155/2016/8709347. Epub 2016 Jul 10.
29. Ozdogan M, Baykal A, Aran O. Amebic perforation of the colon: rare and frequently fatal complication. World J Surg. 2004;28:926–9.
30. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–128.
31. Haque R, Ali IKM, Akther S, Petri WA Jr. Comparison of PCR, isoenzyme analysis, and antigen detection for diagnosis of *Entamoeba histolytica* infection. J Clin Microbiol. 1998;36:449–52.
32. Blessmann J, Buss H, Nu PA, Dinh BT, Ngo QT, Van AL, Alla MD, Jackson TF, Ravdin JI, Tannich E. Real-time PCR for detection and differentiation of Entamoeba histolytica and Entamoeba dispar in fecal samples. J Clin Microbiol. 2002;40(12):4413–7.
33. Moorchung N, Singh V, Srinivas V, Jaiswal SS, Singh G. Caecal amebic colitis mimicking obstructing right sided colonic carcinoma with liver metastases: a rare case. J Cancer Res Ther. 2014;10(2):440–2.
34. Chahine E, Baghadady R, Chahine C, Doghman G, El Kary N, El Khoury L, Safa K, Chouillard MA, Chouillard E. Complete resolution of obstructive colonic amebic pseudotumor with conservative treatment: a case report and literature review. Int J Surg Case Rep. 2019;59:1–3.
35. Petri WA Jr, Singh U. Diagnosis and management of amebiasis. Clin Infect Dis. 1999;29(5):1117–25.
36. Norman FF, Comeche B, Chamorro S, Pérez-Molina JA, López-Vélez R. Update on the major imported protozoan infections in travelers and migrants. Future Microbiol. 2020; https://doi.org/10.2217/fmb-2019-0212. [Epub ahead of print].
37. Wuerz T, Kane JB, Boggild AK, Krajden S, Keystone JS, Fuksa M, Kain KC, Warren R, Kempston J, Anderson J. A review of amoebic liver abscess for clinicians in a nonendemic setting. Can J Gastroenterol. 2012;26(10):729–33.
38. Hochberg NS, Hamer DH. Anisakidosis: perils of the deep. Clin Infect Dis. 2010;51(7):806–12.
39. Couture C, Measures L, Gagnon J, Desbiens C. Human intestinal anisakidosis due to consumption of raw salmon. Am J Surg Pathol. 2003;27(8):1167–72.
40. Pacios E, Arias-Diaz J, Zuloaga J, Gonzalez-Armengol J, Villarroel P, Balibrea JL. Albendazole for the treatment of anisakiasis ileus. Clin Infect Dis. 2005;41(12):1825–6.
41. de Silva NR, Brooker S, Hotez PJ, Montresor A, Engels D, Savioli L. Soil-transmitted helminth infections: updating the global picture. Trends Parasitol. 2003;19(12):547–51.
42. de Silva NR, Guyatt HL, Bundy DA. Worm burden in intestinal obstruction caused by Ascaris lumbricoides. Tropical Med Int Health. 1997;2(2):189–90.
43. Keiser J, Utzinger J. Efficacy of current drugs against soil transmitted helminth infections: systematic review and metaanalysis. JAMA. 2008;299(16):1937–48.
44. Murrell KD, Eriksen L, Nansen P, Slotved HC, Rasmussen T. Ascaris suum: a revision of its early migratory path and implications for human ascariasis. J Parastol. 1997;83(2):255–60.
45. Liu LX, Weller PF. Strongyloidiasis and other intestinal nematode infections. Infect Dis Clin N Am. 1993;7(3):655–82.
46. Vadlamudi RS, Chi DS, Krishnaswamy G. Intestinal strongyloidiasis and hyperinfection syndrome. Clin Mol Allergy. 2006;4:8.
47. Minematsu H, Hokama A, Makishi T, Arakaki K, Kinjo F, Fujita J. Colonoscopic findings and pathologic characteristics of Strongyloides colitis: a case series. Digestion. 2011;83(3):210–4.
48. Drugs for parasitic infections. Med Lett. 2007;5(S):el–15.
49. Bethony J, Brooker S, Albonico M, Geiger SM, Loukas A, Diemert D, Hotez PJ. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. Lancet. 2006;367(9521):1521–32.
50. Steinmann P, Utzinger J, Du Z, Jiang J, Chen J, Hattendorf J, Zhou H, Zhou X. Efficacy of single dose and triple-dose albendazole and mebendazole against soil-transmitted helminth infections and Taenia spp.: a randomized controlled trial. PLoS One. 2011;6(9):e25003.
51. Wang LC, Hwang KP, Chen ER. Enterobius vermicularis infection in schoolchildren: a large-scale survey 6 years after a population-based control. Epidemiol Infect. 2010;138(1):28–36.
52. Dillingham RA, Lima AA, Guerrant RL. Cryptosporidiosis: epidemiology and impact. Microbes Infect. 2002;4(10):1059–66.
53. Pantenburg B, Cabada MM, White AC Jr. Treatment of cryptosporidiosis. Expert Rev Anti-Infect Ther. 2009;7(4):385–91.
54. Checkley W, White AC Jr, Jaganath D, Arrowood MJ, Chalmers RM, Chen XM, Fayer R, Griffiths JK, Guerrant RL, Hedstrom L, Huston CD, Kotloff KL, Kang G, Mead JR, Miller M, Petri WA Jr, Priest JW, Roos DS, Striepen B, Thompson RC, Ward HD, Vanvoorhis WA, Xiao L, Zhu G, Houpt ER. A review of the global burden, novel diagnostics, therapeutics, and vaccine targets for cryptosporidium. Lancet Infect Dis. 2015;15(1):85–94.
55. Schuster FL, Ramirez-Avila L. Current world status of Balantidium coli. Clin Microbiol Rev. 2008;21(4):626–38.
56. Gardner TB, Hill DR. Treatment of giardiasis. Clin Microbiol Rev. 2001;14(1):114–28.

57. Chitsulo L, Engels D, Montresor A, Savioli L. The global status of schistosomiasis and its control. Acta Trop. 2000;77(1):41–51.
58. Ross AG, Bartley PB, Sleigh AC, Olds GR, Li Y, Williams GM, McManus DP. Schistosomiasis. N Engl J Med. 2002;346(16):1212–20.
59. Craig P, Ito A. Intestinal cestodes. Curr Opin Infect Dis. 2007;20(5):524–32.
60. Bocchi EA, Guimaraes G, Tarasoutshi F, Spina G, Mangini S, Bacal F. Cardiomyopathy, adult valve disease and heart failure in South America. Heart. 2009;95(3):181–9.
61. Koberle F. Chagas' disease and Chagas' syndromes: the pathology of American trypanosomiasis. Adv Parasitol. 1968;6:63–116.
62. Lee JT, Dixon MR, Murrell Z, Konyalian V, Agbunag R, Rostami S, French S, Kumar RR. Colonic histoplasmosis presenting as colon cancer in the non-immunocompromised patient: report of a case and review of the literature. Am Surg. 2004;70(11):959–63.
63. Salagre A, Galovart MT, De Los Rios CC, Canga F. Candida colitis: an endoscopic diagnosis. Gastrointest Endosc. 2018;88(4):780.
64. Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Nguyen MH, Segal BH, Steinbach WJ, Stevens DA, Walsh TJ, Wingard JR, Young JA, Bennett JE. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63(4):e1–e60.
65. Daly JS, Porter KA, Chong FK, Robillard RJ. Disseminated, nonmeningeal gastrointestinal cryptococcal infection in an HIV-negative patient. Am J Gastroenterol. 1990;85(10):1421–4.
66. Washington K, Gottfried MR, Wilson ML. Gastrointestinal cryptococcosis. Mod Pathol. 1991;4(6):707–11.
67. Staras SA, Flanders WD, Dollard SC, Pass RF, McGowan JE Jr, Cannon MJ. Cytomegalovirus seroprevalence and childhood sources of infection: a population-based study among preadolescents in the United States. J Clin Virol. 2008;43(3):266–71.
68. Zuhair M, Smit GS, Wallis G, Jabbar F, Smith C, Devleesschauwer, Griffiths P. Estimation of the worldwide seroprevalence of cytomegalovirus: a systematic review and meta-analysis. Rev Med Virol. 2020; https://doi.org/10.1002/rmv.2034.
69. Chaemsupaphan T, Limsrivilai J, Thongdee C, Sudcharoen A, Pongpaibul A, Pausawasdi N, Charatcharoenwitthaya P. Patient characteristics, clinical manifestations, prognosis, and factors associated with gastrointestinal cytomegalovirus infection in immunocompetent patients. BMC Gastroenterol. 2020;20:22.
70. Seo TH, Kim JH, Ko SY, Hong SN, Lee SY, Sung IK, Park HS, Shim CS, Han HS. Cytomegalovirus colitis in immunocompetent patients: a clinical and endoscopic study. Hepato-Gastroenterology. 2012;59(119):2137–41.
71. Siegal DS, Hamid N, Cunha BA. Cytomegalovirus colitis mimicking ischemic colitis in an immunocompetent host. Heart Lung. 2005;34:291–4.
72. Falagas ME, Griffiths J, Prekezes J, Worthington M. Cytomegalovirus colitis mimicking colon carcinoma in an HIV-negative patient with chronic renal failure. Am J Gastroenterol. 1996;91:168–9.
73. Chow PK, Ho MS, Ling AE, Goh HS. CMV colitis masquerading as colon cancer—an unusual presentation of acquired immunodeficiency syndrome. Singap Med J. 1997;38:32–4.
74. Dixon MR. Viral and fungal infectious colitidies. Clin Colon Rectal Surg. 2007;20(1):28–32.
75. Kram HB, Shoemaker WC. Intestinal perforation due to cytomegalovirus infection in patients with AIDS. Dis Colon Rectum. 1990;33(12):1037–40.
76. Galiatsatos P, Shrier I, Lamoureux E, Szilagyi A. Meta-analysis of outcome of cytomegalovirus colitis in immunocompetent hosts. Dig Dis Sci. 2005;50:609–16.
77. Gebhard RL, Greenberg HB, Singh N, Henry P, Sharp HL, Kaplan L, Kapikian AZ. Acute viral enteritis and exacerbations of inflammatory bowel disease. Gastroenterology. 1982;83:1207–9.
78. Robilotti E, Deresinski S, Pinsky BA. Norovirus. Clin Microbiol Rev. 2015;28(1):134–64.
79. Lysy J, Zimmerman J, Sherman Y, Feigin R, Ligumsky M. Crohn's colitis complicated by superimposed invasive amebic colitis. Am J Gastroenterol. 1991;86(8):1063–5.
80. Kandiel A, Lashner B. Cytomegalovirus colitis complicating inflammatory bowel disease. Am J Gastroenterol. 2006;101:2857–65.
81. Soylu A, Dolapcioglu C, Alis H, Dolay K, Yasar N, Boduroglu O, Cildas A, Bolukbas FF, Bolukbas C. Prevalence and importance of amebic infestation in patients with ulcerative colitis in two regions in Turkey. Dig Dis Sci. 2009;54(6):1292–6.
82. Hansen R, Thomson JM, El-Omar EM, Hold GL. The role of infection in the aetiology of inflammatory bowel disease. J Gastroenterol. 2010;45:266–76.
83. Stamtiades GA, Ioannou P, Petrikkos G, Tsioutis C. Fungal infections in patients with inflammatory bowel disease: a systematic review. Mycoses. 2018;61(6):366–76.
84. Mylonaki M, Langmead L, Pantes A, Johnson F, Rampton DS. Enteric infection in relapse of inflammatory bowel disease: importance of microbiological examination of stool. Eur J Gastroenterol Hepat. 2004;16(8):775–8.
85. Meyer AM, Ramzan NN, Loftus EV Jr, Heigh RI, Leighton JA. The diagnostic yield of stool pathogen studies during relapses of inflammatory bowel disease. J Clin Gastroenterol. 2004;38(9):772–5.
86. Issa M, Vijayapal A, Graham MB, Otterson MF, Lundeen S, Skaros S, Weber LR, Komorowski RA, Know JF, Emmons J, Bajaj JS, Binion DG. Impact of Clostridium difficile on inflammatory bowel disease. Clin Gastroenterol Hepatol. 2007;5(3):345–51.
87. Sinh P, Barrett TA, Yun L. Clostridium difficile infection and inflammatory bowel disease: a review. Gastroenterol Res Pract. 2011;2011:136064.
88. Razik R, Rumman A, Bahreini Z, McGeer A, Nguyen GC. Recurrence of Clostridium difficile infection in patients with inflammatory bowel disease: the RECIDIVISM study. Am J Gastroenterol. 2016;111(8):1141–6.
89. Singh H, Nugent Z, Yu BN, Lix LM, Targownik LE, Bernstein CN. Higher incidence of Clostridium difficile infection among individuals with inflammatory bowel disease. Gastroenterology. 2017;153(2):430–8.
90. Takahashi Y, Tange T. Prevalence of cytomegalovirus infection in inflammatory bowel disease patients. Dis Colon Rectum. 2004;47:722–6.
91. Mavropoulou E, Ternes K, Mechie NC, Bremer SC, Kunsch S, Ellenrieder V, Neese A, Amanzada A. Cytomegalovirus colitis in inflammatory bowel disease and after haematopoietic stem cell transplantation: diagnostic accuracy, predictors, risk factors and disease outcome. BMJ Open Gastroenterol. 2019;6(1):e000258. https://doi.org/10.1136/bmjgast-2018-000258.
92. Kim JJ, Simpson N, Klipfel N, Debose R, Barr N, Laine L. Cytomegalovirus infection in patients with active inflammatory bowel disease. Dig Dis Sci. 2010;55(4):1059–65.
93. Nahar S, Iraha A, Hokama A, Uehara A, Parrott G, Ohira T, Kaida M, Kinjo T, Kinjo T, Hirata T, Kinjo N, Fujita J. Evaluation of a multiplex PCR assay for detection of cytomegalovirus in stool samples from patients with ulcerative colitis. World J Gastroenterol. 2015;21(44):12667–75.
94. Ahmad W, Nguyen NH, Boland BS, Dulai PS, Pride DT, Bouland D, Sandborn WJ, Singh S. Comparison of multiplex gastrointestinal pathogen panel and conventional stool testing for evaluation of diarrhea in patients with inflammatory bowel diseases. Dig Dis Sci. 2019;64(2):382–90.

95. Maconi G, Lombardini M, Furfaro F, Bezzio C, Zerbi P, Ardizzone S. Long-term outcome of inflammatory bowel diseases with cytomegalovirus colitis: effect of antiviral treatment. Eur J Gastroenterol Hepatol. 2014;26(10):1146–51.
96. Restrepo JP, Molina MP. Colonic perforation due to invasive amebic colitis during anti-TNF therapy for spondyloarthritis. Rev Bras Reumatol. 2014;54(6):483–5.
97. Kearney DJ, Steuerwald M, Koch J, Cello JP. A prospective study of endoscopy in HIV-associated diarrhea. Am J Gastroenterol. 1999;94(3):556–9.
98. Knox TA, Spiegelman D, Skinner SC, Gorbach S. Diarrhea and abnormalities of gastrointestinal function in a cohort of men and women with HIV infection. Am J Gastroenterol. 2000;95(12):3482–9.
99. Cello JP, Day LW. Idiopathic AIDS enteropathy and treatment of gastrointestinal opportunistic pathogens. Gastroenterology. 2009;136(6):1052–65.
100. Dieterich DT, Rahmin M. Cytomegalovirus colitis in AIDS: presentation in 44 patients and a review of the literature. J Acquir Immune Defic Syndr. 1991;4(6):S29–35.
101. von Both U, Laffer R, Grube C, Bossart W, Gaspert A, Günthard HF. Acute cytomegalovirus colitis presenting during primary HIV infection: an unusual case of an immune reconstitution inflammatory syndrome. Clin Infect Dis. 2008;46(4):e38–40.
102. Feasey NA, Healey P, Gordon MA. Review article: the aetiology, investigation and management of diarrhoea in the HIV-positive patient. Aliment Pharmacol Ther. 2011;34(6):587–603.
103. Sasaki M, Shimizu N, Zushi Y, Saito T, Tsunemine H, Itoh K, Aoyama Y, Goto Y, Kodaka T, Tsuji G, Senda E, Fujimori T, Itoh T, Takahashi T. Analysis of gastrointestinal virus infection in immunocompromised hosts by multiplex virus PCR assay. AIMS Microbiol. 2018;4(2):225–39.
104. Monkemuller KE, Call SA, Lazenby AJ, Wilcox CM. Declining prevalence of opportunistic gastrointestinal disease in the era of combination antiretroviral therapy. Am J Gastroenterol. 2000;95(2):457–62.
105. Costiniuk CT, Angel JB. Human immunodeficiency virus and the gastrointestinal immune system: does highly active antiretroviral therapy restore gut immunity? Mucosal Immunol. 2012;5:596–604.
106. Maes B, Hadaya K, de Moor B, Cambier P, Peeters P, de Meester J, et al. Severe diarrhea in renal transplant patients: results of the DIDACT study. Am J Transplant. 2006;6(6):1466–72.
107. Herrero JI, Benlloch S, Bernardos A, Bilbao I, Castells L, Castrogudin JF, et al. Gastrointestinal complications in liver transplant recipients: MITOS study. Transplant Proc. 2007;39(7):2311–3.
108. Ginsburg PM, Thuluvath PJ. Diarrhea in liver transplant recipients: etiology and management. Liver Transpl. 2005;11(8):881–90.
109. Echenique IA, Penugonda S, Stosor V, Ison MG, Angarone MP. Diagnostic yields in solid organ transplant recipients admitted with diarrhea. Clin Infect Dis. 2015;60(5):729–37.

Clostridium difficile Infection

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Ian M. Paquette and David B. Stewart

Key Concepts

- More virulent strains of *C. difficile* such as ribotype 027 are associated with severe clinical infection.
- CDI in IBD patients should be treated with vancomycin.
- CDI is often associated with an exaggerated leukocytosis.
- Fecal transplant is effective therapy for recurrent CDI.

Introduction

Clostridioides (formerly Clostridium) difficile is an anaerobic, Gram-positive rod bacterium, which often is part of normal colonic flora, but can become a pathogenic organism under the appropriate circumstances when the microbiome is altered. While this was once an uncommon clinical entity, *Clostridium difficile* infection (CDI) is now responsible for at least 20% of the cases of antibiotic-associated diarrhea, and its incidence continues to steadily rise [1]. As the incidence of this disease has increased, the emergence of more virulent strains, such as ribotype 027, has led to increasingly severe clinical presentations [2–4]. As we have seen evolutions in the *Clostridium difficile* bacterium, management strategies have drifted away from the older recommendation of metronidazole as a first-line agent to newer strategies using vancomycin or fidaxomicin [5–9]. This chapter will discuss the epidemiology of CDI and the most pertinent clinical risk factors. We will discuss current microbiological nomenclature and the evolving testing strategies. Finally, we will discuss the current best recommendations for medical and surgical treatment of this disease, as well as the evolving role for fecal microbiota transplantation (FMT) [10] as an alternative to classical medical and surgical options for CDI.

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Epidemiology

Evidence is mounting that both the incidence and severity of CDI are increasing [11–13]. In fact, recent evidence suggests that in many hospital settings, CDI has now become the most common cause of hospital-acquired infection, surpassing methicillin-resistant *Staphylococcus aureus* (MRSA) infection [14, 15]. Data from the Centers for Disease Control and Prevention (CDC) suggested a fourfold increase in CDI from 1993 to 2009, while the incidence in those over age 65 increased by over 200% [16].

In addition to an overall increasing incidence, there appears to be an increasing severity as well. At least one ribotype (ribotype 027) has been associated with >15 times the production of toxins A and B compared to other strains, as well as producing a third toxin called binary toxin. This strain has been associated with a higher incidence of toxic colitis and increased mortality [17, 18]. A study by Falcone examined clinical response to antibiotic treatment in 027^{+} vs. 027^{-} subtypes. Overall, metronidazole monotherapy (HR 2.38, 95% CI 1.55–3.60, $p < 0.001$) and immunosuppressive treatment (HR 3.11, 95% CI 1.91–5.09, $p < 0.001$) were associated with recurrent CDI in ribotype 027-positive patients [4]. The authors advocated for vancomycin as primary treatment over metronidazole in cases where ribotype 027 is identified.

The increasing incidence of this condition is both clinically and financially important. A recent meta-analysis by Nanwa examined studies from 1988 to 2014 to determine the economic impact of CDI. The main outcome was the total direct cost attributable from hospital stays for CDI. Attributable direct costs of CDI ranged from $8911 to $30,049 [19]. A second study by McGlone agreed with these estimates for cost of a hospitalization and extrapolated to an

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annual US economic burden of $496 million (hospital perspective) and $547 million from a third-party payer perspective [20]. When both estimates from an inpatient and outpatient perspective are considered, the cost to the US healthcare system has been estimated to be a staggering $3 billion [21]. Given the increasing incidence and cost of CDI, it is important to fully understand the most current risk factors, diagnostic testing, and treatment strategies.

Clinical Risk Factors

Advanced Age

Though increasing age is commonly cited as a risk factor for CDI [22–25], patients of any age may be affected. The majority of the literature on age in CDI suggests that both young and older patients with CDI have similar clinical presentations and comorbidities, indicating that medical comorbidities rather than age may be the most important risk factors predisposing to CDI [22, 24]. Lee compared patients younger than 65 to those older than 65 and found more severe colitis in older patients and more frequent failure of first-line treatment, suggesting the need for more aggressive initial treatment in older patients hospitalized with CDI [23]. Louie randomized patients to be treated with vancomycin or fidaxomicin for severe CDI. Compared to patients age 18–40, clinical cure rate was lower, and clinical recurrence was higher for each successive decade [25].

Antibiotic Treatment

The most consistent and potentially modifiable risk factor for the development of CDI is antibiotic use. Though the most commonly reported antibiotics implicated are clindamycin, fluoroquinolones, carbapenems, and cephalosporins [26–34], it appears that almost any antibiotic, used over any period of time, can be associated with the development of CDI. A recent systematic review compared the impact of different classes of antibiotics on the development of CDI in the setting of randomized trials. The results compared all classes of antibiotics and quantified individual risks of CDI. Clindamycin and carbapenems appeared to be the most strongly associated antibiotics with CDI [28]. Another contemporary review by Slimings of 13 heterogeneous studies indicated that second-, third-, and fourth-generation cephalosporins (OR 3.2), clindamycin (OR 2.8), and fluoroquinolones (OR 1.6) were the most commonly cited agents [35]. Though these studies are quite heterogeneous and it is difficult to assess the impact of antibiotics in comparison of the other myriad of risk factors, it does serve to remind us that antibiotics should be used judiciously in both the prophylactic and therapeutic settings and that inciting antibiotics should be discontinued as soon as possible once CDI is diagnosed [26, 28–34]. Though it is postulated that antibiotics cause changes in colonic bacterial flora leading to susceptibility to CDI, most of the available data is descriptive in nature. Certain species of bacteria such as *Bacteroides*, *Bifidobacteriae*, *and Lachnospiraceae* seem to be the most prevalent among species which confer resistance to *C. difficile* colonization [36].

There is some degree of controversy as to whether probiotics should be used for primary prevention of CDI when a course of antibiotic therapy is prescribed. There are meta-analyses suggesting that probiotics could decrease the incidence of CDI when given to patients on antibiotics with no prior history of CDI [37–39]. Arguments against this strategy suggest that the incidence of CDI in hospitalized patients > age 65 on antibiotics tends to be <3% even without probiotics [40]. Additionally, the meta-analyses contained some studies with higher than expected incidence of CDI; excluding these studies makes the magnitude of effect of probiotics much less impressive. Additionally, due to the heterogeneity in types of probiotic and the numerous clinical confounding factors, it is difficult to say at this time whether these agents should be used as a means of primary prevention of CDI.

Contact with a Healthcare Facility

CDI is common both in acute care and longer-term health facility stays. This is likely due to a concentration of patients with the typical risk factors for CDI, as well as the transmission from patient to patient via the fecal-oral route. In addition to the usual clinical risk factors, hospital-related factors such as increasing bed occupancy have been associated with an increased risk of developing CDI [41]. It is increasingly clear that hospitals need to be aware of the potential to transmit CDI among patients and to have proper infection control practices in place [42]. These practices include antibiotic stewardship, contact precautions in the appropriate setting, hand washing, disinfection practices, and CDI treatment protocols. Though literature has shown decreased incidence in CDI when proper disinfection practices [43], antibiotic stewardship [30, 44], and hand washing with soap rather than alcohol-based disinfectants [42, 45] decrease the incidence of CDI, not all hospitals follow these practices. A recent study by Aquina used a New York statewide database to study 150,878 patients in New York having either a segmental colectomy or proctectomy. *C. difficile* incidence ranged from 0% to 11.3% among surgeons and 0% to 6.8% among hospitals. Importantly, patient factors only explained 24% of the variation, while approximately 70% of the variation was from unexplained hospital factors [46]. This highlights the

need to be vigilant when caring for hospitalized patients, as the risks for CDI transmission are significant.

Immunocompromised States

Regardless of the cause, compromise of the immune system appears to be associated with the development of CDI. It remains unclear whether immunosuppression alone is sufficient for the development of CDI, or whether immunocompromised patients frequently become hospitalized and have several of the other clinical risk factors for CDI. HIV patients seem to be at risk to develop CDI, with several of the common risk factors for infection also being cited such as low serum albumin, clindamycin use, prolonged hospital stay, and proton pump inhibitor use [47–50]. The strongest risk factor for CDI in HIV patients appears to be a CD4 count ≤50/mm3, with an adjusted odds ratio of 5.2–27.6 [48, 51]. There are many reports in the literature of CDI in other settings of immunocompromise such as general oncology patients [52], solid organ transplant recipients [53, 54], or stem cell transplant recipients [55–57]. Although these patients do have compromised immune systems, most of them seem to exhibit the classic risk factors for CDI as well such as prolonged hospitalization and antibiotic use [52, 54, 55, 57].

Inflammatory Bowel Disease

CDI has been increasing in inflammatory bowel disease (IBD) patients and may be associated with increased morbidity, mortality, and need for surgery [58, 59]. Patients with both Crohn's disease and ulcerative colitis both appear to be at risk, and clinical presentation with CDI most often happens during an acute disease exacerbation. There is some evidence that specific genetic polymorphisms may be associated with the development of CDI. One such study noted that the TNFRSF14 locus was associated with a sixfold increase in development of CDI [60]. Some of the clinical risk factors for the development of CDI in the setting of IBD are low serum albumin, hemoglobin level below 9 g/dl, active colitis from IBD, biologic use, and antibiotic use [61, 62].

Though most studies consistently show a relationship between active colitis, steroid use, and antibiotic use with CDI, some studies failed to show an association between biologic medication use and CDI [63]. Testing for CDI is recommended in patients with IBD and severe colitis. Though the evidence supports the early administration of vancomycin to treat the CDI [64], these patients need close clinical monitoring in the hospital, as at least one study has estimated a sixfold increase in the need for colectomy in this setting [65].

Perioperative Prophylactic Antibiotics and Mechanical Bowel Preparation

In preparation for elective colectomy, patients for several decades have typically received a combination of mechanical and oral antibiotic bowel preparation [66]. This was thought to minimize infectious complications by decreasing both the load of stool and bacteria in the colon. For many years, bowel preparation was used less and less, as the oral antibiotic preparation was abandoned. Recently, many studies have highlighted improved outcomes with mechanical bowel preparation and oral antibiotics including decreased surgical site infection (SSI) and anastomotic leak [67–71]. Some data also suggests that even in the absence of a mechanical bowel preparation, oral antibiotics may still decrease the incidence of SSI following colectomy [72]. It is possible that beneficial changes in the microbiome may be responsible for these improved surgical outcomes [73, 74]. However, there are some concerns that changes in the colonic microbiome may make a patient more susceptible to pathogens such as *C. difficile*. Literature on this topic is quite sparse. While on one hand, a single study by Morris noted that 9.5% of CDI patients had only preoperative oral antibiotic utilization as the only clinical risk factor [75], this likely does not outweigh the benefits of these agents in reducing SSI and potentially anastomotic leak. Further, the comparative data described above actually showed that patients receiving mechanical bowel preparation with oral antibiotics had a *lower* incidence of CDI postoperatively.

Likely the most important factor in reducing CDI is the appropriate adherence to guidelines and cessation of perioperative antibiotics as soon as feasible. A study by Balch showed that patients who had perioperative antibiotics continued for greater than 24 hours had a 6.7-fold increase in the incidence of CDI compared to those who received 24 hours of therapy alone [27].

Proton Pump Inhibitors

There appears to be a clinical association between proton pump inhibitors and CDI, though it is difficult to directly attribute causation owing to the numerous other clinical risk factors that are often present. The exact mechanism for this association remains unclear, but at least one recent in vitro study by Stewart indicated that omeprazole stimulated the production of *C. difficile* toxins in both acidic and basic environments [76]. Since many conflicting studies have been published, there were 4 recent meta-analyses performed, combining data on over 300,000 patients [77–80]. These analyses were limited due to significant heterogeneity of data, and two of the studies noted publication bias. Combined

studies suggest an odds ratio of 1.6–1.7 for the development of CDI for hospitalized patients on PPIs [77–80].

One observational study by Chitnis examined 984 cases of community-acquired CDI. In this population, 36% had not received antibiotics. The most common risk factor was use of PPI medication, which was present in 31% of patients [81]. Though there appears to be a clinical correlation between use of PPIs and development of CDI, the quality of the evidence is poor. Randomized clinical studies with proper consideration of other clinical risk factors are lacking. Though this does not support the global discontinuation of PPIs in hospitalized patients, physicians should be encouraged to use these medications judiciously, when there is a clinical indication to do so. Many patients are routinely placed on PPI medication as a means of "prophylaxis" or for other questionable clinical indications [82]. The risk of CDI could be a reason to call these practices into question.

Nomenclature and Genetics of *C. difficile* Infection

The proper genus designation for this pathogen is *Clostridioides* and not *Clostridium*. This change in terminology, introduced in 2016, was prompted by phylogenetic studies indicating that the genus *Clostridium* should be restricted to *Clostridium butyricum* and similarly evolutionarily related species that shared genetic and functional characteristics common to *Clostridium* cluster [83–85]. Despite being an anaerobic, spore-forming, Gram-positive rod, *Clostridioides* has more in common with genus *Peptoclostridium*. Its official reassignment to this genus never occurred, however, due to concerns that the pathogen's former name recognition would make the introduction of such a different moniker a source of confusion and generate a significant financial burden to research and medical fields due to re-labelling costs. Therefore, a new genus was proposed (*Clostridioides*), one similar enough to the former name to allow continued broad recognition and one clever enough to allow the continued use of the term "*C. difficile*."

CDI is clinically characterized by a colitis that is, in large part, mediated by bacterial envenomation. The genetic basis for *C. difficile* toxin production includes a 19.6 kb region known as the pathogenicity locus (PaLoc) that contains the genes for clostridial toxins A (*tcdA*) and B (*tcdB*) [86, 87]. These toxin genes, and the regulatory genes that increase and decrease their expression, are actually of bacteriophage (viral) origin [88, 89]. With successive replicative errors, loss of portions of these previously viral genes, under selective pressure, resulted in their retention as bacterial genes that increase the fitness of *C. difficile* [90]. Some, though not all, strains of *C. difficile* can produce an additional toxin known as binary toxin (*CDT*) encoded by genes outside of the *PaLoc*. Toxins A (308 kDa) and B (269 kDa) are classified as large clostridial toxins due to their larger molecular weight [91]. Both of these toxins initiate monoglucosylation of a variety of intracellular Rho GTPases that result in depolymerization of cytoskeletal elements, with resultant cytopathy of colonocytes [92]. Binary toxin has an ADP-ribosyltransferase function that requires internalization by colonocytes; to promote this internalization, binary toxin is able to induce colonocytes to alter the apical aspect of their cell membrane to produce microtubular protrusions, increasing the membrane surface area up to fivefold and promoting the adherence of both *C. difficile* and its toxins, promoting further mucosal damage [93, 94]. Although updated studies are needed, the most current data suggests that binary toxin is present in up to 6% of all *C. difficile* isolates [95]. In virtually all symptomatic infections among humans, toxins A and B will be present.

Ribotype and Clinical Severity

Although more frequently incorporated into research than clinical care, efforts at characterizing the dominant *C. difficile* strain on the basis of bacterial genotype have most commonly involved a process called ribotyping, a process using restriction enzymes to characterize the heterogeneity of the bacterial ribosomal intergenic spacer region [96, 97]. The most frequently identified ribotype associated with severe forms of *C. difficile* infection is ribotype 027 [98]. Though there are exceptions to the following, several associations between this ribotype and the clinical characteristics of CDI have emerged [99]. Ribotype 027 is the most frequently encountered strain among patients admitted from long-term healthcare facilities, with one study identifying an odds ratio of 4.87 for 027 being present compared to patients admitted with CDI from a private residence [100]. This may be a reflection of this ribotype having a selective advantage in terms of colonization and the promotion of a carriage state. Ribotype 027 is able to outcompete endemic bacteria for resources while producing larger volumes of bacterial toxins and producing higher rates of symptomatic infections; this strain also frequently has the ability to produce binary toxin in addition to toxins A and B [101]. Investigations focused on comparative bacterial genomics reveals that ribotype 027 has more than 200 genes not found in other strains of *C. difficile*, with many of these genes having a plausible role in promoting virulence [102, 103]. Other ribotypes, such as 078, represent potentially virulent strains that also have a zoonotic link between human and animal CDI. *C. difficile* as a pathogen has soil, animal, and human reservoirs, creating an important interaction between humans and their environment in terms of the emergence of new virulent strains of this bacteria [104, 105].

Diagnosis of *C. difficile* Infection

CDI is a disease capable of producing both toxin-mediated and toxin-independent forms of colitis (160), and thus the hallmark of symptomatic infection is diarrhea. The term "*C. difficile* infection" should be kept distinct from carrier states, defined as patients without symptoms of infection who nonetheless also have a positive stool test for *C. difficile*. The exact incidence of carrier states in the general population is not known, though small studies of patient populations at risk for CDI suggest the incidence is not small. In 1 study of geriatric patients without diarrhea, 43 (16.4%) out of 262 consecutive patients tested positive for toxin B based on PCR stool testing. Of those 43 patients, 7 (16.3%) eventually developed symptomatic CDI, confirming that carrier states are both more common among patients with frequent healthcare facility contacts and predispose patients to symptomatic infection [106]. Studies have suggested that patients who are able to form antibodies to *C. difficile* toxin A are more likely to remain asymptomatic carriers compared to patients who develop symptoms of CDI [107].

Diarrhea, which is typically grossly non-bloody in this disease, is the primary symptom of CDI. Depending on the severity of CDI, other findings will include abdominal distention, abdominal pain that is frequently colicky due to colitis, tachycardia, and hypotension. In fulminant cases, localized or generalized peritonitis may develop, which serves as an indication for surgery. CT findings include colonic wall thickening and pericolic fat stranding, as would be observed with any form of colitis. Colonic wall thickening is characteristic of severe forms of CDI and can provide a heightened index of suspicion for CDI prior to the results of stool testing. Transudative ascites is frequently associated with more severe forms of colitis. Pneumoperitoneum and portal venous gas are rarer radiographic findings and are generally encountered in patients with fulminant forms of the infection with septic shock and the need for vasopressors; the patients often develop non-viable colon due to severe mesenteric vasoconstriction.

Diagnostic Tests for CDI

In general, the diagnosis of CDI is founded on a clinical suspicion with support from specific laboratory testing. The original confirmatory test for CDI was bacterial culture, which proved to be both difficult and was plagued by a lengthy time interval to final results. This technique was replaced by the cell culture cytotoxicity neutralization assay (CCCNA). This approach uses a filtrate of patient stool applied to a monolayer of one of various cell lines. After a 24–48-hour incubation period, cells are evaluated for evidence of cytopathy attributable to *C. difficile* toxins. If cytopathic changes are observed, a neutralization assay is then performed to assure that these changes are due to *C. difficile* toxins. Historically, this technique was considered to be the gold standard; but with sensitivities as low as 65%, this test has been replaced by more sensitive tests that provide more expeditious results and do not require technical expertise that may limit generalizability [108].

Another, now outdated, method involves toxigenic culture. Though there are multiple methods to accomplish this test, all of them focus on isolating *C. difficile* from stool samples and confirming the presence of its toxin. There were numerous steps and difficulties with this approach. First, there is no one superior approach to isolating *C. difficile* from candidate stool samples. Secondly, once *C. difficile* colonies are isolated, those colonies have to be evaluated for their ability to produce toxin. This technique is considered by some to be a gold standard in terms of serving as a reference for new testing methods, though in terms of current practice, it has been supplanted by simpler, quicker, and less exacting approaches.

A current method of testing involves immunoassays that detect glutamate dehydrogenase (GDH), a conserved metabolic enzyme ubiquitous among *C. difficile*. As it is present among toxigenic and non-toxigenic forms of *C. difficile*, GDH alone lacks specificity for clinical purposes. Therefore, GDH is a useful screening test that, when positive, must be followed by a confirmatory test, which generally involves a toxin enzyme immunoassay (EIA). This approach allows for the use of a GDH as a high sensitivity test (80–100%) with an excellent negative predictive value, with limited cost and limited requirement for expertise and with rapid turnaround. When combined with toxin EIA, the cost per test remains less than PCR-based diagnostics while providing rapid results (<24 hours) and excellent sensitivity.

Nucleic acid amplification tests (NAATs) are a collection of PCR-based diagnostics that are designed to amplify highly conserved *C. difficile* genes, such as those related to toxins A (*tcdA*) and B (*tcdB*). The sensitivity of these tests is greater than EIA and possibly GDH-EIA combinations, though their cost is two to three times greater than GDH-EIA, and NAATs may require longer result times depending on the particular test considered. To leverage sensitivity, specificity, and cost-related issues, many hospitals have adopted an algorithmic approach, where diarrheal stools are first tested using a GDH assay. A negative result marks the end of the testing algorithm, while a positive GDH assay is followed by a confirmatory test, usually a toxin EIA. A positive GDH assay followed by a positive toxin EIA in patients with symptoms of CDI is treated as a case of CDI. A stool that is GDH positive and toxin EIA negative is tested using a NAAT. Routine retesting with NAATs to confirm resolution of CDI is not recommended, given the potential for bacterial DNA to linger for

as long as 30 days resulting in patients who no longer have CDI but who test positive for this infection.

Clinical Measures of Severity

Several clinical severity scoring systems are available, though none has emerged clearly superior to the others. Perhaps the two most commonly utilized are the 2017 Infectious Disease Society of America (IDSA) guidelines [109] and those published by the American College of Gastroenterology (ACG) [21]. In the IDSA schema, initial episodes are classified as (1) non-severe, if a patient's white blood cell count is <15,000 cells/mL and if their serum creatinine is <1.5 mg/dL; (2) severe, if a patient's white blood cell is >15,000 cells/mL and if their serum creatinine is >1.5 mg/dL; or (3) fulminant, if the patient demonstrates evidence of cardiovascular shock, ileus, or megacolon. The ACG schema defines severe CDI as patients with a white blood cell count of ≥15,000 cells/mL or a serum albumin of <3 g/dL. Fulminant disease is then defined as any patient requiring ICU admission, with a temperature of ≥38.5 °C, ileus, significant abdominal distention, altered mental status, a white blood cell count of >35,000 cells/mL or <2000 cells/mL, a serum lactate of >2.2 mmol/L, or any evidence of organ dysfunction. Using scoring systems such as these offers the potential advantages of standardizing patient assessments across providers and institutions.

Antibiotic Therapy for CDI

For more than 20 years, the two principal antibiotics used to treat CDI were metronidazole and vancomycin. Data has accumulated to suggest that vancomycin is the superior treatment option compared to metronidazole. For example, in a 2007 randomized, prospective, double-blind, placebo-controlled trial by Zar, 150 patients with either mild or severe CDI were randomized to either oral metronidazole (250 mg 4 times daily) or vancomycin (125 mg 4 times daily). While no significant difference in clinical cure rates was noted among patients with mild disease, for study subjects with severe disease, vancomycin was associated with a significantly higher cure rate (97% versus 76%; $p = 0.02$) [110].

Additionally, retrospective data specifically focused on the treatment of mild disease suggests that vancomycin is superior to metronidazole in these cases as well, with one study reporting that compared to vancomycin, metronidazole was an independent risk factor for treatment failure [110]. Given these data, the most recent IDSA recommendations state "Use of oral metronidazole, however, should be restricted to an initial episode of nonsevere CDI in cases where other therapies are contraindicated or not available, and treatment should be limited to one course due to case reports of neurotoxicity with prolonged or repeated use." Between these two drugs, vancomycin has emerged as the recommended drug for mild and severe forms of CDI [109].

Fidaxomicin is a macrocyclic drug designed to exhibit a narrow antibiotic spectrum mediated through inhibition of the sigma subunit of RNA polymerase. The first Phase III study comparing fidaxomicin to vancomycin enrolled 629 subjects, demonstrating that fidaxomicin was non-inferior to vancomycin with respect to clinical cure rates [111]. Additionally, lower recurrence rates were noted with fidaxomicin, though only with strains that were not NAP-1 (a nomenclature of strains associated with more virulent infections). A more recent study (the EXTEND study) evaluated 364 patients randomly assigned to either vancomycin or extended pulsed fidaxomicin. Fidaxomicin was associated with an 11% improvement in clinical cure at 30 days after the end of treatment compared to vancomycin [112]. Further, fidaxomicin was just as safe as vancomycin, with no difference in treatment-related adverse events. A recent Cochrane Database Systematic Review evaluated 22 studies representing a total of 3215 patients. This study concluded that "moderate quality evidence suggests that vancomycin is superior to metronidazole and fidaxomicin is superior to vancomycin. The differences in effectiveness between these antibiotics were not too large and the advantage of metronidazole is its far lower cost compared to the other two antibiotics" [113].

For a first episode of non-severe CDI, the best available evidence supports the use of either vancomycin 125 mg orally every 6 hours or fidaxomicin 200 mg every 12 hours, either for 10 days. For fulminant cases, the most effective treatment remains the use of oral vancomycin 500 mg every 6 hours. In many instances, patients with fulminant CDI will develop an ileus, potentially decreasing the safety and efficacy of orally administered drugs. Therefore, for patients with fulminant CDI with concerns regarding the appropriateness of orally administered therapies, vancomycin can be administered as a retention enema (500 mg diluted in 100 cc of normal saline every 6 hours) [114], though the quality and strength of clinical data supporting vancomycin enemas is weak. In the setting of fulminant CDI, the Infectious Diseases Society of America also recommends administering 500 mg of parenteral metronidazole every 8 hours in conjunction with oral or rectal vancomycin, as the risks and side effects of a limited course of metronidazole are small in comparison to the risk of progressively worsening CDI.

Surgery for CDI

The incidence of patients who undergo surgery (Figs. 52.1, 52.2, and 52.3) for CDI has been estimated to be as high as 10% [115–117]. Inherent in these estimates are decisions

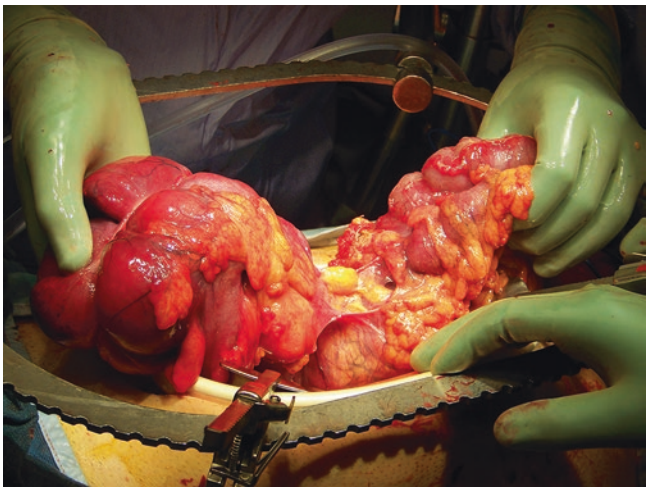

Fig. 52.1 Patient with fulminant CDI with a dilated and thickened colon, with telangiectasias and serositis indicative of severe, transmural inflammation mediated by *C. difficile* toxins

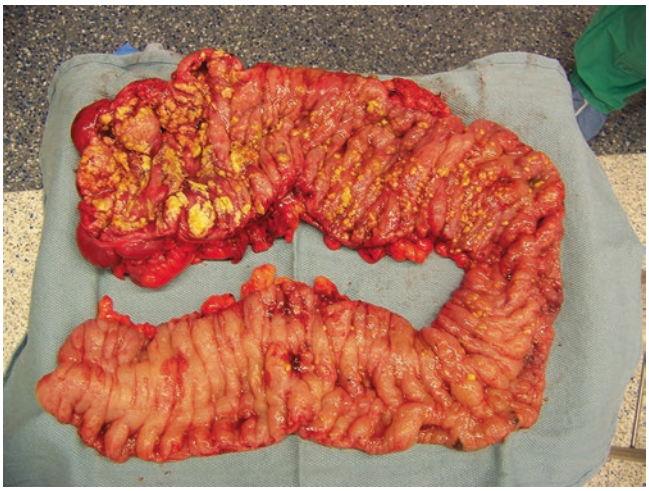

Fig. 52.3 Gross findings of mucosal thickening, inflammation, and pseudopolyps, consistent with severe CDI

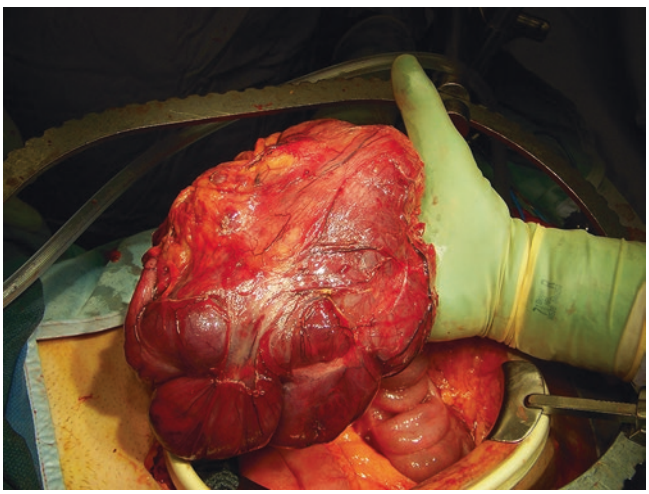

Fig. 52.2 Non-confluent regions of transmural ischemia observed in a patient with fulminant CDI. The combination of bacterial toxins as well as septic shock can produce non-viable large intestine

assessing whether a patient has received maximal medical therapy for CDI with surgery remaining as the only option, as well as selecting which patients might meet this qualification but are not considered to be candidates for surgical intervention. Multiple series indicate that only a small percentage of patients with fulminant CDI will undergo surgery; this suggests that the majority of CDI patients will not develop medically refractory disease severe enough to warrant surgery [115–117]. With the more recent introduction of diversion and colonic lavage [115], if it becomes more commonplace, it may increase the incidence of surgical intervention for CDI as it may be considered a "more survivable" surgery than total colectomy, which serves as the traditional procedure of choice.

There are two systematic reviews that compare the survival benefit of total abdominal colectomy to continued medical therapy in the setting of fulminant CDI, although the particular vantage points by which they evaluate this question differ in important respects. In a review by Bhangu, 31 studies were included in an effort to compare survival rates among patients with fulminant CDI who either underwent colectomy or who continued with medical therapy. In the surgical cohort, 89% of patients underwent a total colectomy, but patients who underwent a partial colectomy were also included. Findings from this review included a statistically significant association between preoperative clinical findings of septic shock and the incidence of postoperative mortality. Of interest, patients who underwent a partial colectomy experienced a 16% reoperation rate with resection of an additional length of colon. This review provided support for a survival benefit for surgical intervention in cases of fulminant CDI, with total colectomy arguably the preferred form of surgery compared to partial colectomy [118].

A second systematic review described outcomes among 510 patients for the purpose of evaluating whether total colectomy was associated with a survival benefit in the setting of medically refractory, fulminant CDI. The pooled odds ratio for mortality was significantly lower in patients undergoing total colectomy (OR = 0.70) [119]. Importantly, this study excluded patients undergoing partial colectomy.

In 2011, Neal described an alternative to total colectomy, involving the construction of a diverting loop ileostomy allowing for intraoperative colonic lavage with 8 liters of polyethylene glycol, followed by postoperative intraluminal vancomycin provided per stoma. In this study, 42 patients with fulminant CDI were treated with intestinal diversion, and their outcomes were compared to a historical control group of patients treated with colectomy and an end ileos-

tomy. The colectomy and diversion populations demonstrated similar preoperative APACHE scores as well as preoperative clinical indices, suggesting similar degrees of CDI severity. The group undergoing diversion was observed to have a significantly lower postoperative mortality (19% versus 50%) and shorter length of surgery, and 83% of the patients undergoing diversion had their surgeries completed laparoscopically [115]. This study provided the first modern description of diversion for life-threatening colitis of an infectious etiology, providing ostensibly superior survival utilizing a much smaller and more tolerable surgery that would also offer a higher likelihood of restoring gut continuity.

Since the study by Neal and colleagues, a number of primarily retrospective studies on diversion for fulminant CDI have been published using either institutional- or population-level data. One such study was undertaken in 2017 by the EAST Multi-Center Trials Committee that collected data from ten participating centers [120]. Certain details, such as the definition of CDI and the form of stool testing used at the participating centers, were not described. Comparing patients who underwent total colectomy to those who underwent diversion, there were no statistically significant differences in median vital sign measurements, white blood cell counts, lactate levels, INRs, or APACHE scores.

There were no differences between the surgical cohorts with respect to postoperative outcomes such as the rate of any complication, pneumonia, acute renal failure, sepsis, and acute respiratory distress syndrome. Just as importantly, there was no difference in rates of overall as well as unplanned reoperations, while ventilator days, ICU, and hospital lengths of stay were also similar between these groups. Unadjusted mortality was comparable between the cohorts (23.8% in the diversion cohort and 33.8% in the colectomy cohort; $p = 0.44$). The authors of this study also performed calculations for what they termed adjusted mortality, which involved an inverse probability of treatment weights propensity score analysis. With this adjustment, mortality was significantly lower among the diversion group (17.2% versus 39.7%; $p = 0.002$) [120].

A 2019 study using data from the Nationwide Inpatient Sample suggests that more surgeons are adopting diversion as the surgery of choice for fulminant CDI. In a retrospective review of this dataset from 2011 to 2015, 2408 patients were identified as undergoing surgery for CDI. Of these, 613 patients (approximately 20% of the study population) underwent diversion with a loop ileostomy; during the study period, the use of this procedure increased from 11% in 2011 to 25% in 2015 [121]. Although important details regarding the severity of CDI and the management of study subjects were not available using this data source, the authors also reported that in-hospital mortality did not significantly differ between these cohorts. One important limitation with the data source used for this study was the inability to identify the selection criteria used for choosing the form of surgical intervention, which has implications for the measured outcomes such as mortality rates.

In summary, patients with severe, complicated/fulminant CDI should be managed in a multidisciplinary fashion. Surgical consultation is recommended when CDI of this severity is first recognized, in an effort to allow for surgical intervention at the earliest appropriate time. CDI is frequently associated with organ failure, including hematologic failure characterized by an exaggerated leukocytosis that is often >30,000 cells/mm. It is critical that patients are euvolemic when assessing severity of sepsis, with a greater emphasis on trending organ function than on absolute cut-off values for laboratory abnormalities. De-escalating or discontinuing antibiotics that are not *C. difficile* targeted is also important; though the data is limited [122], CDI outcomes are worse when the inciting antibiotics are continued while CDI is being treated. While de-escalation of antibiotics is not always appropriate, certain infections (mild bladder infections) that are not life-threatening can have their treatment deferred, while life-threatening CDI is first addressed.

When patients are deemed to be too ill to allow for ongoing medical therapy, or demonstrate continued deterioration, surgery should be recommended for patients who are candidates for surgery. The largest body of evidence supports the use of total abdominal colectomy with an end ileostomy; partial colectomies have an extremely limited utility given a significantly higher incidence of reoperation due to postoperative fulminant CDI. Loop ileostomy has enough data at this juncture to be an acceptable alternative to total colectomy, though as described in a letter to the editor [123] in response to the recent EAST study [120] on loop ileostomy, there are several unanswered questions regarding this newer surgery. In the EAST study, diversion provided no advantage compared to total colectomy in terms of postoperative sepsis, renal failure, acute lung injury, overall mortality, and mortality related to unplanned reoperation. This may indicate that the particular strain of *C. difficile*, which is information frequently missing from the surgical literature on CDI, may influence postoperative outcomes, especially when a diverting stoma is created and an infected colon is left in situ.

Fecal Microbiota Transplant (FMT)

With access to commercially screened and prepared stool from vendors, FMT in either a liquid form for endoscopic or nasogastric application, or in capsule form for oral consumption, is now more readily available for inpatient use than in earlier times when providers had to collect, screen, and prepare stool from donors. FMT is extremely effective for treating recurrent CDI, with cure rates greater than 80% routinely

described [124]. FMT for fulminant CDI has the least exploration of all FMT applications, though the few studies on this topic are promising [125, 126]. One of the challenges with FMT for fulminant CDI is that of disease recrudescence and a measurable mortality from that disease recurrence. The incorporation of vancomycin in addition to FMT for fulminant cases appears to be important for ensuring reliable cure rates [127].

FMT is no longer an experimental therapeutic for outpatients, or inpatients, with CDI. Its cure rates for recurrent forms of CDI are superior to conventional antibiotics, leading some to question whether FMT should be the first intervention to address the recurrence of this infection. Of note, FMT does not currently represent the first-line therapy for a primary case of FMT. The availability of commercial vendors who can provide screened and prepared transplant material has simplified the process of FMT, making it more accessible for clinicians. The use of inpatient FMT for inpatient cases of CDI has increased in recent years, though physicians continue to treat the majority of cases of this infection with conventional antibiotics. At this time, there is insufficient data to recommend the routine use of FMT for the treatment of fulminant CDI; though there are limited numbers of small series that suggest safety and efficacy with FMT, more data in this patient population is required before FMT can be recommended for patients with life-threatening CDI.

References

1. Luo R, Barlam TF. Ten-year review of Clostridium difficile infection in acute care hospitals in the USA. J Hosp Infect. 2005-2014;98:40–3.
2. Pepin J, Valiquette L, Gagnon S, Routhier S, Brazeau I. Outcomes of Clostridium difficile-associated disease treated with metronidazole or vancomycin before and after the emergence of NAP1/027. Am J Gastroenterol. 2007;102:2781–8.
3. Krutova M, Matejkova J, Tkadlec J, Nyc O. Antibiotic profiling of Clostridium difficile ribotype 176--A multidrug resistant relative to C. difficile ribotype 027. Anaerobe. 2015;36:88–90.
4. Falcone M, Tiseo G, Iraci F, Raponi G, Goldoni P, Delle Rose D, Santino I, Carfagna P, Murri R, Fantoni M, Fontana C, Sanguinetti M, Farcomeni A, Antonelli G, Aceti A, Mastroianni C, Andreoni M, Cauda R, Petrosillo N, Venditti M. Risk factors for recurrence in patients with Clostridium difficile infection due to 027 and non-027 ribotypes. Clin Microbiol Infect. 2019;25:474–80.
5. Wilcox MH, Rooney CM. Comparison of the 2010 and 2017 Infectious Diseases Society of America guidelines on the diagnosis and treatment of Clostridium difficile infection. Curr Opin Gastroenterol. 2019;35:20–4.
6. Steele SR, McCormick J, Melton GB, Paquette I, Rivadeneira DE, Stewart D, Buie WD, Rafferty J. Practice parameters for the management of Clostridium difficile infection. Dis Colon Rectum. 2015;58:10–24.
7. Martin M, Zingg W, Knoll E, Wilson C, Dettenkofer M, Group PS. National European guidelines for the prevention of Clostridium difficile infection: a systematic qualitative review. J Hosp Infect. 2014;87:212–9.
8. Madden GR, Poulter MD, Sifri CD. Diagnostic stewardship and the 2017 update of the IDSA-SHEA Clinical Practice Guidelines for Clostridium difficile Infection. Diagnosis (Berl). 2018;5:119–25.
9. Bauer MP, Kuijper EJ, van Dissel JT, European Society of Clinical M, Infectious D. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for Clostridium difficile infection (CDI). Clin Microbiol Infect. 2009;15:1067–79.
10. Camacho-Ortiz A, Gutierrez-Delgado EM, Garcia-Mazcorro JF, Mendoza-Olazaran S, Martinez-Melendez A, Palau-Davila L, Baines SD, Maldonado-Garza H, Garza-Gonzalez E. Randomized clinical trial to evaluate the effect of fecal microbiota transplant for initial Clostridium difficile infection in intestinal microbiome. PLoS One. 2017;12:e0189768.
11. Kuijper EJ, Coignard B, Tull P, difficile ESGfC, States EUM, European Centre for Disease P, Control. Emergence of Clostridium difficile-associated disease in North America and Europe. Clin Microbiol Infect. 2006;12(Suppl 6):2–18.
12. Freeman J, Bauer MP, Baines SD, Corver J, Fawley WN, Goorhuis B, Kuijper EJ, Wilcox MH. The changing epidemiology of Clostridium difficile infections. Clin Microbiol Rev. 2010;23:529–49.
13. Gravel D, Miller M, Simor A, Taylor G, Gardam M, McGeer A, Hutchinson J, Moore D, Kelly S, Boyd D, Mulvey M, Canadian Nosocomial Infection Surveillance P. Health care-associated Clostridium difficile infection in adults admitted to acute care hospitals in Canada: a Canadian Nosocomial Infection Surveillance Program Study. Clin Infect Dis. 2009;48:568–76.
14. Magill SS, Edwards JR, Beldavs ZG, Dumyati G, Janelle SJ, Kainer MA, Lynfield R, Nadle J, Neuhauser MM, Ray SM, Richards K, Rodriguez R, Thompson DL, Fridkin SK, Emerging Infections Program Healthcare-Associated I, Antimicrobial Use Prevalence Survey T. Prevalence of antimicrobial use in US acute care hospitals, May-September 2011. JAMA. 2014;312:1438–46.
15. Miller BA, Chen LF, Sexton DJ, Anderson DJ. Comparison of the burdens of hospital-onset, healthcare facility-associated Clostridium difficile Infection and of healthcare-associated infection due to methicillin-resistant Staphylococcus aureus in community hospitals. Infect Control Hosp Epidemiol. 2011;32:387–90.
16. Gupta A, Khanna S. Community-acquired Clostridium difficile infection: an increasing public health threat. Infect Drug Resist. 2014;7:63–72.
17. Warny M, Pepin J, Fang A, Killgore G, Thompson A, Brazier J, Frost E, McDonald LC. Toxin production by an emerging strain of Clostridium difficile associated with outbreaks of severe disease in North America and Europe. Lancet. 2005;366:1079–84.
18. Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, Bourgault AM, Nguyen T, Frenette C, Kelly M, Vibien A, Brassard P, Fenn S, Dewar K, Hudson TJ, Horn R, Rene P, Monczak Y, Dascal A. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. N Engl J Med. 2005;353:2442–9.
19. Nanwa N, Kendzerska T, Krahn M, Kwong JC, Daneman N, Witteman W, Mittmann N, Cadarette SM, Rosella L, Sander B. The economic impact of Clostridium difficile infection: a systematic review. Am J Gastroenterol. 2015;110:511–9.
20. McGlone SM, Bailey RR, Zimmer SM, Popovich MJ, Tian Y, Ufberg P, Muder RR, Lee BY. The economic burden of Clostridium difficile. Clin Microbiol Infect. 2012;18:282–9.
21. Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, McFarland LV, Mellow M, Zuckerbraun BS. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol. 2013;108:478–98; quiz 99.

22. Kim HH, Kim YS, Han DS, Kim YH, Kim WH, Kim JS, Kim H, Kim HS, Park YS, Song HJ, Shin SJ, Yang SK, Ye BD, Eun CS, Lee KM, Lee SH, Jang BI, Jung SA, Cheon JH, Choi CH, Huh K, Diseases IBDSGotKAftSoI. Clinical differences in Clostridium difficile infection based on age: a multicenter study. Scand J Infect Dis. 2008;46:46–51.
23. Lee HC, Kim KO, Jeong YH, Lee SH, Jang BI, Kim TN. Clinical outcomes in hospitalized patients with Clostridium difficile infection by age group. Korean J Gastroenterol. 2016;67:81–6.
24. Dharmarajan T, Sipalay M, Shyamsundar R, Norkus E, Pitchumoni C. Co-morbidity, not age predicts adverse outcome in clostridium difficile colitis. World J Gastroenterol. 2000;6:198–201.
25. Louie TJ, Miller MA, Crook DW, Lentnek A, Bernard L, High KP, Shue YK, Gorbach SL. Effect of age on treatment outcomes in Clostridium difficile infection. J Am Geriatr Soc. 2013;61:222–30.
26. Bernatz JT, Safdar N, Hetzel S, Anderson PA. Antibiotic overuse is a major risk factor for Clostridium difficile infection in surgical patients. Infect Control Hosp Epidemiol. 2017;38:1254–7.
27. Balch A, Wendelboe AM, Vesely SK, Bratzler DW. Antibiotic prophylaxis for surgical site infections as a risk factor for infection with Clostridium difficile. PLoS One. 2017;12:e0179117.
28. Vardakas KZ, Trigkidis KK, Boukouvala E, Falagas ME. Clostridium difficile infection following systemic antibiotic administration in randomised controlled trials: a systematic review and meta-analysis. Int J Antimicrob Agents. 2016;48:1–10.
29. Deshpande A, Pant C, Jain A, Fraser TG, Rolston DD. Do fluoroquinolones predispose patients to Clostridium difficile associated disease? A review of the evidence. Curr Med Res Opin. 2008;24:329–33.
30. Cruz-Rodriguez NC, Hernández-Garcia R, Salinas-Caballero AG, Perez-Rodriguez E, Garza-Gonzalez E, Camacho-Ortiz A. The effect of pharmacy restriction of clindamycin on Clostridium difficile infection rates in an orthopedics ward. Am J Infect Control. 2014;42:e71–3.
31. Lee S, Prasad P, Lin M, Garritson S, Nichols A, Liu C. Ertapenem prophylaxis associated with an increased risk of Clostridium difficile infection among surgical patients. Infect Control Hosp Epidemiol. 2015;36:1351–4.
32. McCusker ME, Harris AD, Perencevich E, Roghmann MC. Fluoroquinolone use and Clostridium difficile-associated diarrhea. Emerg Infect Dis. 2003;9:730–3.
33. McFarl, LV, Clarridge JE, Beneda HW, Raugi GJ. Fluoroquinolone use and risk factors for Clostridium difficile-associated disease within a Veterans Administration health care system. Clin Infect Dis. 2007;45:1141–51.
34. Bruns AH, Oosterheert JJ, Kuijper EJ, Lammers JW, Thijsen S, Troelstra A, Hoepelman AI. Impact of different empirical antibiotic treatment regimens for community-acquired pneumonia on the emergence of Clostridium difficile. J Antimicrob Chemother. 2010 Nov;65(11):2464–71.
35. Slimings C, Armstrong P, Beckingham WD, Bull AL, Hall L, Kennedy KJ, Marquess J, McCann R, Menzies A, Mitchell BG, Richards MJ, Smollen PC, Tracey L, Wilkinson IJ, Wilson FL, Worth LJ, Riley TV. Increasing incidence of Clostridium difficile infection, Australia, 2011-2012. Med J Aust. 2014;200:272–6.
36. Reeves AE, Koenigsknecht MJ, Bergin IL, Young VB. Suppression of Clostridium difficile in the gastrointestinal tracts of germ-free mice inoculated with a murine isolate from the family Lachnospiraceae. Infect Immun. 2012;80:3786–94.
37. Goldenberg JZ, Ma SS, Saxton JD, Martzen MR, vik PO, Thorlund K, Guyatt GH, Johnston BC. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database Syst Rev:CD006095.
38. Johnson S, Maziade PJ, McFarl, LV, Trick W, Donskey C, Currie B, Low DE, Goldstein EJ. Is primary prevention of Clostridium difficile infection possible with specific probiotics? Int J Infect Dis;16:e786–92.
39. Pattani R, Palda VA, Hwang SW, Shah PS. Probiotics for the prevention of antibiotic-associated diarrhea and Clostridium difficile infection among hospitalized patients: systematic review and meta-analysis. Open Med. 2013;7:e56–67.
40. Dubberke ER, Reske KA, Noble-Wang J, Thompson A, Killgore G, Mayfield J, Camins B, Woeltje K, McDonald JR, McDonald LC, Fraser VJ. Prevalence of Clostridium difficile environmental contamination and strain variability in multiple health care facilities. Am J Infect Control. 2007;35:315–8.
41. Ahyow LC, Lambert PC, Jenkins DR, Neal KR, Tobin M. Bed occupancy rates and hospital-acquired Clostridium difficile infection: a cohort study. Infect Control Hosp Epidemiol. 2013;34:1062–9.
42. Stuart RL, Marshall C, Harrington G, Sasko L, McLaws ML, Ferguson J. ASID/ACIPC position statement – Infection control for patients with Clostridium difficile infection in healthcare facilities. Infect Dis Health. 2019;24:32–43.
43. Ray AJ, Deshp, e A, Fertelli D, Sitzlar BM, Thota P, Sankar CT, Jencson AL, Cadnum JL, Salata RA, Watkins RR, Sethi AK, Carling PC, Wilson BM, Donskey CJ. A Multicenter Randomized Trial to Determine the Effect of an Environmental Disinfection Intervention on the Incidence of Healthcare-Associated Clostridium difficile Infection. Infect Control Hosp Epidemiol. 2017;38:777–83.
44. Baur D, Gladstone BP, Burkert F, Carrara E, Foschi F, Dobele S, Tacconelli E. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and Clostridium difficile infection: a systematic review and meta-analysis. Lancet Infect Dis. 2017;17:990–1001.
45. Brown KA, Daneman N, Jones M, Nechodom K, Stevens V, Adler FR, Goetz MB, Mayer J, Samore M. The Drivers of Acute and Long-term Care Clostridium difficile Infection Rates: A Retrospective Multilevel Cohort Study of 251 Facilities. Clin Infect Dis. 2014;65:1282–8.
46. Aquina CT, Probst CP, Becerra AZ, Hensley BJ, Iannuzzi JC, Noyes K, Monson JR, Fleming FJ. High Variability in Nosocomial Clostridium difficile Infection Rates Across Hospitals After Colorectal Resection. Dis Colon Rectum. 2017;59:323–31.
47. Di Bella S, Friedrich AW, Garcia-Almodovar E, Gallone MS, Taglietti F, Topino S, Galati V, Johnson E, D'Arezzo S, Petrosillo N. Clostridium difficile infection among hospitalized HIV-infected individuals: epidemiology and risk factors: results from a case-control study (2002–2013). BMC Infect Dis. 2015;15:194.
48. Barbut F, Meynard JL, Guiguet M, Avesani V, Bochet MV, Meyohas MC, Delmee M, Tilleul P, Frottier J, Petit JC. Clostridium difficile-associated diarrhea in HIV-infected patients: epidemiology and risk factors. J Acquir Immune Defic Syndr Hum Retrovirol. 1997;16:176–81.
49. Imlay H, Kaul D, Rao K. Risk factors for Clostridium difficile infection in HIV-infected patients. SAGE Open Med. 2016;4:2050312116684295.
50. Hutin Y, Molina JM, Casin I, Daix V, Sednaoui P, Welker Y, Lagrange P, Decazes JM, Modai J. Risk factors for Clostridium difficile-associated diarrhoea in HIV-infected patients. AIDS. 1993;7:1441–7.
51. Haines CF, Moore RD, Bartlett JG, Sears CL, Cosgrove SE, Carroll K, Gebo KA. Clostridium difficile in a HIV-infected cohort: incidence, risk factors, and clinical outcomes. AIDS. 2013;27:2799–807.
52. Abughanimeh O, Qasrawi A, Kaddourah O, Al Momani L, Abu GM. Clostridium difficile infection in oncology patients: epidemiology, pathophysiology, risk factors, diagnosis, and treatment. Hosp Pract. 1995;46:266–77.

53. Boutros M, Al-Shaibi M, Chan G, Cantarovich M, Rahme E, Paraskevas S, Deschenes M, Ghali P, Wong P, Fern, ez M, Giannetti N, Cecere R, Hassanain M, Chaudhury P, Metrakos P, Tchervenkov J, Barkun JS. Clostridium difficile colitis: increasing incidence, risk factors, and outcomes in solid organ transplant recipients. Transplantation. 2013;93:1051–7.
54. Honda H, Dubberke ER. Clostridium difficile infection in solid organ transplant recipients. Curr Opin Infect Dis. 2014;27:336–41.
55. Aldrete SD, Kraft CS, Magee MJ, Chan A, Hutcherson D, Langston AA, Greenwell BI, Burd EM, Friedman-Moraco R. Risk factors and epidemiology of Clostridium difficile infection in hematopoietic stem cell transplant recipients during the peritransplant period. Transpl Infect Dis. 2017;19(1).
56. Alonso CD, Dufresne SF, Hanna DB, Labbe AC, Treadway SB, Neofytos D, Belanger S, Huff CA, Laverdiere M, Marr KA. Clostridium difficile infection after adult autologous stem cell transplantation: a multicenter study of epidemiology and risk factors. Biol Blood Marrow Transplant. 2013;19:1502–8.
57. Alonso CD, Kamboj M. Clostridium difficile Infection (CDI) in Solid Organ and Hematopoietic Stem Cell Transplant Recipients. Curr Infect Dis Rep. 2014;16:414.
58. Ananthakrishnan AN, Binion DG. Impact of Clostridium difficile on inflammatory bowel disease. Expert Rev Gastroenterol Hepatol. 2010;4:589–600.
59. Bossuyt P, Verhaegen J, Van Assche G, Rutgeerts P, Vermeire S. Increasing incidence of Clostridium difficile-associated diarrhea in inflammatory bowel disease. J Crohns Colitis. 2009;3:4–7.
60. Ananthakrishnan AN, Oxford EC, Nguyen DD, Sauk J, Yajnik V, Xavier RJ. Genetic risk factors for Clostridium difficile infection in ulcerative colitis, Aliment Pharmacol Ther. 2013;38:522–30.
61. Ananthakrishnan AN, Guzman-Perez R, Gainer V, Cai T, Churchill S, Kohane I, Plenge RM, Murphy S. Predictors of severe outcomes associated with Clostridium difficile infection in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2012;35:789–95.
62. Balram B, Battat R, Al-Khoury A, D'Aoust J, Afif W, Bitton A, Lakatos PL, Bessissow T. Risk factors associated with Clostridium difficile infection in inflammatory bowel disease: a systematic review and meta-analysis. J Crohns Colitis. 2019;13:27–38.
63. Schneeweiss S, Korzenik J, Solomon DH, Canning C, Lee J, Bressler B. Infliximab and other immunomodulating drugs in patients with inflammatory bowel disease and the risk of serious bacterial infections. Aliment Pharmacol Ther. 2009;30:253–64.
64. Horton HA, Dezfoli S, Berel D, Hirsch J, Ippoliti A, McGovern D, Kaur M, Shih D, Dubinsky M, Targan SR, Fleshner P, Vasiliauskas EA, Grein J, Murthy R, Melmed GY. Antibiotics for treatment of Clostridium difficile infection in hospitalized patients with inflammatory bowel disease. Antimicrob Agents Chemother. 2014;58:5054–9.
65. Ananthakrishnan AN, McGinley EL, Binion DG. Excess hospitalisation burden associated with Clostridium difficile in patients with inflammatory bowel disease. Gut. 2008;57:205–10.
66. Nichols RL, Condon RE, DiSanto AR. Preoperative bowel preparation. Erythromycin base serum and fecal levels following oral administration. Arch Surg. 1977;112:1493–6.
67. Al-Mazrou AM, Hyde LZ, Suradkar K, Kiran RP. Effect of inclusion of oral antibiotics with mechanical bowel preparation on the risk of Clostridium Difficile infection after colectomy. J Gastrointest Surg. 2018;22:1968–75.
68. Kiran RP, Murray AC, Chiuzan C, Estrada D, Forde K. Combined preoperative mechanical bowel preparation with oral antibiotics significantly reduces surgical site infection, anastomotic leak, and ileus after colorectal surgery. Ann Surg. 2015;262:416–25; discussion 23–5
69. Murray AC, Kiran RP. Bowel preparation: are antibiotics necessary for colorectal surgery? Adv Surg. 2016;50:49–66.
70. Murray AC, Kiran RP. Benefit of mechanical bowel preparation prior to elective colorectal surgery: current insights. Langenbeck's Arch Surg. 2016;401:573–80.
71. Midura EF, Jung AD, Hanseman DJ, Dhar V, Shah SA, Rafferty JF, Davis BR, Paquette IM. Combination oral and mechanical bowel preparations decreases complications in both right and left colectomy. Surgery. 2018;163:528–34.
72. Atkinson SJ, Swenson BR, Hanseman DJ, Midura EF, Davis BR, Rafferty JF, Abbott DE, Shah SA, Paquette IM. In the absence of a mechanical bowel prep, does the addition of pre-operative oral antibiotics to parental antibiotics decrease the incidence of surgical site infection after elective segmental colectomy? Surg Infect. 2015;16:728–32.
73. Gaines S, Shao C, Hyman N, Alverdy JC. Gut microbiome influences on anastomotic leak and recurrence rates following colorectal cancer surgery. Br J Surg. 2018;105:e131–e41.
74. Alverdy JC, Hyoju SK, Weigerinck M, Gilbert JA. The gut microbiome and the mechanism of surgical infection. Br J Surg. 2017;104:e14–23.
75. Morris AM, Jobe BA, Stoney M, Sheppard BC, Deveney CW, Deveney KE. Clostridium difficile colitis: an increasingly aggressive iatrogenic disease? Arch Surg. 2002;137:1096–100.
76. Stewart DB, Hegarty JP. Correlation between virulence gene expression and proton pump inhibitors and ambient pH in Clostridium difficile: results of an in vitro study. J Med Microbiol. 2013;62:1517–23.
77. Janarthanan S, Ditah I, Adler DG, Ehrinpreis MN. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. Am J Gastroenterol. 2012;107:1001–10.
78. Tleyjeh IM, Bin Abdulhak AA, Riaz M, Alasmari FA, Garbati MA, AlGhamdi M, Khan AR, Al Tannir M, Erwin PJ, Ibrahim T, Allehibi A, Baddour LM, Sutton AJ. Association between proton pump inhibitor therapy and clostridium difficile infection: a contemporary systematic review and meta-analysis. PLoS One. 2012;7:e50836.
79. Kwok CS, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, Loke YK. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. Am J Gastroenterol. 2012;107:1011–9.
80. Garey KW, Sethi S, Yadav Y, DuPont HL. Meta-analysis to assess risk factors for recurrent Clostridium difficile infection. J Hosp Infect. 2008;70:298–304.
81. Chitnis AS, Holzbauer SM, Belflower RM, Winston LG, Bamberg WM, Lyons C, Farley MM, Dumyati GK, Wilson LE, Beldavs ZG, Dunn JR, Gould LH, MacCannell DR, Gerding DN, McDonald LC, Lessa FC. Epidemiology of community-associated Clostridium difficile infection, 2009 through 2011. JAMA Intern Med. 2013;173:1359–67.
82. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Overutilization of proton pump inhibitors: a review of cost-effectiveness and risk [corrected]. Am J Gastroenterol. 2009;104(Suppl 2):S27–32.
83. The Lancet Infectious D. C difficile-a rose by any other name. Lancet Infect Dis. 2019;19:449.
84. Lawson PA, Rainey FA. Proposal to restrict the genus Clostridium Prazmowski to Clostridium butyricum and related species. Int J Syst Evol Microbiol. 2016;66:1009–16.
85. Dohrmann AB, Walz M, Lowen A, Tebbe CC. Clostridium cluster I and their pathogenic members in a full-scale operating biogas plant. Appl Microbiol Biotechnol. 2015;99:3585–98.
86. Monot M, Eckert C, Lemire A, Hamiot A, Dubois T, Tessier C, Dumoulard B, Hamel B, Petit A, Lalande V, Ma L, Bouchier C, Barbut F, Dupuy B. Clostridium difficile: new insights into the evolution of the pathogenicity locus. Sci Rep. 2015;5:15023.
87. Aktories K, Schwan C, Jank T. Clostridium difficile toxin biology. Annu Rev Microbiol. 2017;71:281–307.

88. El Meouche I, Peltier J, Monot M, Soutourina O, Pestel-Caron M, Dupuy B, Pons JL. Characterization of the SigD regulon of C. difficile and its positive control of toxin production through the regulation of tcdR. PLoS One. 2013;8:e83748.
89. Popoff MR, Bouvet P. Genetic characteristics of toxigenic clostridia and toxin gene evolution. Toxicon. 2013;75:63–89.
90. Fortier LC. The contribution of bacteriophages to the biology and virulence of pathogenic clostridia. Adv Appl Microbiol. 2017;101:169–200.
91. Chandrasekaran R, Lacy DB. The role of toxins in Clostridium difficile infection. FEMS Microbiol Rev. 2017;41:723–50.
92. Jank T, Giesemann T, Aktories K. Rho-glucosylating Clostridium difficile toxins A and B: new insights into structure and function. Glycobiology. 2007;17:15R–22R.
93. Holbourn KP, Shone CC, Acharya KR. A family of killer toxins. Exploring the mechanism of ADP-ribosylating toxins. FEBS J. 2006;273:4579–93.
94. Schwan C, Stecher B, Tzivelekidis T, van Ham M, Rohde M, Hardt WD, Wehland J, Aktories K. Clostridium difficile toxin CDT induces formation of microtubule-based protrusions and increases adherence of bacteria. PLoS Pathog. 2009;5:e1000626.
95. Carter GP, Lyras D, Allen DL, Mackin KE, Howarth PM, O'Connor JR, Rood JI. Binary toxin production in Clostridium difficile is regulated by CdtR, a LytTR family response regulator. J Bacteriol. 2007;189:7290–301.
96. Gurtler V, Grando D. New opportunities for improved ribotyping of C. difficile clinical isolates by exploring their genomes. J Microbiol Methods. 2013;93:257–72.
97. Janezic S. Direct PCR-Ribotyping of Clostridium difficile. Methods Mol Biol. 2016;1476:15–21.
98. Peretz A, Tkhawkho L, Pastukh N, Brodsky D, Halevi CN, Nitzan O. Correlation between fecal calprotectin levels, disease severity and the hypervirulent ribotype 027 strain in patients with Clostridium difficile infection. BMC Infect Dis. 2016;16:309.
99. Sirard S, Valiquette L, Fortier LC. Lack of association between clinical outcome of Clostridium difficile infections, strain type, and virulence-associated phenotypes. J Clin Microbiol. 2011;49:4040–6.
100. Archbald-Pannone LR, Boone JH, Carman RJ, Lyerly DM, Guerrant RL. Clostridium difficile ribotype 027 is most prevalent among inpatients admitted from long-term care facilities. J Hosp Infect. 2014;88:218–21.
101. Yakob L, Riley TV, Paterson DL, Marquess J, Magalhaes RJ, Furuya-Kanamori L, Clements AC. Mechanisms of hypervirulent Clostridium difficile ribotype 027 displacement of endemic strains: an epidemiological model. Sci Rep. 2015;5:12666.
102. Gerding DN, Johnson S, Rupnik M, Aktories K. Clostridium difficile binary toxin CDT: mechanism, epidemiology, and potential clinical importance. Gut Microbes. 2014;5:15–27.
103. Stabler RA, He M, Dawson L, Martin M, Valiente E, Corton C, Lawley TD, Sebaihia M, Quail MA, Rose G, Gerding DN, Gibert M, Popoff MR, Parkhill J, Dougan G, Wren BW. Comparative genome and phenotypic analysis of Clostridium difficile 027 strains provides insight into the evolution of a hypervirulent bacterium. Genome Biol. 2009;10:R102.
104. Wu YC, Lee JJ, Tsai BY, Liu YF, Chen CM, Tien N, Tsai PJ, Chen TH. Potentially hypervirulent Clostridium difficile PCR ribotype 078 lineage isolates in pigs and possible implications for humans in Taiwan. Int J Med Microbiol. 2016;306:115–22.
105. Stewart DB, Sr., Wright JR, Fowler M, McLimans CJ, Tokarev V, Amaniera I, Baker O, Wong HT, Brabec J, Drucker R, Lamendella R. Integrated meta-omics reveals a fungusassociated bacteriome and distinct functional pathways in clostridioides difficile infection. mSphere. 2019 Aug 28;4(4):e00454–19.
106. Nissle K, Kopf D, Rosler A. Asymptomatic and yet C. difficile-toxin positive? Prevalence and risk factors of carriers of toxigenic Clostridium difficile among geriatric in-patients. BMC Geriatr. 2016;16:185.
107. Crobach MJT, Vernon JJ, Loo VG, Kong LY, Pechine S, Wilcox MH, Kuijper EJ. Understanding Clostridium difficile Colonization. Clin Microbiol Rev. 2018 Mar 14;31(2):e00021–17.
108. Burnham CA, Carroll KC. Diagnosis of Clostridium difficile infection: an ongoing conundrum for clinicians and for clinical laboratories. Clin Microbiol Rev. 2013;26:604–30.
109. McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, Dubberke ER, Garey KW, Gould CV, Kelly C, Loo V, Shaklee Sammons J, Sandora TJ, Wilcox MH. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66:987–94.
110. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. Clin Infect Dis. 2007;45:302–7.
111. Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, Gorbach S, Sears P, Shue YK, Group OPTCS. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med. 2011;364:422–31.
112. Guery B, Menichetti F, Anttila VJ, Adomakoh N, Aguado JM, Bisnauthsing K, Georgopali A, Goldenberg SD, Karas A, Kazeem G, Longshaw C, Palacios-Fabrega JA, Cornely OA, Vehreschild M, Group ECS. Extended-pulsed fidaxomicin versus vancomycin for Clostridium difficile infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial. Lancet Infect Dis. 2018;18:296–307.
113. Nelson RL, Suda KJ, Evans CT. Antibiotic treatment for Clostridium difficile-associated diarrhoea in adults. Cochrane Database Syst Rev. 2017;3:CD004610.
114. Malamood M, Nellis E, Ehrlich AC, Friedenberg FK. Vancomycin enemas as adjunctive therapy for Clostridium difficile infection. J Clin Med Res. 2015;7:422–7.
115. Neal MD, Alverdy JC, Hall DE, Simmons RL, Zuckerbraun BS. Diverting loop ileostomy and colonic lavage: an alternative to total abdominal colectomy for the treatment of severe, complicated Clostridium difficile associated disease. Ann Surg. 2011;254:423–7; discussion 7–9
116. Dallal RM, Harbrecht BG, Boujoukas AJ, Sirio CA, Farkas LM, Lee KK, Simmons RL. Fulminant Clostridium difficile: an underappreciated and increasing cause of death and complications. Ann Surg. 2002;235:363–72.
117. Sailhamer EA, Carson K, Chang Y, Zacharias N, Spaniolas K, Tabbara M, Alam HB, DeMoya MA, Velmahos GC. Fulminant Clostridium difficile colitis: patterns of care and predictors of mortality. Arch Surg. 2009;144:433–9; discussion 9–40
118. Bhangu A, Nepogodiev D, Gupta A, Torrance A, Singh P, Midl W, Research C. Systematic review and meta-analysis of outcomes following emergency surgery for Clostridium difficile colitis. Br J Surg. 2012;99:1501–13.
119. Stewart DB, Hollenbeak CS, Wilson MZ. Is colectomy for fulminant Clostridium difficile colitis life saving? A systematic review. Colorectal Dis. 2013;15:798–804.
120. Ferrada P, Callcut R, Zielinski MD, Bruns B, Yeh DD, Zakrison TL, Meizoso JP, Sarani B, Catalano RD, Kim P, Plant V, Pasley A, Dultz LA, Choudhry AJ, Haut ER, Committee EM-IT. Loop ileostomy versus total colectomy as surgical treatment for Clostridium difficile-associated disease: an Eastern Association for the Surgery of Trauma multicenter trial. J Trauma Acute Care Surg. 83:36–40.

121. Juo YY, Sanaiha Y, Jabaji Z, Benharash P. Trends in diverting loop ileostomy vs total abdominal colectomy as surgical management for Clostridium Difficile colitis. JAMA Surg. 2019.
122. Appaneal HJ, Caffrey AR, Beganovic M, Avramovic S, LaPlante KL. Predictors of Clostridioides difficile recurrence across a national cohort of veterans in outpatient, acute, and longtermcare settings. Am J Health Syst Pharm. 2019 Apr 17;76(9):581–90.
123. Stewart DB. Loop ileostomy for Clostridium difficile infection: know thy enemy. J Trauma Acute Care Surg. 83:1214–5.
124. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kuijper EJ, Bartelsman JF, Tijssen JG, Speelman P, Dijkgraaf MG, Keller JJ. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med. 2013;368:407–15.
125. Zainah H, Hassan M, Shiekh-Sroujieh L, Hassan S, Alangaden G, Ramesh M. Intestinal microbiota transplantation, a simple and effective treatment for severe and refractory Clostridium difficile infection. Dig Dis Sci. 2015;60:181–5.
126. Weingarden AR, Hamilton MJ, Sadowsky MJ, Khoruts A. Resolution of severe Clostridium difficile infection following sequential fecal microbiota transplantation. J Clin Gastroenterol. 2013;47:735–7.
127. Fischer M, Sipe BW, Rogers NA, Cook GK, Robb BW, Vuppalanchi R, Rex DK. Faecal microbiota transplantation plus selected use of vancomycin for severe-complicated Clostridium difficile infection: description of a protocol with high success rate. Aliment Pharmacol Ther. 2015;42:470–6.

Radiation, Microscopic, and Ischemic Colitis

53

Jamie A. Cannon and Gregory D. Kennedy

Key Concepts

- Radiation injury to the colon and rectum can cause significant morbidity, and effects can be seen many years after initial exposure.
- Surgery should be considered the last resort for radiation injury as complications are frequent. Surgical treatment should be individualized and based on symptoms and clinical context.
- Microscopic colitis is a rare cause of non-bloody diarrhea characterized by nonspecific inflammation in the lamina propria with infiltrates of lymphocytes and plasma cells.
- Budesonide is the only evidence-based treatment of microscopic colitis.
- Ischemic colitis results from disruption of blood flow from small vessels and is distinct from mesenteric ischemia. The treatment of ischemic colitis is based on symptom management and patient optimization.
- Long-term complications of ischemic colitis include strictures and chronic ischemia which may be indications for elective surgery in an otherwise medically optimized patient.

Radiation Colitis

Radiation therapy is routinely used to treat anal, cervical, prostate, and rectal cancers and less often bladder and endometrial cancers. An estimated 400,000 patients are diagnosed annually with these conditions, so encountering patients with previous pelvic radiation is routine in any colorectal surgery practice. While radiation is quite effective in treating these malignancies, managing the consequences of radiation treatment has become an important part of survivorship.

Definition and Manifestation

Radiation colitis or proctitis is classified as acute or chronic. Acute colitis occurs during therapy or within 6 months of completion of therapy. The vast majority of patients undergoing pelvic radiation will experience some side effects during the course of their treatment. Acute symptoms are related to radiation-induced cell loss of the rapidly turning over superficial rectal mucosa. Over time, as cellular turnover replaces the damaged epithelium, symptoms resolve. These treatment-related side effects are seen in between 50 and 75% of patients and manifested by diarrhea, mucous discharge, cramping, tenesmus, urgency, incontinence, and pain. Diarrhea is the most common symptom [1].

Chronic radiation colitis is defined as symptoms from the acute phase that persist beyond 6 months or development of symptoms after a latent period. The most common time for radiation colitis to present is between 8 and 12 months after cessation of treatment [2]. Hemorrhagic proctitis is the most common manifestation. It can range from mild bleeding to life-threatening hemorrhage. This is a result of microvascular changes that lead to ischemia, fibrosis, and bleeding. Other symptoms of chronic radiation colitis are similar to those of acute colitis and include pain, urgency, incontinence, mucous discharge, and tenesmus. Chronic colitis can also manifest with strictures and rarely perforations or fistulas. Unfortunately, unlike acute colitis, chronic colitis is not a condition that improves over time. Chronic hemorrhagic proctitis has been diagnosed as late as 30 years after radiation treatment. Several grading systems exist, with the most commonly used one developed by the Radiation Therapy Oncology Group (RTOG) (Table 53.1).

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Table 53.1 Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer Radiation Morbidity Scoring Criteria

Grades	Acute	Late
Grade 1	Increased frequency, change in bowel habits, or rectal discomfort not requiring medications or analgesics	Mild diarrhea, mild cramping, bowel movement five times daily, slight rectal discharge, or bleeding
Grade 2	Diarrhea requiring parasympatholytic drugs, mucous discharge not necessitating sanitary pads, abdominal or rectal pain requiring analgesics	Moderate diarrhea or colic, bowel movement > 5 times daily, excessive rectal mucus, or intermittent bleeding
Grade 3	Diarrhea requiring parenteral support, severe bloody or mucous discharge necessitating sanitary pads, abdominal distention	Obstruction or bleeding requiring surgery
Grade 4	Obstruction, fistula, perforation, bleeding requiring transfusion, abdominal pain, or tenesmus requiring tube decompression or diversion	Necrosis, perforation, or fistula

Etiology and Risk Factors

The incidence and severity of chronic radiation colitis vary with the effective dose of radiation therapy administered and are influenced by patient-related factors. The incidence of chronic radiation colitis has been previously described as high as 30% [3]. Improvement in the delivery of radiation therapy places estimates in the current era from 1 to 5% [4]. Patients with preexisting inflammation, such as inflammatory bowel disease, are at increased risk for the development of chronic radiation colitis. Risk factors for vascular disease, such as diabetes, hypertension, nicotine use, peripheral vascular disease, adjuvant chemotherapy, and previous surgery, also predispose patients to radiation-associated vascular injury [5].

The likelihood of developing radiation colitis is dose related. Standard long-course radiation treatment for rectal cancer is delivery of 45–54 Gray (Gy). In contrast, treatment for cervical cancer involves administration of 45–50 Gy with external beam therapy, followed by a brachytherapy dose that focally escalates to 90 Gy. Doses less than 45 Gy rarely lead to chronic radiation colitis, while doses greater than 70 lead to significant injury [6]. While fistulization is a rare complication of radiation treatment, rectovaginal fistulas are most often seen after treatment of cervical cancer and rectourethral fistulas after treatment of prostate cancer. Such complications are unusual with standard rectal cancer treatment.

Prevention

The primary method of prevention is to limit radiation exposure to adjacent tissues. Classic methods of protecting uninvolved bowel include changing patient position during treatment and administering radiation when the patient has a full bladder to displace bowel out of the pelvis. Techniques in administration of the external beam continue to advance which has decreased the incidence of radiation colitis [7]. CT-based planning has helped radiation oncologists move the dose away from uninvolved bowel. Complex methods of treatment delivery, such as intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT), use a combination of multiple beams of varying intensities and real-time organ motion managements to precisely deliver the external beam to the target tissue.

Both medications as well as surgical maneuvers have been proposed to protect uninvolved bowel during the administration of radiation, but are not routinely utilized. Sucralfate enemas, short-chain fatty acids, and probiotics have all been studied without demonstration of a clear benefit [8, 9, 10]. Nascimento demonstrated a reduction in symptoms when glutamine enemas were administered during treatment [11], but Vidal-Casriego did not find the same benefit [12]. The most promising agent appears to be amifostine, an oxygen free radical scavenger. Amifostine is thought to protect normal tissue and has shown some success in reduction of radiation-related symptoms [13, 14], but is not used in routine practice. Surgical prevention, by placing either mesh or omentum to exclude the small bowel from the pelvis, has been described, but has not been shown to decrease the incidence of radiation colitis or enteritis. If postoperative treatment is expected, exclusion of the small bowel can be considered if anatomically appropriate. Preoperative laparotomy for this sole purpose is not recommended.

Diagnosis

There are no specific laboratory studies used to diagnose radiation colitis. Those with severe hemorrhagic colitis may present with significant anemia, and patients presenting with obstruction from a stricture may have associated metabolic disturbances. Imaging studies are also nonspecific. Thickened, inflamed bowel may be present but is not specific to radiation colitis, and not seen when the damaged tissue is limited to the mucosa. Complications associated with radiation colitis may be seen on CT, such as obstruction, perforation, or fistula.

Clinical history and endoscopic appearance are the mainstays of diagnosis. The classic endoscopic appearance

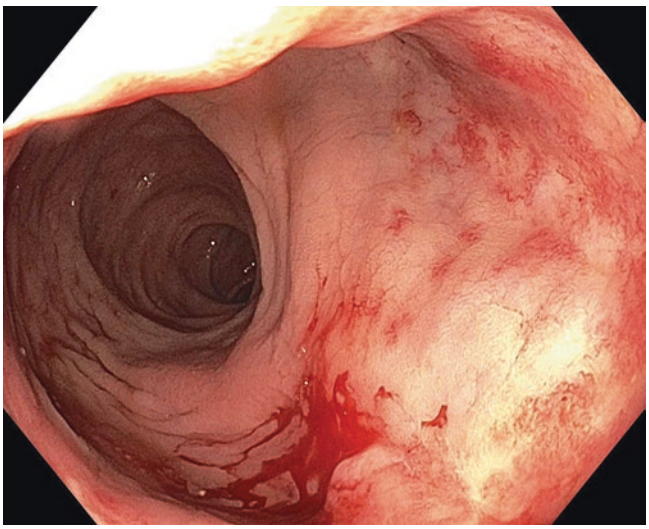

Fig. 53.1 Telangiectasias and easy friability associated with radiation proctitis

includes pallor with telangectasias and easy friability (Fig. 53.1) [15]. Biopsies can be performed to rule out malignancy and confirm the diagnosis. However, if the diagnosis is not in question, biopsies are not necessary and have been demonstrated to increase the risk of fistula development [16].

Mucosal biopsies of acute radiation colitis demonstrate inflammatory changes, including eosinophilic infiltration of the submucosa, crypt atrophy, and crypt abscesses. In the chronic phase, the vascular component becomes apparent, with small vessel vasculopathy that is not seen in the acute phase [17]. There is obliterative endarteritis with ulceration and fibrous induration [18], focal distortion of small arterioles, and vascular intimal fibrosis without inflammation.

Management

Medical

Medical management focuses on control of pain, mucous discharge, tenesmus, and rectal hemorrhage. Multiple anti-inflammatory agents have been investigated, including sucralfate, metronidazole, antioxidant vitamins, ASA derivatives, and short-chain fatty acids (SCFA). Of these agents, sucralfate has the best data supporting its use and is thought to help repair microvascular injury. Kochhar treated 26 patients with 20 mL sucralfate enemas administered twice daily. Seventy-seven percent of patients had improvement in symptoms at 1 month and 92% at 4 months [19]. While this shows promise, the difficulty of long-term self-administration of enemas for moderate improvement of symptoms limits its practical utility.

Metronidazole has been demonstrated in two studies to reduce symptoms [20, 21], but an ideal treatment regimen has not been developed. It is unknown how durable these effects are once the metronidazole is discontinued. Antioxidants such as vitamins A, E, and C have been shown in small studies to reduce symptoms [22, 23]. While there is likely little harm to adding an antioxidant regimen, sufficient data does not exist to make this a standard recommendation. Mesalamine and other ASA derivatives, as well as steroids, have been proposed but without sufficient data to recommend their use. SCFA, which are the primary nutrient for healing colonocytes, may speed recovery in the acute phase but have not been shown to be effective in the management of chronic colitis [24].

Hyperbaric oxygen therapy (HBOT) has been demonstrated to be effective in the treatment of radiation proctitis [25, 26]. Oscarsson published one of the larger series, in which 39 patients were treated with an 89% success rate [26]. While HBOT appears effective, practical constraints limit its applicability. The studies examining HBOT report 36–40 treatments at a considerable financial and time expense. Endoscopic therapies, discussed below, are more readily available with equivalent or superior results.

Endoscopic

Formalin

Multiple studies have demonstrated the effectiveness of topical formalin in the treatment of hemorrhagic radiation proctitis. While formalin is a medication, it is usually administered endoscopically. When topically applied to telangiectatic neovasculature, formalin induces a chemical-mediated necrosis, thereby sclerosing the small vessels [27]. A number of different techniques for administration of formalin have been described.

Sharma described using 50 mL of 4% formalin [28]. A flexible sigmoidoscope was used to spray the formalin over the involved mucosa. The formalin was left on the mucosa for a period of 3 minutes, suctioned out, and the rectum was rinsed with saline. They repeated these maneuvers three times during each treatment session, for a total exposure time of 9 minutes. Patients underwent from one to three treatment sessions depending on response. Of a total of 29 patients, all but 1 had either complete cessation of bleeding (62%) or a reduction in bleeding (34%). They reported no complications.

Raman administered 100 cc of 2% formalin as an enema, which patients held for 2 minutes if able [29]. Of 24 patients, 48% had complete resolution of bleeding, and an additional 30% had a reduction in bleeding. All patients experienced subjective improvement in their overall symptoms, and endoscopic findings were improved in all patients. Complications were limited to transient tenesmus and bleeding.

An alternative method of administration is described by Haas, in one of the largest series investigating formalin [30].

They report a 93% success rate in 100 patients. In this series, a proctoscope is used to visualize the affected mucosa. A 16″ cotton-tipped applicator dipped in 10% formalin was held against the mucosa for 60 seconds.

Variations on the above techniques include instillation of formalin while instructing patients to roll around to maximize contact surface area [31] and placing formalin-soaked gauze on tissue until it blanches [32]. Some studies have reported success rates as high as 100% [33, 34], and all studies have reported very promising results.

The use of sedation and pre-procedure bowel prep varies among protocols. Most of the above studies report from one to three treatment sessions to produce the desired result. Care should be taken not to allow the formalin to come in contact with skin, particularly the perianal skin. Sharma described using lidocaine jelly on the perianal skin in order to protect it [28]. While some authors have recommended caution due to concerns about serious toxicity (Luna-Perez reported a 20% rate of severe complications [35]), the vast majority of studies demonstrate excellent success with few or no complications.

The ease of use, ready availability, excellent success rate, and low rate of complications make the use of formalin the authors' choice for management of hemorrhagic radiation proctitis. While there are clearly multiple options for administration, we find that the simplest method of administration is using a flexible sigmoidoscope. In our practice, patients undergo a fleet enema pre-procedure. This is done in the clinic; setting and sedation are not required. With patients in the left lateral decubitus position, 4% formalin is injected through the scope over the affected mucosa. After 3 minutes, it is suctioned out and the colon irrigated with saline. This is similar to the technique describe by Sharma [28], with the exceptions that we do not find full bowel preparation or sedation necessary, and just one application is performed per session.

Argon Beam Coagulation (ABC)

The use of the argon beam to coagulate the involved mucosa appears to have an effectiveness similar to that of formalin. ABC involves the delivery of high-frequency energy to the tissue through ionized argon, administered through the working channel of a flexible sigmoidoscope. Flow is generally 1–2 L/min, with a power of 40–65 watts, at pulses of 1–2 seconds. Sebastian reported on treatment in 25 patients, all of whom showed improvement, and 81% had complete cessation of bleeding [36]. Zinicola reported an 86% success rate [37]. Failures were seen in patients with the most severe disease, who then responded to formalin. Advantages of ABC include uniform, predictable application, with a depth of penetration generally 1–3 mm. Care must be taken to make sure the probe is not discharged too close to the mucosa, as this can create a deeper injury. Yeoh performed a direct comparison of ABC to formalin and found nearly equivalent results [38]. Complications appear to be rare. One study reported a 20% rectal ulcer rate. However these ulcers were only detected on endoscopy, were asymptomatic, and resolved over time, and so were likely not clinically significant [39]. ABC therefore appears to be an acceptable alternative to formalin therapy, though its use may be limited by lack of training and access to the equipment.

Other endoscopic treatments that have been studied include bipolar electrocoagulation, laser treatment, radiofrequency ablation (RFA), and cryotherapy. Administration of these treatments requires specialized equipment. While they may be effective, less data is available to support their use. One study performed a direct comparison of bipolar electrocoagulation with ABC and found equivalent results [40]. The use of the Nd:YAG (neodymium-doped yttrium aluminum garnet) appears to be effective. However, the depth of penetration is more variable (estimated at 5 mm), so there is a higher risk of perforation, and increased rates of complications have been seen [41]. RFA uses a needle electrode to transmit an alternating radio frequency current into the tissue adjacent to the electrode's tip. Ions in adjacent tissue attempt to change direction following the alternating current, and this movement creates a friction that generates heat. There is very limited data concerning its use. Cryoablation, via spraying liquid nitrogen over the affected tissue, has also been described, again with very limited data.

For radiation-related strictures, endoscopic dilation is an option. While these strictures tend to be firm and do not stretch well, success with endoscopic balloon dilation has been reported [42]. Distal strictures that are accessible transanally can be dilated via Hegar dilators, which allows for a more aggressive dilation to a larger diameter.

Surgical

Surgery is a last resort for the treatment of radiation colitis. Surgical treatment consists of either resection, with or without reconstruction, or diversion alone. Surgery is reserved for complications of radiation colitis such as refractory bleeding, strictures leading to obstruction, fistulas, or disabling symptoms. Resectional procedures are by definition technically difficult. Radiation causes alteration of anatomical planes, loss of tissue compliance, altered anatomy, and severe adhesions. Patients need to be counseled concerning the greatly increased risk of complications, such as small bowel injuries, anastomotic leak, fistula formation, and injury to other structures. The degree of difficulty correlates with the degree of radiation damage. Rectovaginal fistulas secondary to cervical cancer treatment are particularly challenging due to the high doses of radiation and often preclude successful reconstruction. The management of complex rectourethral and rectovaginal fistulas is addressed in a separate chapter.

An older French study reviewed 85 patients that underwent laparotomy for radiation injury to the small bowel or colon and reported a mortality rate of 33% and enterocutaneous fistula rate of 30% [43]. This study was published in 1985, and the exceedingly high rate of morbidity and mortality may reflect selection bias as perhaps only the most complicated patients underwent surgery. Nonetheless, it demonstrates the complexity and high risk of these operations. The Mayo Clinic also published data on patients undergoing resection secondary to radiation colitis from 1950 to 1983 and found a complication rate of 80% and mortality of 14% [44]. Zelga found that in patients with a radiation-induced rectovaginal fistula, resection was only possible in 4% of patients and the remaining patients underwent diversion alone [45]. Zhong reported on 26 patients with rectovaginal fistulas from radiation from gynecologic cancers [46]. While resection was successful in 10 of 26 patients (the remaining 16 underwent diversion alone), only 3 patients were ever able to have their ostomies closed.

The complexity and complication rate associated with these operations can make diversion alone an appealing alternative, and diversion does indeed improve quality of life [47, 48]. While diversion can improve incontinence and symptoms related to obstruction or fistula, other symptoms such as rectal bleeding, pain, mucous drainage, and tenesmus generally persist. In patients with reasonable health status, resection should be considered as it offers the potential to remove all active disease. Reconstruction should be attempted when tissues are amenable, but both the surgeon and the patient need to be prepared that reconstruction is often not technically feasible or medically appropriate, and a permanent ostomy is often required.

Summary

Radiation colitis is a common condition in the current era, where radiation is used to treat a number of pelvic malignancies. Familiarity with radiation colitis is essential for a practicing colorectal surgeon. The severity of symptoms corresponds with quantity of radiation. Treatment options include anti-inflammatory medications, generally administered topically. The most common complication of pelvic radiation is hemorrhagic radiation proctitis. Topical formalin application is very effective in the management of this condition and is readily available and easily performed. Argon beam coagulation is also effective. Surgical treatment is reserved for patients with refractory bleeding, obstructing strictures, medical refractory symptoms, and fistulas. Surgical reconstruction can be very difficult, and patients must be counseled that these operations are associated with a high rate of morbidity and mortality; many such patients will require a permanent ostomy.

Microscopic Colitis

Definition

Microscopic colitis is a chronic, relapsing, and recurring inflammatory condition of the colon that results in nonbloody diarrhea. It is characterized by grossly normal appearance of the colonic mucosa, with characteristic abnormal findings on histologic biopsies. Because the symptoms of microscopic colitis (MC) can be fairly vague and attributable to a number of conditions, establishing the diagnosis requires a high level of suspicion. When patients with consistent symptoms are identified, colonoscopy with biopsy is required to rule this condition in or out. Microscopic colitis is classified as either collagenous colitis (CC) or lymphocytic colitis (LC). These two conditions have the same presentation and are managed in the same way, with minimal differences in epidemiology and response to treatment. Lymphocytic and collagenous colitis are differentiated based on histologic assessment. There is some debate as to whether these are differing presentations of the same entity, versus two separate diseases with many similarities.

Etiology and Risk Factors

A number of epidemiology studies from multiple countries over the last few decades have attempted to determine the actual incidence of this disease [49–51]. A study from Minnesota found that the incidence in the late 1980s was 3.1/100,000 for collagenous colitis and 5.5/100,000 for lymphocytic colitis but by 2001 had increased to 19.6/100,000 [52]. European studies over the same time period found similar results, with the incidence increasing during the 1990s from 1.1 to 5.2/100,000. Whether these changes reflect an actual increase in the prevalence of the disease versus an increase in awareness and diagnosis is not clear. Some more recent studies have suggested an incidence as high as 219/100,000 [53].

Microscopic colitis most often presents later in life. The mean age at time of diagnosis is 61, with an increasing incidence with age. Presentation in middle age is not uncommon, and rare cases in children have been seen [54, 55]. There is a female predominance, with an odds ratio for women estimated at 2–8, so there is likely a hormonal or genetic link. Autoimmune diseases have an increased incidence in women, and there is a very strong link between MC and other autoimmune disorders; this may suggest that this disease is autoimmune in nature. Forty percent of patients diagnosed with MC have another autoimmune disorder [56]. Associated conditions include type 1 diabetes mellitus, autoimmune thyroiditis, and polyarteritis. A diagnosis of polyarteritis is associated with an odds ratio of 20.8 for collagenous

colitis and 8 for lymphocytic colitis [51]. Forty percent of patients with celiac disease also demonstrate the histologic changes of MC.

While no direct genetic link has been identified, familiar clustering has been observed. The pathophysiology of MC is not well understood, but one theory is that affected patients have a mucosal barrier dysfunction that predisposes them to an increased epithelial inflammatory response to antigens. An increased frequency of pleomorphisms of genes that code for HLA and TNF-alpha, which predispose to autoimmune disorders, has been demonstrated in patients affected by MC.

Alterations in the microbiome have been observed in MC patients. This is an interesting area of future research, though not clinically applicable currently. It has been noted that there is an increased incidence of previous infection with yersinia enterocolitica in patients with MC [57], and previous Clostridia difficile infection has been proposed as a cause. These observations support the theory that an outside antigen in patients with a genetic predisposition leads to MC, but there is no direct evidence to identify causation.

Smoking is associated with an increased incidence of MC and an earlier age at diagnosis [58, 59]. A study from 2013 investigating 248 patients with MC found smoking was associated with an odds ratio of having collagenous colitis of 2.4 and lymphocytic colitis of 3.8 [51]. Smoking cessation is therefore recommended in the management of MC, although no studies have demonstrated that smoking cessation results in MC remission.

Multiple studies have demonstrated a correlation between MC and various medications, including NSAIDS, PPIs, SSRIs [60], and statins. The use of NSAIDS has an estimated odds ratio of developing collagenous colitis of 3.8 and in lymphocytic colitis of 4.7 [51]. PPIs have an estimated odds ratio of developing collagenous colitis of 6.4 and lymphocytic colitis 2.7 [51, 61]. However, a direct cause and effect relationship has not been identified, and a large database study out of Pennsylvania failed to show a medication-related correlation [62]. One theory to explain this contradiction is that diarrhea can be a side effect of these medications. This may prompt colonoscopic evaluation in otherwise normal individuals, which may increase the rate of diagnosis in patients who otherwise may not have been evaluated. While cause and effect has not been established, cessation of suspect medications can be an initial step in managing this condition.

Manifestations

Patients with microscopic colitis present with watery, non-bloody diarrhea as the predominant symptom. Active disease is defined as three or more bowel movements/day and one or more episodes of night time diarrhea. Other associated symptoms include abdominal pain, fecal incontinence, weight loss, and fatigue. While this disease causes significant impact on quality of life, it does resolve in most patients. Symptoms once resolved often recur, so it can be an intermittent, relapsing, and recurring chronic disease. Seventy-five percent of patients will achieve remission, defined as no symptoms without any medication for 1 year. Those who undergo spontaneous remission without the use of medication are more likely to experience a prolonged remission, as compared to those who undergo a drug-induced remission [51].

MC is generally considered to be a benign disease. It does not lead to an increased colorectal cancer risk [60] and has actually been associated with a decreased incidence of colorectal adenomas [63]. Serious complications are very rare, but incidences of colonic perforation, both spontaneous and during colonoscopy, have been reported [64].

Diagnosis

Criteria for diagnosis have been defined by the Spanish Microscopic Colitis Group [51]:

- Chronic or intermittent diarrhea without blood
- Macroscopically normal or near normal colonic mucosa on colonoscopy
- Characteristic histopathological appearance on colonoscopic biopsies

Any patient with non-bloody diarrhea that does not respond to simple conservative measures should undergo colonoscopy with biopsies, which are diagnostic. The differential diagnosis includes inflammatory bowel disease, irritable bowel syndrome, bile acid malabsorptionq, celiac disease, small intestinal bacterial overgrowth, and lactose intolerance. There may also be overlap between these conditions and MC.

Laboratory Studies

No laboratory studies are diagnostic of the disease. Fecal calprotectin has been studied as a fecal marker of MC. Batista et al. found average levels in those with MC 175 micrograms/gram as compared to 28 for the control group [65]. This is a nonspecific finding, however, as elevated fecal calprotectin levels are seen in other diseases as well; there is no evidence to suggest that this can establish the diagnosis or monitor treatment of this disease.

Imaging Studies

Imaging studies may be useful to look for other causes of colitis but will be normal in patients with microscopic colitis.

Endoscopic

Colonoscopy is mandatory to establish the diagnosis of MC. This disease is characterized by normal appearing colonic mucosa. Signs of inflammatory bowel disease should not be present. While uncommon, some have described altered vascular patterns, which may present as pale mucosa, erythema, edema, or linear ulcers [66]. Biopsies for histology need to be taken throughout the colon. Two biopsies should be taken in each segment. Sampling individual areas of the colon, such as the rectum or sigmoid, decreases the diagnostic sensitivity, as characteristic changes may not be present throughout the entire colon. Full colonoscopy, and not flexible sigmoidoscopy, is mandatory. When colonoscopy with appropriate biopsies is performed in patients with symptoms consistent with MC, 10–15% of patients will be found to have MC [53].

Histology

MC is characterized by inflammation in the lamina propria, with an increase in lymphocytes and plasma cells. While some patients may have cryptitis, crypt architecture is generally preserved [67]. Collagenous colitis is characterized by a subepithelial collagen band that is 10 or more micrometers in thickness (see Fig. 53.2). While this is the defining criterion for collagenous colitis, the significance of the collagen band itself is unclear. The collagen band has been shown to decrease in thickness with treatment [68, 69], but the severity of symptoms correlates with the degree of inflammation in the lamina propria, rather than the size of the collagen band [67]. Lymphocytic colitis is characterized by an increased proportion of surface intraepithelial lymphocytes. The collagen layer may be present or absent but is less than 10 μm. Routine H&E staining is generally sufficient (Fig. 53.3); but in cases where the diagnosis is in question, CD3 staining better visualizes the intraepithelial lymphocytes (Fig. 53.4) [70].

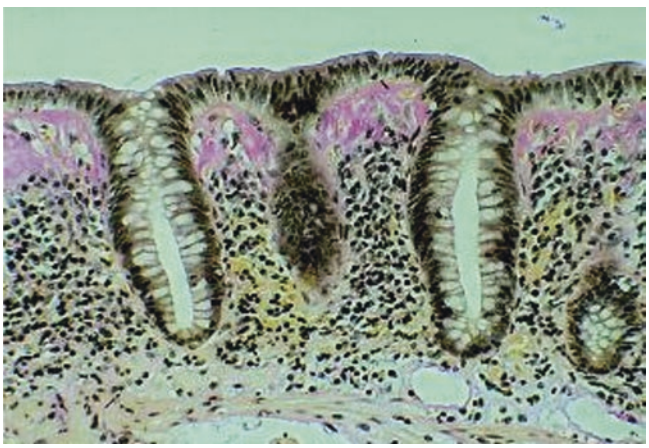

Fig. 53.2 Collagenous colitis [105]. Reused with permission. (Copyright © Elsevier)

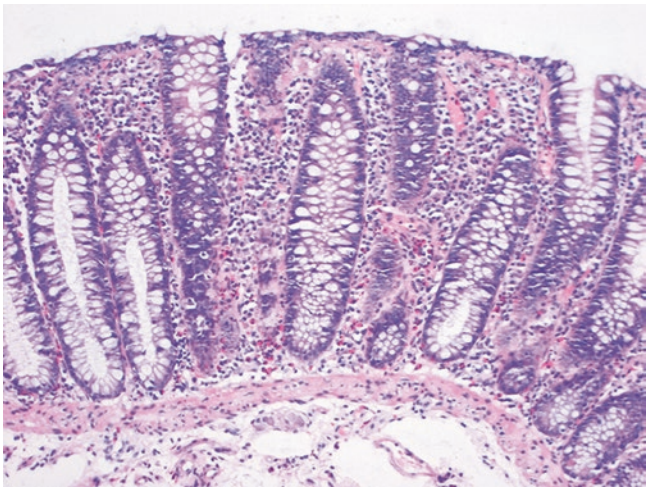

Fig. 53.3 H&E lymphocytic colitis [105]. Reused with permission. (Copyright © Elsevier)

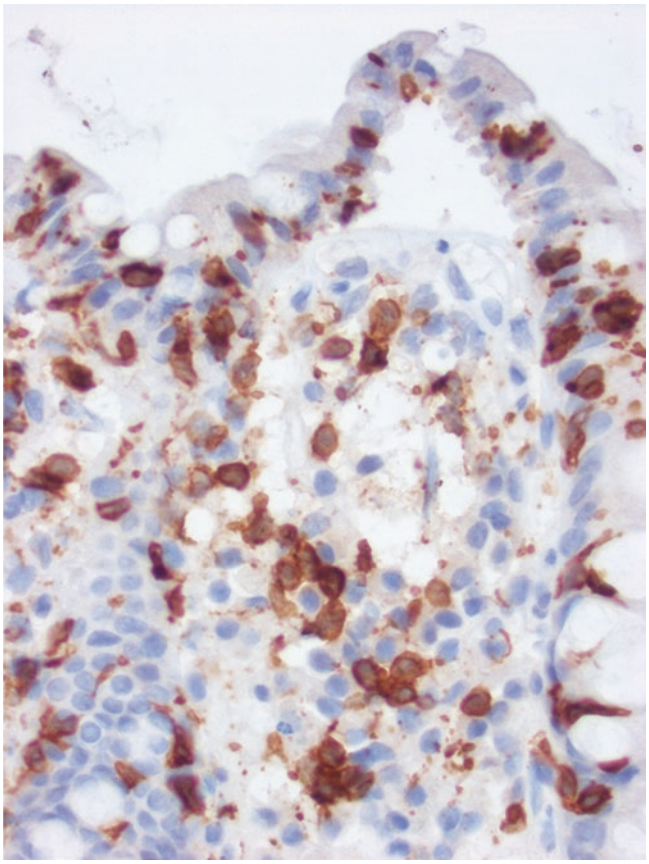

Fig. 53.4 Lymphocytic colitis CD3 staging [105]. Reused with permission. (Copyright © Elsevier)

Management

Medical

The majority of patients with this condition are on antidiarrheal medication, such as loperamide and/or diphenoxyl-

ate. These medications may improve symptoms but do not induce remission or decrease histologic inflammation. Probiotics have been investigated and show no improvement over placebo [71]. In one study of 64 patients, mesalamine showed promising results, with an 84% induction of clinical remission in 2 weeks [72]. The response rate was even higher when co-administered with cholestyramine. However, there was no control group in this study, and a large randomized trial investigating mesalamine did not demonstrate improvement over placebo [73].

While the data is limited, a number of small studies have demonstrated improvement in symptoms with administration of bismuth salicylate [69]. Dosage is three 262 mg tablets tid for 8 weeks, with a mean response occurring at 2 weeks. One small study randomized 14 patients to placebo vs bismuth salicylate and found 100% clinical success with bismuth and no response to placebo. While the study was small, it was double blinded and reported a dramatic treatment effect. A meta-analysis showed an 81% response rate to bismuth salicylate [74].

Antibiotics have been investigated. There are only a few studies with a small number of patients, so antibiotics cannot be recommended as treatment currently. Metronidazole is attractive in that it has both anti-inflammatory and antibiotic properties. Other antibiotics that have been investigated include erythromycin and penicillin, which have shown response in very small groups of patients [57, 75].

Budesonide is the mainstay of treatment for this disease. A potent corticosteroid, budesonide, concentrates its effects on the bowel, as extensive first pass metabolism minimizes systemic effects. A number of randomized trials demonstrate the superiority of budesonide over placebo with minimal side effects [73, 76–78]. Miehlke randomized 57 patients in a double-blind fashion to receive either budesonide, mesalamine, or placebo. Budesonide had a 68% success rate as compared to 21% for placebo and 26% for mesalamine [73]. Unfortunately, the recurrence of disease is common once budesonide is stopped [79].

Munch administered budesonide to 110 patients with an 84% treatment success [78]. Those that responded were then randomized to continue budesonide as maintenance therapy vs placebo. The initial induction dose was 9 mg/day, and the maintenance dose was 4.5 mg/day. At 1 year, 61% of the patients on maintenance budesonide remained in remission as compared to only 16% for placebo [78]. This demonstrates that budesonide can be used not only as initial treatment but also for recurrent disease or to maintain remission. Given the efficacy of budesonide, it is not surprising that prednisolone can also induce remission. Munck studied prednisolone at a dose of 50 mg daily. A moderate response was seen at 2 weeks but at the cost of steroid-associated side effects [80]. As systemic prednisolone has not been shown to be superior to budesonide and is associated with a higher rate of side effects, it should not be considered for primary therapy.

In very small studies and case reports, immunomodulators have been used with good results. As the side effects associated with these medications can be severe and MC generally has a benign course, the use of such medications is fairly limited. Because of this, there is no large-scale data supporting their use. However, Vennamaneni demonstrated success with 6-MP and azathioprine [81] and Esteve with anti-TNF-alpha medications [82].

Surgical management is not considered part of a standard algorithm for this disease. However, occasional patients present with failure to respond to medical treatment and such life-disabling symptoms that surgery is warranted. Diversion is the mainstay of surgical treatment, with or without colonic resection. Both result in symptomatic improvement. The purported benefit of diversion alone is the potential for restoration of continuity. However, if the ostomy is reversed, symptoms recur. In addition to clinical improvement with diversion, the diverted segment demonstrates a decrease in inflammation on biopsy. In collagenous colitis, the size of the collage band decreases after diversion [68]. There are two case reports of total proctocolectomy with ileal pouch-anal anastomosis to treat this disease with acceptable results [83, 84], but there is no data to support this as a management strategy.

To summarize, medical therapy is the mainstay of treatment. Given the association of MC with tobacco use, smoking cessation should be encouraged, although there is no evidence that this leads to remission. Associated medications should be discontinued if possible. For very mild disease, anti-diarrheal medications can be used to treat symptoms. If patients continue to experience significant symptoms after these conservative measures, treatment with budesonide should be initiated. If budesonide induces remission, the drug can be stopped, with the recognition that many patients will again become symptomatic. Budesonide can be restarted to maintain remission. In rare circumstances, severe symptoms continue, in which case treatment with immunomodulators, such as 6-MP, azathioprine, or anti-TNF medications, can be tried. The severity of symptoms and the effect on the patient's quality of life must be balanced with the risks associated with these medications. The creation of an ostomy with or without colon resection is a last alternative.

Ischemic Colitis

Definition

Ischemic colitis (IC) occurs when the metabolic demands of the colon mucosa is greater than the resources provided through the vascular system. While a common cause of isch-

emia is the complete disruption of blood flow or mesenteric ischemia, such a situation is different than classic IC (Table 53.2). Mesenteric ischemia results from disruption of blood flow through some type of vascular accident—embolic, thrombotic, or other mechanical forces that impair blood flow. These types of accidents tend to affect the large, named blood vessels resulting in injury to extensive regions of both the small and large intestine. In contrast, ischemic colitis is thought to occur from disruption of blood flow in the small mesenteric vessels that are near the wall of the colon (Fig. 53.5). The disruption of blood flow can certainly occur as a result of a vascular accident such as thrombosis; however, it commonly occurs as a result of decrease in blood flow without major vascular disruption.

Table 53.2 Differences between mesenteric ischemic and ischemic colitis

Characteristic	Mesenteric ischemia	Ischemic colitis
Symptom onset	Sudden	Hours
Cause	Vascular accident (thrombotic, embolic, dissection, etc.)	Multifactorial
Blood supply loss	Total to effected segment	Transient
Symptoms	Pain out of proportion to exam	Moderate pain and tenderness over affected segment, hematochezia
Management	Emergent surgery	Most managed medically, surgery may be indicated if disease progresses

Anatomy, Epidemiology, and Risk Factors

Branches from the superior and inferior mesenteric arteries and the paired internal iliac arteries supply blood to the colon and rectum. While these named vessels arising directly from the aorta are important, almost as important is the collateral vasculature of the colon. The marginal artery of Drummond parallels the wall of the colon and gives rise to the vasa recta. This meandering artery receives blood flow from the terminal branches of each colic artery. The regions of the large intestine can be very dependent upon this collateral flow as the splanchnic vessels are some of the most reactive in the body and can receive anywhere from 10% to 35% of the cardiac output depending on physiologic or pathologic conditions [85]. During states of low flow, the major watershed regions of the colon require that this collateral circulation be fairly robust. If the marginal artery of Drummond is not intact when these times of low flow occur, symptomatic ischemia may result [86]. Griffith's area at the splenic flexure and Sudeck's point at the rectosigmoid junction are two major watershed regions, and states of reduced blood flow can cause relative ischemia in these areas.

The colon is the most frequent site of gastrointestinal ischemia [87, 88]. While the exact rate of ischemic colitis in the general population is difficult to know, it is clear that certain groups of patients are at increased risk for developing IC [89]. In a large review by Higgins, rates of IC in the general population were estimated to be between 4 and 9 per 100,000 patients. In this review, the authors did note that patients with COPD had rates of IC as high as 100 per

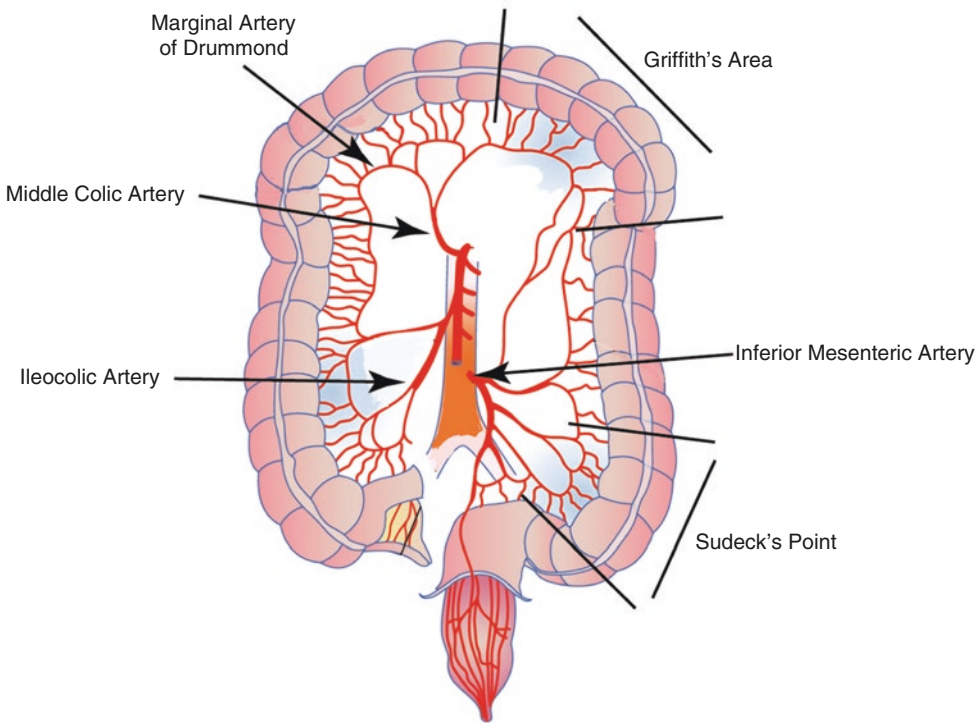

Fig. 53.5 Vascular anatomy

100,000 patients with a relative risk between 2.6 and 4.3 [89]. Other groups of patients are also known to have an increased risk for IC. For example, there is a classic association between IC and AAA repair. In fact, a recent review of the topic including 110,000 patients revealed rates of IC to be 0–4.6% after elective repair and as high as 21% after emergency repair of a ruptured AAA [90].

Clinical Presentation

Abdominal pain and rectal bleeding are often the earliest symptoms associated with acute IC. In a review of patients presenting with lower GI bleed, Newman found that IC was the cause of the bleed in nearly 20% of patients, second only to diverticulosis [91]. This observation has been confirmed by others in similar local studies. For example, Hreinsson examined patients presenting with an acute GI bleed in their hospital in Iceland and found that almost 15% had bleeding as a result of IC [92]. Given these results, ischemic colitis should be high in the differential diagnosis for lower GI bleeding.

Other symptoms might include pain, nausea, vomiting, abdominal distention, dizziness, and syncope. Right-sided colitis is less likely to be associated with rectal bleeding and should be kept in mind in those patients with isolated right-sided abdominal pain [93]. Physical examination often reveals only mild to moderate tenderness over the involved segment. Of course, if full-thickness necrosis occurs and the segment perforates, diffuse peritonitis will ensue. However, most patients present early without evidence of transmural involvement.

Diagnosis

Diagnosis of ischemic colitis requires one to think about the diagnosis first and foremost. IC should be prominent on the differential diagnosis in someone presenting with lower GI bleeding and abdominal pain. Laboratory evaluation is nonspecific. Increased white blood cell count and acidosis may indicate full-thickness ischemia. However, there is no reliable marker of ischemia. One must consider all causes of bloody diarrhea including infectious causes such as *Klebsiella* or *Salmonella*.

Imaging with plain films can be normal or show nonspecific findings of distention and ileus. Free air can be seen with free perforation. Classic findings of bowel ischemia such as thumbprinting and pneumatosis are present in 20–30% of plain films in patients with IC [88]. Contrast enemas have little to no use in the acute phase of the disease, as they may worsen tissue ischemia through unnecessary distention. However, such a study can be useful to assess stricture formation in patients who have recovered from IC [88].

Abdominal CT scan is frequently performed as the initial evaluation in patients presenting with abdominal pain and bloody diarrhea. The accuracy of CT scan in determining bowel ischemia varies between 74 and 79% depending on the protocol used and the experience of the radiologist [94]. Most patients with IC will have findings consistent with ischemia on CT scan if imaged in the acute phase. In fact, in a recent review of 130 patients undergoing CT for the suspected diagnosis of IC, Iacobellis found that 100% of patients with IC had a CT finding consistent with the diagnosis [95]. Most frequently, they found pericolonic and free fluid, change in bowel wall densities, and bowel wall thickening [95].

While pneumatosis is a particularly ominous finding, it is present in only a small fraction of examinations in patients with the diagnosis of IC. In the study by Iacobellis, <5% of patients in the acute phase had findings consistent with pneumatosis [95]. In general, the findings of pneumatosis and portal venous gas do not always signify bowel necrosis [96]. However, in the clinical setting of IC, the presence of pneumatosis and bowel wall necrosis portends a mortality rate over 70% [96].

Colonoscopy can be used to confirm the diagnosis of IC and to exclude other causes of colitis. It goes without saying that colonoscopy should not be done in patients with findings consistent with free perforation or with signs of peritonitis. Luminal findings consistent with ischemia include erythema (84% of cases), edema (70%), friability (43%), superficial ulceration (57%), deep ulceration (22%), stenosis (8%), and intraluminal blood (8%) [88]. As the ischemic process progresses, evidence of submucosal bluish-black blebs or nodules protruding into the lumen of the bowel can be seen. These lesions create the characteristic thumb printing seen on radiographic studies [88].

In addition to visual inspection, colonoscopy allows for biopsy of the superficial mucosa. Histologic evaluation of the endoscopic findings helps differentiate IC from changes due to infections or inflammation. The pathognomonic finding of IC is the presence of ghost cells [97]. Other features of acute ischemic colitis include preserved architecture of the colonic crypts, necrosis of the superficial portion of the crypts, sparing of the deep portion of the crypts, mucin depletion, and reactive changes in the residual crypt epithelium. Sloughed necrotic mucosa may produce a microscopic appearance of a pseudomembrane, composed of fibrin admixed with numerous neutrophils and mucin.

Management

When the diagnosis of ischemic colitis is made and the patient does not show signs of perforation or toxicity, it is generally appropriate to start with conservative treatment. This includes bowel rest, intravenous hydration, and broad-

spectrum antibiotics. While antibiotics have not been shown to alter the disease, they are thought to be beneficial for 2 reasons: (1) colonic ischemia increases mucosal permeability, thereby increasing bacterial translocation, and (2) animal studies have shown that antibiotics may reduce the length and severity of bowel damage [98, 99]. The choice of antibiotics is based on expert opinions. In general, coverage should include the gut flora, including anaerobic coliforms [93].

The use of anticoagulants is not routinely recommended for patients with IC due to microvascular pathology or low-flow states. If the patient has an ileus and suffers from intractable nausea and vomiting, nasogastric decompression may be indicated. Medications should be carefully reviewed, and those promoting splanchnic vasoconstriction should be stopped if possible, and cardiac output should be optimized. No medications have been shown to increase blood flow to the colonic mucosa and shorten the duration of the ischemic insult [88]. Improvement should be seen in a relatively short timeframe measured in hours to days. The absence of improvement or delayed improvement may indicate chronic progression towards transmural ischemia.

After symptom resolution patients should undergo an elective diagnostic colonoscopy to ensure complete healing and assess for possible stricture [100]. Strictures that are not clinically significant can be observed, and some may resolve on their own over 12–24 months with no further therapy [101].

Signs of clinical deterioration such as fever, hypotension, tachycardia, increased abdominal tenderness, and increasing white blood cell count indicate that the disease is progressing and surgical intervention may be warranted. If colonic infarction is suspected, exploratory laparotomy or laparoscopy is necessary. The use of laparoscopy in this patient population will be dictated by the clinical situation and the comfort of the surgeon. Surgical resection will be driven by how much of the colon is involved; resection should be from normal bowel to normal bowel. Primary anastomosis should be avoided in general, and the fundamental goal should be to perform a safe operation. Stoma creation does not necessarily need to be permanent, and elective reversals can be performed once the patient has functionally recovered. Regardless of procedure performed, patients requiring an operation for ischemic colitis have mortality rates as high as 40% [102].

Prognosis

In most cases of IC, the signs and symptoms resolve within 24–48 hours, and complete clinical and radiological resolution occurs within 1–2 weeks, after which no further therapy is required [103]. Approximately 10% of patients who initially recover from the ischemic event may present several months later with obstructive symptoms secondary to a significant stricture [104]. Diagnosis of a stricture can be made by colonoscopy, CT colonography, or barium enema. Surgical resection may be indicated in patients with symptomatic strictures, but these should be done on an elective basis with anticipation of a primary anastomosis. In addition to strictures, another 20–30% of patients go on to develop chronic colitis from irreversible ischemic injury, manifested by persistent diarrhea, rectal bleeding, and/or weight loss [100]. If confirmed, this too may be an indication for elective surgery.

References

1. Anseline PF, et al. Radiation injury of the rectum: evaluation of surgical treatment. Ann Surg. 1981;194(6):716–24.
2. Eifel PJ, et al. Time course and incidence of late complications in patients treated with radiation therapy for FIGO stage IB carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys. 1995;32(5):1289–300.
3. Denham JW, et al. Is there more than one late radiation proctitis syndrome? Radiother Oncol. 1999;51(1):43–53.
4. Nelamangala Ramakrishnaiah VP, Krishnamachari S. Chronic haemorrhagic radiation proctitis: a review. World J Gastrointest Surg. 2016;8(7):483–91.
5. Lanciano RM, et al. Influence of age, prior abdominal surgery, fraction size, and dose on complications after radiation therapy for squamous cell cancer of the uterine cervix. A patterns of care study. Cancer. 1992;69(8):2124–30.
6. Coia LR, Myerson RJ, Tepper JE. Late effects of radiation therapy on the gastrointestinal tract. Int J Radiat Oncol Biol Phys. 1995;31(5):1213–36.
7. Maggio A, et al. Daily sodium butyrate enema for the prevention of radiation proctitis in prostate cancer patients undergoing radical radiation therapy: results of a multicenter randomized placebo-controlled dose-finding phase 2 study. Int J Radiat Oncol Biol Phys. 2014;89(3):518–24.
8. Sanguineti G, et al. Sucralfate versus mesalazine versus hydrocortisone in the prevention of acute radiation proctitis during conformal radiotherapy for prostate carcinoma. A randomized study. Strahlenther Onkol. 2003;179(7):464–70.
9. Hovdenak N, Sorbye H, Dahl O. Sucralfate does not ameliorate acute radiation proctitis: randomised study and meta-analysis. Clin Oncol (R Coll Radiol). 2005;17(6):485–91.
10. Mansouri-Tehrani HA, et al. Effect of supplements: probiotics and probiotic plus honey on blood cell counts and serum IgA in patients receiving pelvic radiotherapy. J Res Med Sci. 2015;20(7):679–83.
11. Nascimento M, et al. Efficacy of synbiotics to reduce acute radiation proctitis symptoms and improve quality of life: a randomized, double-blind, placebo-controlled pilot trial. Int J Radiat Oncol Biol Phys. 2014;90(2):289–95.
12. Vidal-Casariego A, et al. Effects of oral glutamine during abdominal radiotherapy on chronic radiation enteritis: a randomized controlled trial. Nutrition. 2015;31(1):200–4.
13. Athanassiou H, et al. Protective effect of amifostine during fractionated radiotherapy in patients with pelvic carcinomas: results of a randomized trial. Int J Radiat Oncol Biol Phys. 2003;56(4):1154–60.
14. Liu T, et al. Use of radiation with or without WR-2721 in advanced rectal cancer. Cancer. 1992;69(11):2820–5.
15. O'Brien PC, et al. Spontaneous improvement in late rectal mucosal changes after radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys. 2004;58(1):75–80.

16. Theodorescu D, Gillenwater JY, Koutrouvelis PG. Prostatourethral-rectal fistula after prostate brachytherapy. Cancer. 2000;89(10):2085–91.
17. Hasleton PS, Carr N, Schofield PF. Vascular changes in radiation bowel disease. Histopathology. 1985;9(5):517–34.
18. Haboubi NY, Schofield PF, Rowland PL. The light and electron microscopic features of early and late phase radiation-induced proctitis. Am J Gastroenterol. 1988;83(10):1140–4.
19. Kochhar R, et al. Natural history of late radiation proctosigmoiditis treated with topical sucralfate suspension. Dig Dis Sci. 1999;44(5):973–8.
20. Cavcic J, et al. Metronidazole in the treatment of chronic radiation proctitis: clinical trial. Croat Med J. 2000;41(3):314–8.
21. Sahakitrungruang C, et al. A randomized controlled trial comparing colonic irrigation and oral antibiotics administration versus 4% formalin application for treatment of hemorrhagic radiation proctitis. Dis Colon Rectum. 2012;55(10):1053–8.
22. Kennedy M, et al. Successful and sustained treatment of chronic radiation proctitis with antioxidant vitamins E and C. Am J Gastroenterol. 2001;96(4):1080–4.
23. Ehrenpreis ED, et al. A prospective, randomized, double-blind, placebo-controlled trial of retinol palmitate (vitamin A) for symptomatic chronic radiation proctopathy. Dis Colon Rectum. 2005;48(1):1–8.
24. Vernia P, et al. Topical butyrate for acute radiation proctitis: randomised, crossover trial. Lancet. 2000;356(9237):1232–5.
25. Woo TC, Joseph D, Oxer H. Hyperbaric oxygen treatment for radiation proctitis. Int J Radiat Oncol Biol Phys. 1997;38(3):619–22.
26. Oscarsson N, et al. Hyperbaric oxygen treatment in radiation-induced cystitis and proctitis: a prospective cohort study on patient-perceived quality of recovery. Int J Radiat Oncol Biol Phys. 2013;87(4):670–5.
27. Laterza L, et al. Management of radiation-induced rectal bleeding. Curr Gastroenterol Rep. 2013;15(11):355.
28. Sharma B, et al. Four percent formalin application for the management of radiation proctitis in carcinoma cervix patients: an effective, safe, and economical practice. J Cancer Res Ther. 2019;15(1):92–5.
29. Raman RR. Two percent formalin retention enemas for hemorrhagic radiation proctitis: a preliminary report. Dis Colon Rectum. 2007;50(7):1032–9.
30. Haas EM, Bailey HR, Faragher I. Application of 10 percent formalin for the treatment of radiation-induced hemorrhagic proctitis. Dis Colon Rectum. 2007;50(2):213–7.
31. Cullen SN, Frenz M, Mee A. Treatment of haemorrhagic radiation-induced proctopathy using small volume topical formalin instillation. Aliment Pharmacol Ther. 2006;23(11):1575–9.
32. Vyas FL, et al. Endoluminal formalin application for haemorrhagic radiation proctitis. Color Dis. 2006;8(4):342–6.
33. Seow-Choen F, et al. A simple and effective treatment for hemorrhagic radiation proctitis using formalin. Dis Colon Rectum. 1993;36(2):135–8.
34. Li YD, et al. Application of 4% formaldehyde under electronic colonoscope as a minimally invasive treatment of chronic hemorrhagic radiation proctitis. World J Emerg Med. 2019;10(4):228–31.
35. Luna-Perez P, Rodriguez-Ramirez SE. Formalin instillation for refractory radiation-induced hemorrhagic proctitis. J Surg Oncol. 2002;80(1):41–4.
36. Sebastian S, et al. Argon plasma coagulation as first-line treatment for chronic radiation proctopathy. J Gastroenterol Hepatol. 2004;19(10):1169–73.
37. Zinicola R, et al. Haemorrhagic radiation proctitis: endoscopic severity may be useful to guide therapy. Int J Color Dis. 2003;18(5):439–44.
38. Yeoh E, et al. Argon plasma coagulation therapy versus topical formalin for intractable rectal bleeding and anorectal dysfunction after radiation therapy for prostate carcinoma. Int J Radiat Oncol Biol Phys. 2013;87(5):954–9.
39. Ravizza D, et al. Frequency and outcomes of rectal ulcers during argon plasma coagulation for chronic radiation-induced proctopathy. Gastrointest Endosc. 2003;57(4):519–25.
40. Lenz L, et al. Comparative study of bipolar eletrocoagulation versus argon plasma coagulation for rectal bleeding due to chronic radiation coloproctopathy. Endoscopy. 2011;43(8):697–701.
41. Barbatzas C, et al. Nd:YAG laser treatment for bleeding from radiation proctitis. Endoscopy. 1996;28(6):497–500.
42. Karanikas M, et al. Benign post-radiation rectal stricture treated with endoscopic balloon dilation and intralesional triamcinolone injection. Case Rep Gastroenterol. 2012;6(3):583–9.
43. Lasser P, et al. Surgical treatment of severe radiation injuries of the small intestine and colon-rectum. Apropos of 85 patients surgically-treated at the Gustave-Roussy Institute. J Chir (Paris). 1985;122(1):27–35.
44. Jao SW, Beart RW Jr, Gunderson LL. Surgical treatment of radiation injuries of the colon and rectum. Am J Surg. 1986;151(2):272–7.
45. Zelga P, et al. Radiation-induced rectovaginal fistulas in locally advanced gynaecological malignancies-new patients, old problem? Langenbeck's Arch Surg. 2017;402(7):1079–88.
46. Zhong Q, et al. Restorative resection of radiation rectovaginal fistula can better relieve anorectal symptoms than colostomy only. World J Surg Oncol. 2017;15(1):37.
47. Pricolo VE, Shellito PC. Surgery for radiation injury to the large intestine. Variables influencing outcome. Dis Colon Rectum. 1994;37(7):675–84.
48. Ayerdi J, et al. Diverting loop colostomy for the treatment of refractory gastrointestinal bleeding secondary to radiation proctitis. Mil Med. 2001;166(12):1091–3.
49. Olesen M, et al. Microscopic colitis: a common diarrhoeal disease. An epidemiological study in Orebro, Sweden, 1993-1998. Gut. 2004;53(3):346–50.
50. Williams JJ, et al. Microscopic colitis-defining incidence rates and risk factors: a population-based study. Clin Gastroenterol Hepatol. 2008;6(1):35–40.
51. Fernandez-Banares F, et al. Current concepts on microscopic colitis: evidence-based statements and recommendations of the Spanish Microscopic Colitis Group. Aliment Pharmacol Ther. 2016;43(3):400–26.
52. Pardi DS, et al. The epidemiology of microscopic colitis: a population based study in Olmsted County. Minnesota Gut. 2007;56(4):504–8.
53. Pardi DS, Kelly CP. Microscopic colitis. Gastroenterology. 2011;140(4):1155–65.
54. Agnarsdottir M, et al. Collagenous and lymphocytic colitis in Iceland. Dig Dis Sci. 2002;47(5):1122–8.
55. Andrews CN, et al. Evaluation of endoscopist and pathologist factors affecting the incidence of microscopic colitis. Can J Gastroenterol. 2012;26(8):515–20.
56. Costagliola S, et al. Second generation assay for thyrotropin receptor antibodies has superior diagnostic sensitivity for Graves' disease. J Clin Endocrinol Metab. 1999;84(1):90–7.
57. Bohr J, et al. Yersinia species in collagenous colitis: a serologic study. Scand J Gastroenterol. 2002;37(6):711–4.
58. Vigren L, et al. An epidemiological study of collagenous colitis in southern Sweden from 2001-2010. World J Gastroenterol. 2012;18(22):2821–6.
59. Yen EF, et al. Current and past cigarette smoking significantly increase risk for microscopic colitis. Inflamm Bowel Dis. 2012;18(10):1835–41.
60. Bonderup OK, et al. Drug exposure and risk of microscopic colitis: a nationwide Danish case-control study with 5751 cases. Inflamm Bowel Dis. 2014;20(10):1702–7.

61. Wilcox GM, Mattia AR. Microscopic colitis associated with omeprazole and esomeprazole exposure. J Clin Gastroenterol. 2009;43(6):551–3.
62. Pascua MF, et al. Microscopic colitis and medication use. Clin Med Insights Gastroenterol. 2010;2010(3):11–9.
63. Yen EF, et al. Decreased colorectal cancer and adenoma risk in patients with microscopic colitis. Dig Dis Sci. 2012;57(1):161–9.
64. Freeman HJ, James D, Mahoney CJ. Spontaneous peritonitis from perforation of the colon in collagenous colitis. Can J Gastroenterol. 2001;15(4):265–7.
65. Batista L, et al. Usefulness of fecal calprotectin as a biomarker of microscopic colitis in a cohort of patients with chronic watery diarrhoea of functional characteristics. Dig Liver Dis. 2019;51(12):1646–51.
66. Koulaouzidis A, Saeed AA. Distinct colonoscopy findings of microscopic colitis: not so microscopic after all? World J Gastroenterol. 2011;17(37):4157–65.
67. Warren BF, Edwards CM, Travis SP. 'Microscopic colitis': classification and terminology. Histopathology. 2002;40(4):374–6.
68. Jarnerot G, et al. Collagenous colitis and fecal stream diversion. Gastroenterology. 1995;109(2):449–55.
69. Fine KD, Lee EL. Efficacy of open-label bismuth subsalicylate for the treatment of microscopic colitis. Gastroenterology. 1998;114(1):29–36.
70. Liszka L, Woszczyk D, Pajak J. Histopathological diagnosis of microscopic colitis. J Gastroenterol Hepatol. 2006;21(5):792–7.
71. Wildt S, et al. Probiotic treatment of collagenous colitis: a randomized, double-blind, placebo-controlled trial with Lactobacillus acidophilus and Bifidobacterium animalis subsp. Lactis Inflamm Bowel Dis. 2006;12(5):395–401.
72. Calabrese C, et al. Mesalazine with or without cholestyramine in the treatment of microscopic colitis: randomized controlled trial. J Gastroenterol Hepatol. 2007;22(6):809–14.
73. Miehlke S, et al. Budesonide is more effective than mesalamine or placebo in short-term treatment of collagenous colitis. Gastroenterology. 2014;146(5):1222–30 e1–2.
74. Chande N, MacDonald JK, McDonald JW. Interventions for treating microscopic colitis: a Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Review Group systematic review of randomized trials. Am J Gastroenterol. 2009;104(1):235–41; quiz 234, 242.
75. Tremaine WJ. Collagenous colitis and lymphocytic colitis. J Clin Gastroenterol. 2000;30(3):245–9.
76. Baert F, et al. Budesonide in collagenous colitis: a double-blind placebo-controlled trial with histologic follow-up. Gastroenterology. 2002;122(1):20–5.
77. Madisch A, et al. Oral budesonide therapy improves quality of life in patients with collagenous colitis. Int J Color Dis. 2005;20(4):312–6.
78. Munch A, et al. Low-dose budesonide for maintenance of clinical remission in collagenous colitis: a randomised, placebo-controlled, 12-month trial. Gut. 2016;65(1):47–56.
79. Stewart MJ, Seow CH, Storr MA. Prednisolone and budesonide for short- and long-term treatment of microscopic colitis: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2011;9(10):881–90.
80. Munck LK, et al. Incomplete remission with short-term prednisolone treatment in collagenous colitis: a randomized study. Scand J Gastroenterol. 2003;38(6):606–10.
81. Vennamaneni SR, Bonner GF. Use of azathioprine or 6-mercaptopurine for treatment of steroid-dependent lymphocytic and collagenous colitis. Am J Gastroenterol. 2001;96(9):2798–9.
82. Esteve M, et al. Efficacy of anti-TNF therapies in refractory severe microscopic colitis. J Crohns Colitis. 2011;5(6):612–8.
83. Williams RA, Gelfand DV. Total proctocolectomy and ileal pouch anal anastomosis to successfully treat a patient with collagenous colitis. Am J Gastroenterol. 2000;95(8):2147.
84. Varghese L, et al. Lymphocytic colitis treated with proctocolectomy and ileal J-pouch-anal anastomosis: report of a case. Dis Colon Rectum. 2002;45(1):123–6.
85. Rosenblum JD, Boyle CM, Schwartz LB. The mesenteric circulation. Anatomy and physiology. Surg Clin North Am. 1997;77(2):289–306.
86. Yamazaki T, et al. Ischemic colitis arising in watershed areas of the colonic blood supply: a report of two cases. Surg Today. 1997;27(5):460–2.
87. Gandhi SK, et al. Ischemic colitis. Dis Colon Rectum. 1996;39(1):88–100.
88. Sun MY, Maykel JA. Ischemic colitis. Clin Colon Rectal Surg. 2007;20(1):5–12.
89. Higgins PD, Davis KJ, Laine L. Systematic review: the epidemiology of ischaemic colitis. Aliment Pharmacol Ther. 2004;19(7):729–38.
90. Lee MJ, et al. Risk factors for ischaemic colitis after surgery for abdominal aortic aneurysm: a systematic review and observational meta-analysis. Int J Color Dis. 2016;31(7):1273–81.
91. Newman JR, Cooper MA. Lower gastrointestinal bleeding and ischemic colitis. Can J Gastroenterol. 2002;16(9):597–600.
92. Hreinsson JP, Ægisdottir S, Bjornsson ES. Acute lower gastrointestinal bleeding: a population-based five-year follow-up study. United European Gastroenterol J. 2019;7(10):1330–6.
93. Brandt LJ, et al. ACG clinical guideline: epidemiology, risk factors, patterns of presentation, diagnosis, and management of colon ischemia (CI). Am J Gastroenterol. 2015;110(1):18–44; quiz 45.
94. Blachar A, et al. Radiologists' performance in the diagnosis of acute intestinal ischemia, using MDCT and specific CT findings, using a variety of CT protocols. Emerg Radiol. 2011;18(5):385–94.
95. Iacobellis F, et al. CT findings in acute, subacute, and chronic ischemic colitis: suggestions for diagnosis. Biomed Res Int. 2014;2014:895248.
96. Lassandro F, et al. Imaging assessment and clinical significance of pneumatosis in adult patients. Radiol Med. 2015;120(1):96–104.
97. Habu Y, et al. Reevaluation of clinical features of ischemic colitis. Analysis of 68 consecutive cases diagnosed by early colonoscopy. Scand J Gastroenterol. 1996;31(9):881–6.
98. Path EJ, Mc CJ Jr. Intestinal obstruction; the protective action of sulfasuxidine and sulfathalidine to the ileum following vascular damage. Ann Surg. 1950;131(2):159–70, illust.
99. Sarnoff SJ, Fine J. The effect of chemotherapy on the ileum subjected to vascular injury. Ann Surg. 1945;121(1):74–82.
100. Cappell MS. Intestinal (mesenteric) vasculopathy. II. Ischemic colitis and chronic mesenteric ischemia. Gastroenterol Clin N Am. 1998;27(4):827–60. vi
101. Brandt LJ, Feuerstadt P. Beyond low flow: how I manage ischemic colitis. Am J Gastroenterol. 2016;111(12):1672–4.
102. Scharff JR, et al. Ischemic colitis: spectrum of disease and outcome. Surgery. 2003;134(4):624–9; discussion 629–30.
103. Brandt LJ, Boley SJ. Colonic ischemia. Surg Clin North Am. 1992;72(1):203–29.
104. Bower TC. Ischemic colitis. Surg Clin North Am. 1993;73(5):1037–53.
105. Munch A, et al. Microscopic colitis: current status, present and future challenges: statements of the European Microscopic Colitis Group. J Crohns Colitis. 2012;6(9):932–45.

Intestinal Stomas

54

Michael F. McGee and Peter A. Cataldo

Key Concepts

- Preoperative stoma site marking and patient education improve stoma-related clinical outcomes, patient quality of life and experience, while decreasing healthcare resource utilization.
- The finished stoma should protrude from the skin, thereby improving the seal between the appliance and the peristomal skin and decreasing complications.
- Optimal care for patients undergoing ostomy surgery includes preoperative and postoperative care by an ostomy nurse specialist, such as a WOCN-certified nurse.
- Early stoma-related complications such as leakage, peristomal dermatitis, and dehydration can often be remedied with stoma care and patient education.
- Loop ileostomy is preferred over transverse loop colostomy for temporary fecal diversion in most circumstances.
- Stapled and hand-sutured techniques are both acceptable for loop ileostomy closure.

Introduction

Stomas are employed as temporary or permanent means of fecal diversion in the management of a variety of gastrointestinal, neurologic, and genitourinary conditions. Dated estimates suggest that approximately 120,000 stomas are created annually in North America, with an estimated prevalence of 450,000–800,000 ostomates [1]. Stomas can be fashioned in an "end" or "loop" configuration depending on surgical strategy and perioperative conditions and are classified by the location of exteriorized bowel (e.g., colostomy, ileostomy, jejunostomy).

Intestinal stoma creation, often relegated as a minor component of a larger operation, will significantly impact the patient and their support system. Stoma-related complications are common, but even absent complications patient dissatisfaction with stoma appearance and body image can negatively impact quality of life. Societal stigmas, ignorance, and misunderstandings can further complicate care. Conscientious surgical stewardship and collaborative nursing care can decrease complications and improve quality of life for ostomates. As such, mastery of preparing, creating, caring for, and reversing stomas are a hallmark of the colorectal surgeon's armamentarium.

Colostomy

Configuration

Creation of an end colostomy may be indicated in several benign and malignant diseases for permanent or temporary fecal drainage (Fig. 54.1a). Low rectal cancer, recurrent anal cancer, severe anorectal Crohn's disease, and severe radiation proctitis may require a permanent end colostomy. An end colostomy may be used emergently for severe sigmoid diverticulitis (i.e., Hartmann's procedure) and as means of trauma-related damage control. An end colostomy may be a better option for patients who are not suitable candidates for restorative procedures; examples may include fecal incontinence, severe neurologic impairment, the elderly, prohibitive medical comorbidities, and prior resection of the anal sphincter complex. Although sphincter-preserving operations increasingly garner attention, the end colostomy remains the preferred option in many cases.

A loop colostomy can be used to divert fecal flow proximal to a tenuous anastomosis or problematic distal bowel, on

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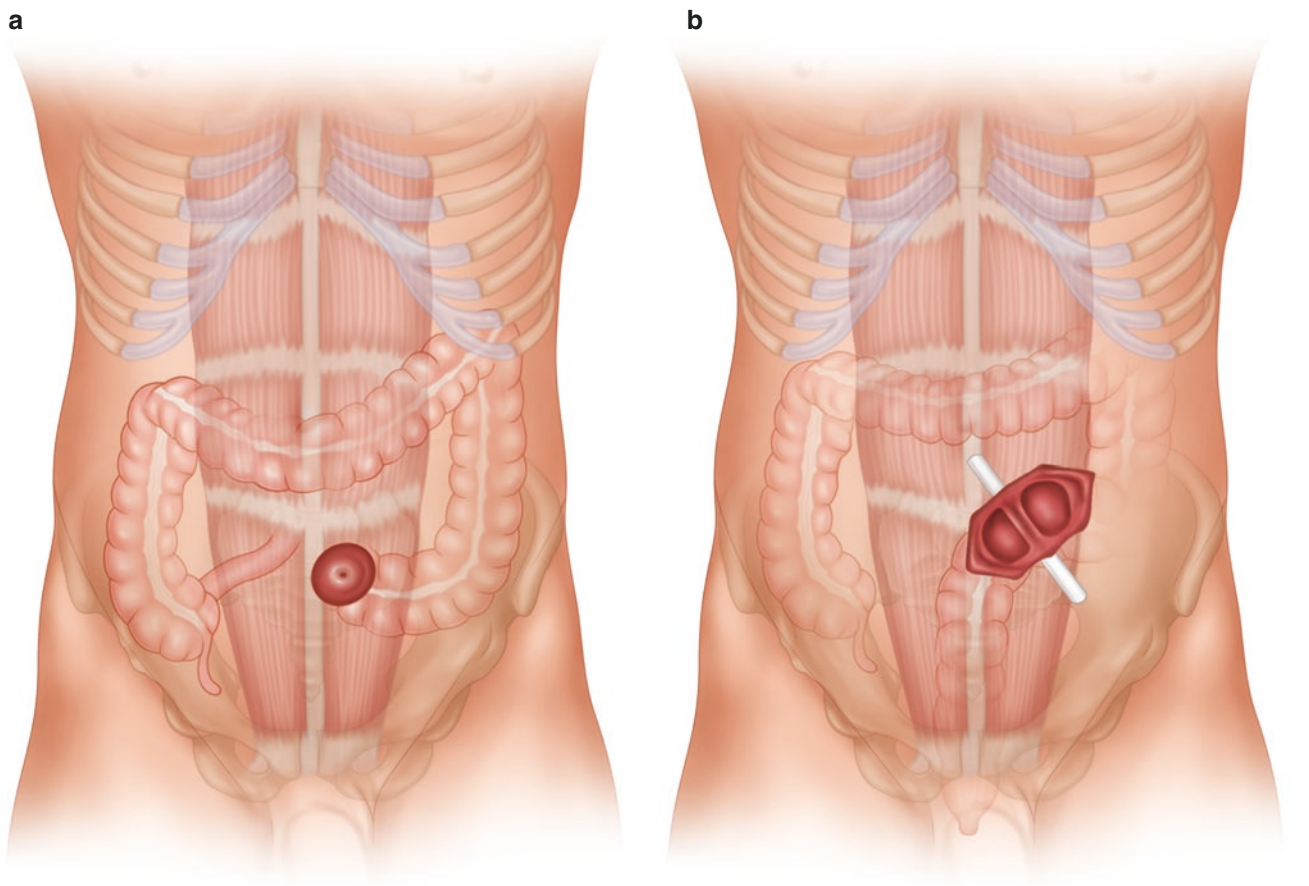

Fig. 54.1 (**a**) End descending colostomy. (**b**) Loop sigmoid colostomy

a temporary or permanent basis (Fig. 54.1b). The redundant, non-peritonealized nature of the sigmoid and transverse colon make each suitable for a loop colostomy, although high outputs and prolapse may hinder transverse colostomies. The dual lumen nature of the loop colostomy allows proximal diversion with retrograde venting of the distal segment, rendering the loop colostomy an excellent option for palliative diversion of obstructing lesions of the distal bowel. The loop colostomy may be used to temporarily protect a colorectal or coloanal anastomosis.

A loop colostomy may also be used to temporarily divert stool and facilitate staged repair for pelvic sepsis, rectal trauma, nonhealing sacral decubitus ulcers, and anorectal fistulizing processes. Rarely, an iatrogenic or traumatic perforation of the colon can be mobilized and exteriorized as a loop colostomy, with the injury incorporated as the stoma orifice. Although a transverse loop colostomy is a relatively simple stoma to create, it is often poorly tolerated by patients due to its large size, cephalad location on the abdominal wall, and frequent stoma-related complications. In most instances, a loop ileostomy provides better short-term and long-term outcomes. Since both proximal and distal bowel conduits are readily accessed through the stoma trephine, loop stomas can often be closed easily through a local peristomal dissection, thereby avoiding laparotomy.

Physiology

Colostomy function is dependent upon the level of diversion. The colon receives approximately 1500–2000 mL of liquid stool from the small bowel daily, of which it reabsorbs approximately 90% of the water (1350 mL) and excretes 100–150 mL of water within solid waste [2, 3]. The majority of colonic fluid and electrolyte reabsorption occurs in the right colon. Distal colostomies arising from the sigmoid or left colon tend to produce more solid stool than proximal stomas fashioned from the transverse or ascending colon. Transverse colostomies may be more prone to fluid and electrolyte imbalances akin to small bowel stomas.

Similar to the wide range in bowel movement frequency and consistency observed in individuals, colostomies function variably. Since colonic transit time varies between 24 and 150 hours [2], distal colostomies may function periodi-

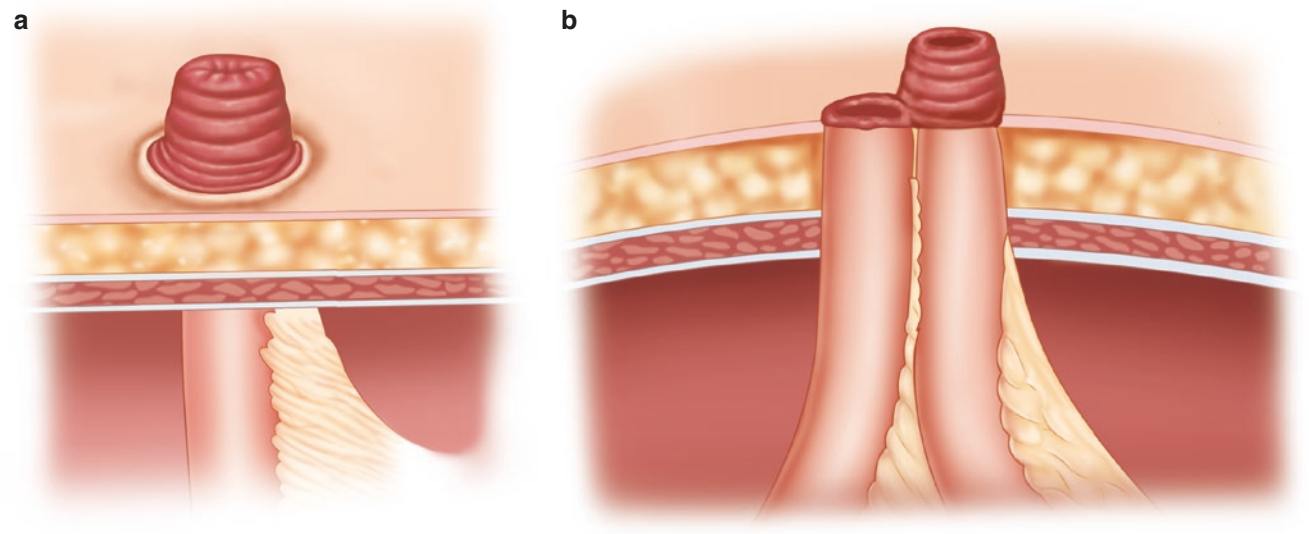

Fig. 54.2 (**a**) End ileostomy. (**b**) Loop ileostomy

cally as solid stool is propelled through the colon, whereas gas tends to pass more continuously. The episodic nature of stool passage through distal colostomies can lend itself to specialized colostomy irrigation techniques, which may enable patients to regulate stool passage or occasionally avoid a stoma appliance altogether [4, 5]. Proximal colostomies with liquid stool tend to function more continuously akin to small bowel stomas, and are not well suited for stoma irrigation techniques.

Small Bowel Stomas

Configuration

Like colostomies, small bowel stomas (e.g., ileostomy, jejunostomy) can be used for permanent or temporary enteric drainage. A permanent end ileostomy (Fig. 54.2a) is commonly used following a total proctocolectomy for Crohn's disease, whereas a temporary end ileostomy may be used following a total abdominal colectomy for ulcerative colitis in a staged ileal pouch-anal anastomosis. Patients with hereditary cancer syndromes (e.g., familial adenomatous polyposis, hereditary nonpolyposis colon cancer) or ulcerative colitis who are poor candidates for restorative procedures may be offered a permanent end ileostomy. Repetitive bowel resections, which may be seen occasionally in Crohn's disease, may require creation of a jejunostomy since no ileum may remain from prior resections. As with colostomy, a temporary small bowel end stoma may be created in a damage control situation when anastomosis creation is inadvisable due to contamination, hemodynamic instability, poor tissue quality, or preoperative patient factors including malnutrition and immunosuppression.

Like a loop colostomy, a loop small bowel stoma (Fig. 54.2b) is a helpful adjunct commonly utilized as temporary means of fecal diversion, although a well-constructed loop stoma can be permanent if needed. The small bowel caliber, robust vascularity, and distance from the distal colon and rectum make loop ileostomy a favorable choice for temporary diversion by many surgeons. Liquid ileostomy output can lead to pouching problems, dehydration, electrolyte imbalance, and renal failure. A comparison of temporary diverting loop ileostomy and colostomy is debated elsewhere in the text.

Physiology

Since small bowel stomas obviate colonic sodium and water reabsorption, they may render patients with variable, but occasionally profound, fluid and electrolyte imbalances. Small bowel length is highly variable ranging from 275 cm to 850 cm [6, 7] with a mean in situ length of approximately 500 cm [8] and receives between 9 to 10 L of fluid daily from proximal gastrointestinal sources. The majority of small intestinal nutritional absorption occurs within the first 150 of intestine, as nearly 6 L of fluid is reabsorbed from the jejunum while only 2.5 L is reabsorbed in the ileum [2]. Normal end ileostomy outputs can be highly variable ranging from 200–1200 mL daily (see Table 54.1). As a result, stomas created more proximally in the small bowel (e.g., jejunostomy) bypass absorptive intestinal surface area and may cause nutritional, electrolyte, and fluid imbalance. Since fat-soluble

Table 54.1 Composition of normal ileostomy effluent

	Daily excretion	Range	Concentration	Range
Wet weight	500 g	200–600 g		
Dry weight	38 g	24–48 g		
Water content			92%	88–94%
pH			6.3	6.1–6.5
Sodium	55 mEq	30–80 mEq	115 mEq/L	100–130 mEq/L
Potassium	4 mEq	3–6 mEq	8 mEq/L	5–11 mEq/L
Chloride	20 mEq	15–30 mEq	45 mEq/L	15–40 mEq/L
Calcium	18 mEq	15–40 mEq	25 mEq/L	10–64 mEq/L
Magnesium	8 mEq	7–9 mEq	15 mEq/L	10–28 mEq/L
Phosphorus	150 mEq	122–202 mEq		
Nitrogen	1 g	0.6–2.4 g		
Fat	2.2 g	1.5–3.8 g		

Adapted from Rombeau [2]

nutrients are absorbed in the terminal ileum, proximal fecal diversion (greater than 100 cm proximal to the ileocecal valve) can render a patient with steatorrhea and vitamin B12 deficiency. Even creation of a new terminal end ileostomy that preserves the total length of small bowel may be transiently prone to high outputs due to diversion of the ileocecal valve and colon. Management of high ileostomy outputs is detailed later in the chapter.

Preoperative Considerations for the Ostomate

As with most aspects of surgery, conscientious preoperative preparation is essential and can profoundly impact the patient. Preoperative stoma site marking and patient education improves stoma-related clinical outcomes, as well as patient quality of life and experience, while decreasing healthcare resource utilization. Although many medical centers provide robust complimentary ancillary resources to assist the ostomate and surgeon, the surgeon is ultimately responsible for perioperative care and should be competent in preoperative stoma preparation.

Stoma Site Marking

Routine preoperative identification of potential stoma sites is crucial when stoma creation is being considered and is recommended by national care guidelines and professional societies such as ASCRS and the Wound, Ostomy, and Continence Nurses Society [9–13]. Preoperative stoma site marking decreases postoperative complications [14–16]; improves stoma-specific quality of life, and overall patient quality of life, patient confidence, and independence compared to non-marked patients and may decrease stoma care costs [17]. Creating any intestinal stoma, whether permanent or temporary, in a properly chosen location is the most important predictor of an ostomate's quality of life following stoma construction.

The ideal stoma site is based on individualized assessment of the patient with respect to body habitus, contours, scars, bony prominences, and the umbilicus assessed in the standing, sitting, and laying position [18]. Special consideration to the patient's lifestyle, occupation, impairments, and preferences should be sought in conjunction with the patient. The "stoma triangle" (Fig. 54.3a) is bounded by the anterior superior iliac spine, the pubic tubercle, and the umbilicus and has been used by some groups to initially direct the surgeon to a preliminary area suitable for stomas [19]. The stoma site is at the geometric center of the triangle within the rectus sheath. Alternatively, the surgeon may identify the intersection of the infraumbilical fat pat summit and the rectus sheath as a preliminary stoma site (Fig. 54.3b, c) [20]. Efforts are typically made to locate the stoma centered within the rectus sheath, as this may decrease the risk of parastomal herniation, although this premise has been challenged in the literature [21–24].

After preliminary selection of a site, the surrounding peristomal skin must be carefully inspected ensuring the site avoids scars, folds, creases, and the umbilicus, which may hinder stoma appliance application and cause leakage (Fig. 54.4a–c). Ideally, the site should have a 2-inch perimeter of clear, intact skin to adequately seal with a stoma appliance; a commercially available stoma siting disk may help with siting (Fig. 54.3c). The costal margin, anterior superior iliac spine, and pubic symphysis should be avoided since these bony prominences may dislodge the stoma appliance (Fig. 54.4b). Skin folds and creases are not typically appreciated until the patient is sitting, so the correct site should be reconfirmed once the patient is sitting (Fig. 54.4c).

While the patient is sitting, it is equally important that the patient has a clear sight line to the stoma site. Patients with a large pannus may require moving the site superiorly along the rectus to a supraumbilical location, ensuring sight lines to the intended area. Moreover, an obese pannus may be thinner superiorly compared to inferiorly, easing stoma trephine

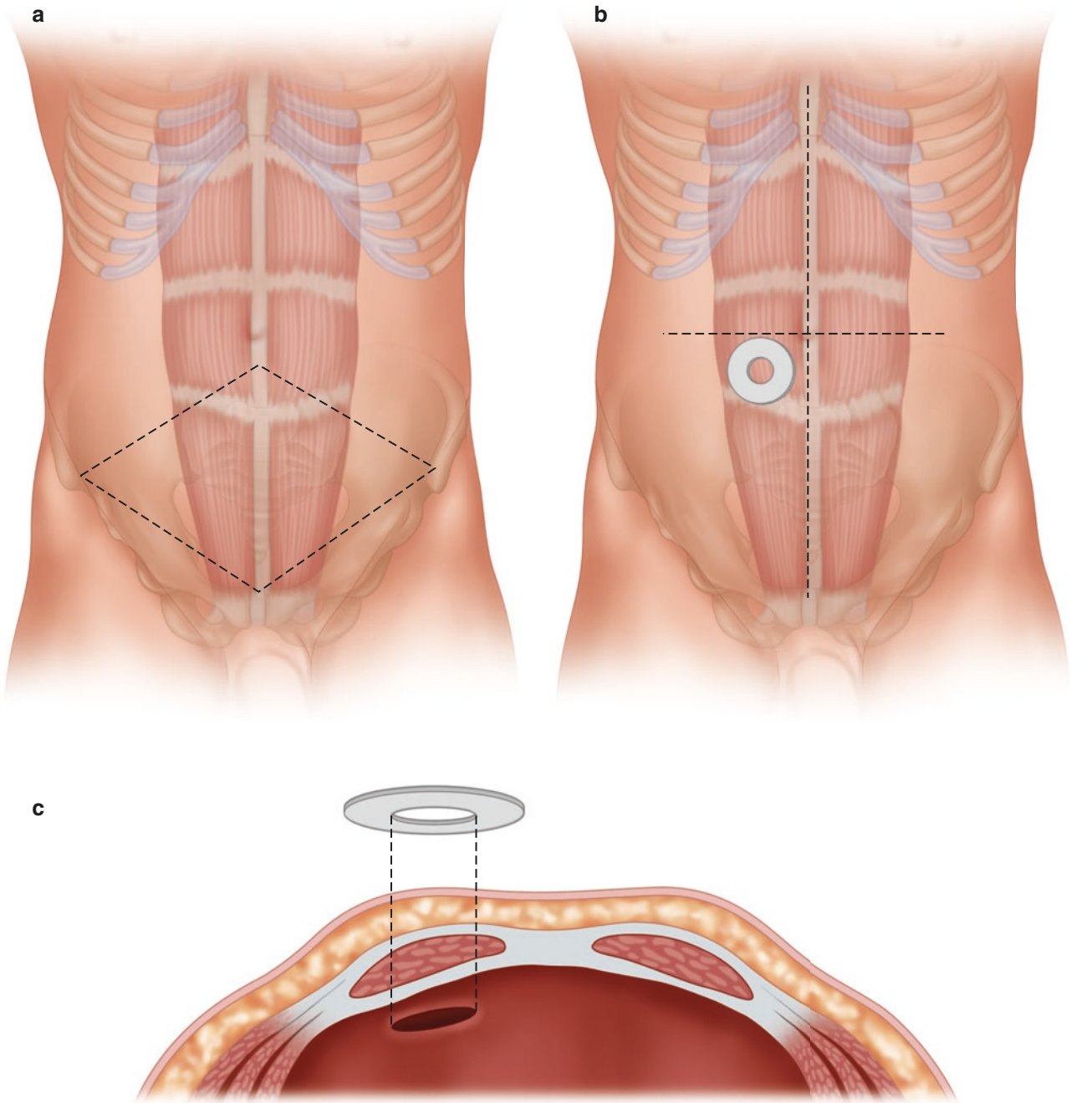

Fig. 54.3 (**a**) The "stoma triangle.". (**b**) Intersection of the infraumbilical fat pad and rectus sheath, marked by a stoma siting ring. (**c**) Cross-sectional view of the stoma trephine path and stoma siting ring, fashioned perpendicular to the abdominal wall without veering medially or laterally

creation. Lastly, the patient should be assessed while standing to confirm that the intended site avoids the pants waistline, pendulous breasts, or hernias. While standing, attention to the patient's posture, contractures, and stoma site location while bending should be assessed. Finally, reviewing potential stoma sites with the preoperative patient confirms suitable sites for both patient and practitioner.

Stoma sites should be marked with an indelible marker or tattooed with a fine gauge needle (26 gauge) and India ink [20]. Stoma sites can be marked several days in advance and protected with an occlusive transparent dressing to minimize effects of bathing. Multiple potential stoma sites can be identified, marked, and ranked in order of preference affording the surgeon options should intraoperative findings require

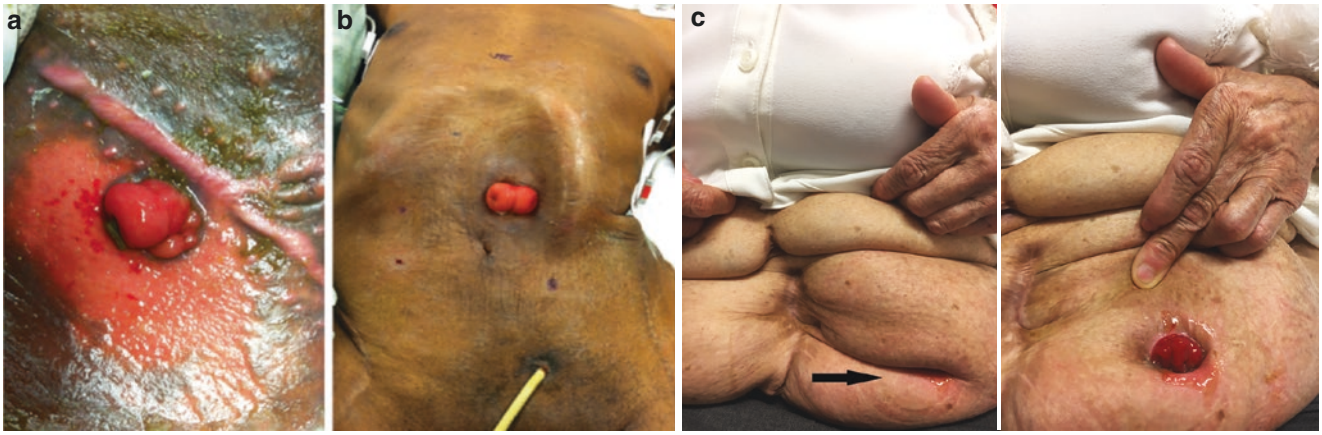

Fig. 54.4 (**a**) A loop ileostomy created too close to an incision which interfered with stoma appliance sealing, resulting in leaks and marked skin excoriation. (**b**) A transverse loop colostomy created too close to the costal margin, causing frequent appliance dislodgement. (**c**) Stomas created in a skin fold, which may not be realized until the patient is sitting or bending over. (Courtesy of Michael McGee, MD)

alternate stoma locations. Rarely, two stomas may be required for urinary and fecal drainage (e.g., for pelvic exenteration), and each stoma site should be created on opposite sides and at different levels, avoiding interference in case a stoma belt is needed. Since preoperative stoma site markings may wipe away with antiseptic skin preparations, the surgeon may find it helpful to etch a small epidermal scratch mark at each site with an 18-gauge needle following anesthesia induction to mark the site for the duration of the operation.

Preoperative Stoma Education

The mainstay of stoma education traditionally occurs in the postoperative period; however evidence suggests that preoperative educational programs may be equally important. Accordingly, societal care guidelines recommend patients receive preoperative stoma education by a specialty nurse, such as a wound and ostomy, and continence nurse before undergoing ostomy surgery [13]. Several factors may hinder postoperative stoma education. Pain, medications, and psychological stress may diminish educational effectiveness in the early postoperative period, thereby increasing the value of preoperative education. Chaudhri reported that two 45-minute preoperative visits with audiovisual aids and instruction, decreased time to postop stoma proficiency from 9 to 5.5 days, decreased hospital length of stay from 10 to 8 days, and decreased unplanned provider encounters with a net cost savings of $2104 per patient [25].

Similarly, Younis reported that preoperative patient education sessions reviewing stoma models, sample appliances, and supplies decreased inpatient length of stay from 14 to 8 days [26]. Free or low-cost commercially prepared preoperative resources are available from stoma supply manufacturers and through the American College of Surgeons (ACS). The ACS Ostomy Home Skills Kit (Fig. 54.5) contains an instructional DVD demonstrating stoma care techniques, sample stoma supplies, and a plastic model stoma that allows the patient to simulate preoperative stoma care.

The standardized interactive program has been developed by the American College of Surgeons (ACS) in collaboration with the American Society of Colon and Rectal Surgeons (ASCRS) and other societies and organizations. Over 134,000 kits have been distributed since release in 2010. Preliminary unpublished data from the ACS reveals that patients receiving the Ostomy Home Skills Kit preoperatively were more confident with stoma care, were less likely to have problems, required less provider help once home, and were more satisfied with their care compared to patients receiving standard postoperative stoma education.

Technical Considerations of Stoma Creation

Small Bowel End Stoma

Small bowel end stomas are typically easy to create owing to the mobility of the robustly collateralized small bowel mesentery. Laparoscopic or open approaches may be used, although the laparoscopic approach is favored, if feasible [9]. After selecting the target small bowel segment, care is taken to ensure the mesentery is fully mobilized and all adhesions are freed to allow tension-free reach beyond the abdominal wall. Division of some mesenteric vessels may be necessary to obtain adequate reach, particularly in patients with thick abdominal walls. If mesenteric vessels are divided to gain sufficient reach, care should be taken to ensure adequate perfusion at the tip of the stoma conduit as evidenced by palpable mesenteric pulses, arterial bleeding from the cut

Fig. 54.5 The American College of Surgeons Ostomy Home Skills Kit. Reused with permission from the American College of Surgeons

edge of the mesentery, or novel imaging perfusion assessments such as indocyanine green (ICG)-enhanced fluorescence (see section "End Colostomy" for a discussion of ICG perfusion assessment).

During open surgery, identification of mesenteric vessels can be facilitated by transillumination of the mesentery with a light source, providing guidance on which vessels to preserve or sacrifice to sustain stomal perfusion, if needed. Akin to preparing bowel for an anastomosis, careful assessment of bowel perfusion can avoid ischemia-related stomal complications such as stenosis and retraction. Obese patients or those with thickened or inflamed small bowel mesentery may require additional lengthening maneuvers detailed later in this chapter (see section "Special Circumstances: The Difficult Stoma").

Once adequate mobilization of the small bowel segment is obtained, a cylindrical stoma trephine is created at the previously marked stoma site. For an end ileostomy with normal caliber bowel and mesentery, the authors prefer to excise an approximately 2-cm diameter skin disk and vertically divide the subcutaneous tissues down to the level of the anterior rectus sheath without "coring" or removing subcutaneous tissues. During open surgery, an assistant's two fingers firmly pushing a folded gauze sponge anteriorly at the intended point of peritoneal entry may ease trephine creation by compressing the tissue girth and ensuring the trephine cylinder remains orthogonal to the abdominal wall (Fig. 54.6). The anterior rectus sheath is incised with a 3-cm vertical incision. The exposed fibers of the rectus muscle are carefully spread with a large clamp to allow lateral and medial distraction of the split rectus muscle to expose the posterior rectus sheath. Special care is taken to ensure all fibers of the rectus muscle and inferior epigastric vessels are completely retracted to avoid pesky muscular bleeding. With the posterior rectus sheath exposed, cautery is used to make a 3-cm vertical incision directly onto the assistant's gauze sponge, whereby completing the stoma trephine. Passage of one or two fingers through the completed trephine gently dilates and confirms trephine size. If necessary, the trephine diameter can be further enlarged by making a radial skin incision at the skin level or extending either anterior or posterior rectus sheath incisions.

Laparoscopic approaches follow the same general principles as open surgery. After assuring adequate mobilization laparoscopically, an abdominal wall trephine is made. If an extraction site is present, a trephine can be made akin to open surgery with an assistant using two digits pressing upward. If no extraction site exists, careful trephine creation is needed to avoid injuring intra-abdominal contents while incising the posterior rectus sheath and peritoneum. Once the trephine is completed, pneumoperitoneum is quickly lost, and it can be difficult to locate the target segment of bowel through the small trephine. An extra-small plastic sleeve wound retractor placed in the stoma trephine may aid visualization. The authors suggest placing a locking atraumatic bowel grasper on the tip of target loop of bowel, left immediately under the peritoneal side of the stoma trephine, so that the bowel can easily be visualized once pneumoperi-

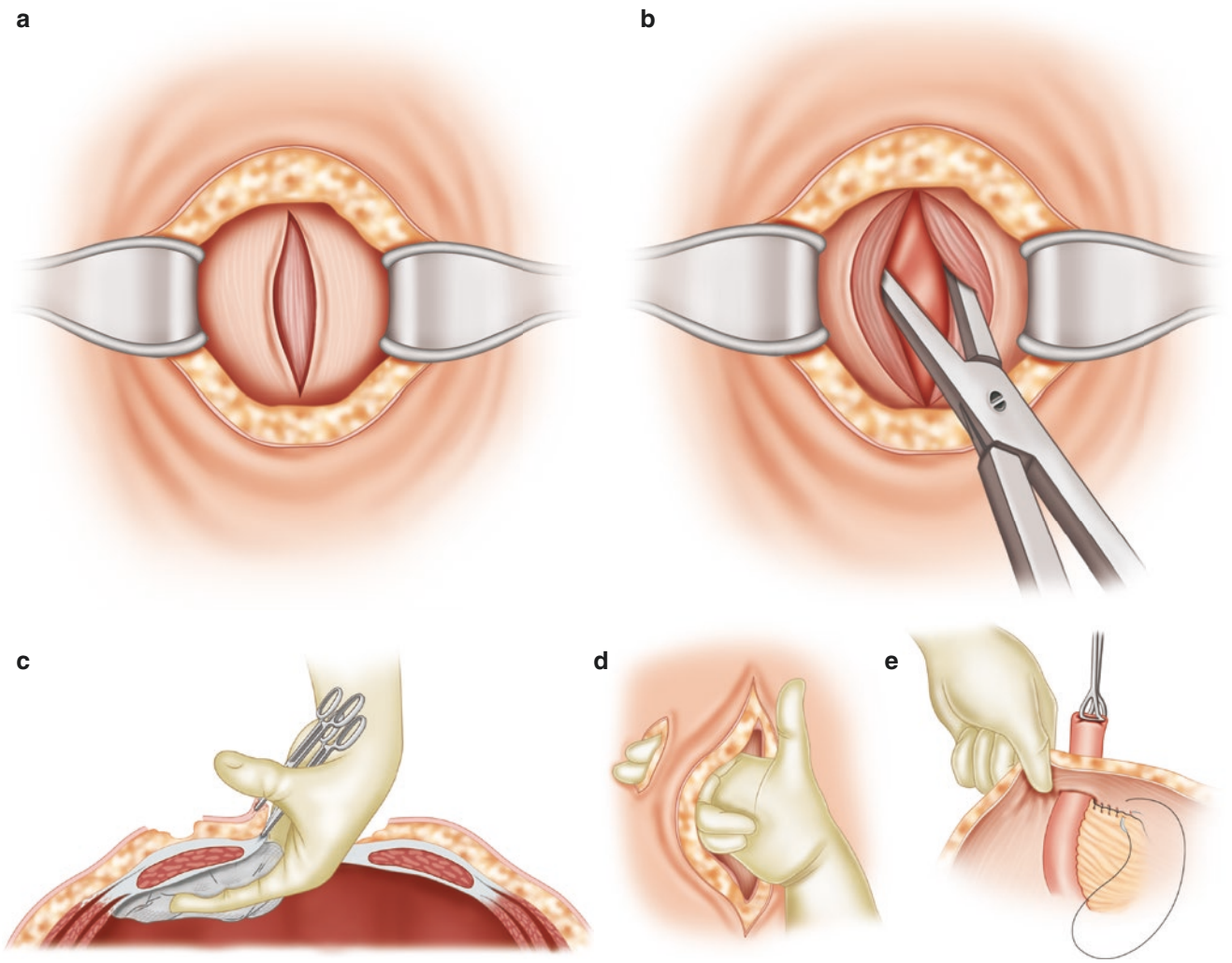

Fig. 54.6 Creation of an end small bowel stoma. (**a**) A 2-cm skin disk is excised, and the subcutaneous tissues are split to the level of the anterior rectus sheath. (**b**) The anterior and posterior rectus sheaths are incised vertically, and the rectus muscle is split. (**c**) An assistant may assist in stoma creation by pushing anteriorly using a folded sponge to protect intra-abdominal contents. (**d**) Two fingers are passed through the completed stoma trephine to assure adequate sizing. (**e**) The ileostomy is eviscerated with assistance of a Babcock clamp

toneum is lost. Once the abdomen is desufflated, the laparoscopic bowel grasper can be directed to a stoma trephine. Once the target bowel is identified through the trephine, it can then be transferred to a Babcock clamp placed through the trephine.

For both open and laparoscopic techniques, the previously mobilized bowel segment is carefully delivered through the properly sized trephine with assistance of a Babcock clamp. To avoid stoma retraction, 5–6 cm of small bowel and corresponding mesentery should be completely pulled through and be left above the level of the skin. The authors generally recommend to pull slightly more intestine through than needed to ensure adequate mobilization. Care should be taken to carefully coax the corresponding bowel mesentery through the trephine without injury or avulsion. A bimanual approach may be necessary to gently push and guide the bowel mesentery from the peritoneal trephine while the surgeon is gently pulling. The blunt side of an Adson tissue forceps can be used as a shoehorn and facilitate the stoma mesentery mobilization, if it lodges at the rectus sheaths or subcutaneous tissues. Additional techniques are described to help coax the difficult stoma through the abdominal wall later in the chapter (see section "Special Circumstances: The Difficult Stoma").

With an adequate length of bowel exteriorized through the abdominal wall, the stoma should be assessed for tension, viability, and mesenteric bleeding. A persistently dusky stoma may be related to mesenteric vascular injury, venous outflow occlusion from a narrow trephine, or unin-

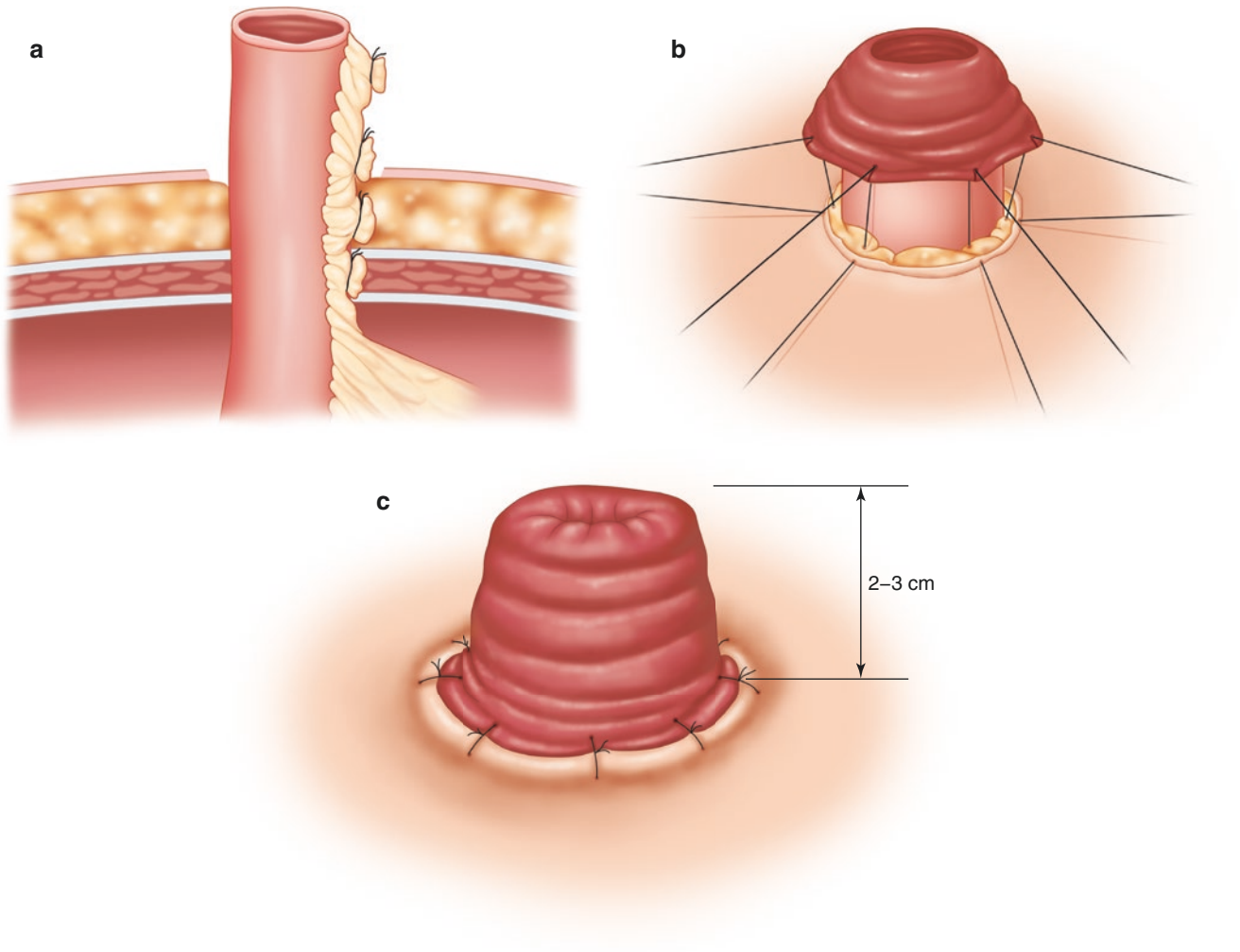

Fig. 54.7 Maturation of an end small bowel stoma. (**a**) An adequately mobilized, tension-free, length of small bowel is eviscerated through the stoma trephine. (**b**) Multiple interrupted absorbable sutures are used to mature the stoma. (**c**) The completed small bowel stoma should ideally protrude 2–3 cm from the skin level

tentional vascular division during mesenteric mobilization and should be revised prior to closing the abdomen. Typically, the stoma is left for maturation until all other abdominal wounds are closed to minimize incisional contamination.

Once all remaining abdominal wounds are closed and protected from topical contamination, the end ileostomy is matured to ideally protrude 2–3 cm. Ileostomy maturation is necessary to cover and protect the eviscerated bowel serosa with mucosa, whereby shielding it from the caustic bowel effluent which can cause inflammatory serositis and ileostomy stricture. If the ileostomy was stapled closed, the staple line is excised, and the full thickness of the bowel wall is everted. Occasionally, thick or fatty mesentery may require careful debulking to allow complete bowel wall eversion; however these maneuvers should be performed carefully to avoid devascularizing the stoma. Multiple interrupted absorbable sutures are used to suture the everted bowel wall to the skin (Fig. 54.7).

Classically, such "Brooke" sutures also incorporate a seromuscular purchase of the bowel at the skin level that fixes the everted structure at the skin. Historically, dogma dictated that sutures should carefully be placed through the dermis, but not the epidermis, to avoid mucosal cellular implants that have been reported to migrate along suture lines and colonize the epidermis with ectopic mucosal islands. Such dermal mucosal islands were thought to secrete mucus on the peristomal skin and interfere with stoma appliance adhesion [27]. A recent prospective, randomized study showed a modest reduction in postoperative peristomal excoriation using full-thickness (dermal and epidural) skin fixation sutures compared to "intradermal" (dermal but no

epidermal) fixation during ileostomy maturation [28]. Despite a reduction in nurse-assessed skin excoriation from 52% to 41% using full-thickness skin sutures, there was no difference in stoma-specific quality of life outcomes, stoma supply costs, or other complications between skin fixation modes. Broader applicability of the study may be limited by the short 3-month study follow-up and suture material variation between groups.

The finished end small bowel stoma should ideally protrude 2–3 cm from the skin, which improves sealing and decreases complications [9, 12, 15]. Flush or inadequately protruding small bowel stomas may be fraught with leakage since caustic liquid small bowel contents can easily leak underneath the stoma flange causing painful, excoriated, weeping skin wounds that are difficult to pouch. Ileostomy heights less than 2 cm are associated with problems, and the height of the stoma is inversely proportional to likelihood of complications [29]. Since a significant portion of end stomas will be permanent, the surgeon should take great care in making the perfect stoma, which may save the patient, surgeon, and family a lifetime of frustration.

Small Bowel Loop Stoma

Small bowel loop stomas are fashioned with either laparoscopic or open techniques with a segment of well-mobilized bowel free of adhesions. For open loop stomas, a fine-tipped clamp is passed to create a small defect at the bowel wall mesentery interface, and a thin Penrose drain or umbilical tape is passed underneath the bowel (Fig. 54.8). Some prefer to place different colored seromuscular marking stitches to orient the bowel limbs and prevent twisting and inadvertently maturing the distal limb of the loop. Alternatively, correct bowel orientation can be insured by drawing an arrow on the anti-mesenteric border of the bowel indicating the proper direction of intestinal flow. A 2.5-cm diameter stoma trephine is made at a previously marked site using the previously described technique. Generally, the stoma trephine is made slightly larger for loop stomas than end stomas, and the final trephine typically accommodates two fingers easily. The Penrose drain is then used to safely pull the loop of bowel through the stoma trephine while minimizing trauma to the bowel. The surgeon confirms that there is no twisting

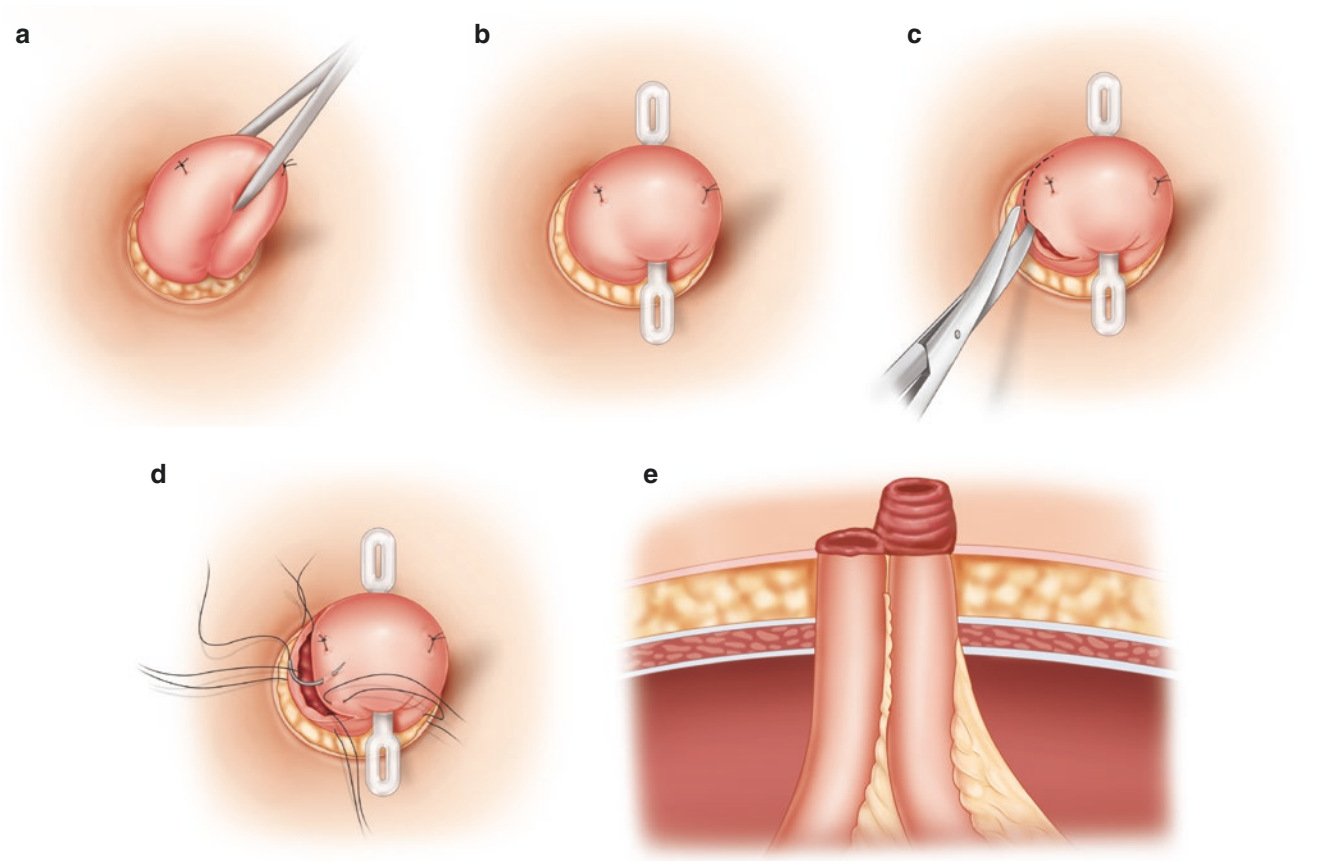

Fig. 54.8 Creation of a loop small bowel stoma. (**a**) A narrow Penrose drain is passed through a mesenteric defect and used to gently pull the target loop through the stoma trephine. (**b**) The Penrose drain may be exchanged for a stoma rod. (**c**) The distal segment of the loop stoma is opened at the skin level. (**d**) The distal "hood" of small bowel is then everted and sutured over the proximal limb to create a spout. (**e**) The completed small bowel loop stoma

of the mesentery. The blunt paddle-like back end of an Adson forceps is again helpful if the bowel is caught at the fascia or dermal level. Laparoscopic loop stomas are made similarly to laparoscopic end stomas as detailed above.

The Penrose drain may be exchanged for a plastic stoma rod to temporarily support the bowel loop above the skin until adhesions form between the trephine and bowel wall, although the utility and type of a supporting rod is debatable [30]. If used, the rod should not be under significant posterior tension, and additional bowel should be mobilized or pulled through the trephine if the rod is causing a deep indentation. A 2019 meta-analysis of five studies suggested that the use of stoma rods did not alter rates of stoma retraction and were associated with increased rates of stoma necrosis and peristomal dermatitis. Broader applicability of the study is limited by assignment biases, low BMI patients, and questionably long periods of stoma rod use that ranged from 7 from 14 postoperative days [31]. Given the ambiguity surrounding the therapeutic index of stoma rods, the authors espouse conditional use of stoma rods until more conclusive data is available.

Following closure and protection of all abdominal wounds, a near-circumferential incision is made along the distal limb bowel wall at the level of the skin. The mesenteric portion of the bowel wall is left intact and is not divided. Absorbable sutures are used to secure the defunctioned segment to the dermis. The remaining "hood" of bowel is then everted with the blunt back end of an Adson clamp and sutured to the dermis. As with end small bowel stomas, the proximal bowel limb should protrude 2–3 cm from the skin when finished allowing a watertight fit between the stoma appliance and the peristomal skin, whereby decreasing postoperative stoma-related complications. When used, the stoma rod is typically removed in 3–5 days once adhesions have formed assuming there is no tension between the rod and skin. Although loop stomas are often considered temporary, they should be constructed durably in the event that distal intestinal continuity cannot be restored. The use of intra-abdominal anti-adhesion materials may be considered to decrease adhesions and possibly ease subsequent reversal at temporary ostomy sites [9, 32–34].

End Colostomy

Creation of an end colostomy follows similar techniques as described for small bowel stomas, but the tenuous colonic blood supply requires special consideration. Both laparoscopic and open approaches can be used. For either approach, great care should be taken to assuredly and completely mobilize the intended segment of colon so that several centimeters of bowel reaches above skin level in a tension-free manner. Unlike the relatively mobile small bowel mesentery, the colonic conduit and mesentery may require substantial mobilization depending upon the level of diversion. An end sigmoid colostomy may not require significant mobilization due to the redundant nature of the sigmoid loop in a thin patient; however a proximal end descending colostomy may require full mobilization of the splenic flexure with high vascular ligation to obtain sufficient reach in an obese patient. The authors strongly suggest that the surgeon treats the colonic conduit akin to an anastomosis by eliminating tension with adequate colonic mobilization and assuring adequate perfusion. It may be helpful to excise all epiploic appendages from the anti-mesenteric bowel wall easing eventual evisceration.

For open end colostomies, once the segment of colonic conduit is chosen and prepared, a 2.5-cm diameter stoma muscle-splitting trephine is fashioned at the site of previous marking using the previously described techniques. An end colostomy may require a larger trephine depending upon the bowel caliber and mesentery thickness. Epiploic appendages may be excised to ease colon passage through the abdominal wall trephine. The colon is passed through the stoma trephine with a Babcock clamp and eviscerated. The surgeon confirms a pink, well-perfused stoma that rests comfortably for 3–4 cm above the skin level without tension or retraction. Following closure and protection of abdominal wounds, the colostomy is opened everted and sutured to the skin to produce a colostomy that protrudes 1–2 cm. Typically, the solid nature of colostomy effluent is not toxic to surrounding skin, and a lengthy stoma eversion is not necessary. If necessary, a colostomy can be made flush with the skin, but the authors suggest 1–2 cm of protrusion helps patients with stoma pouching and skin care. Once matured, the colostomy should be evaluated to confirm adequate perfusion with a pink glistening mucosa. Laparoscopic end colostomies utilize the same principles as detailed above.

When creating end stomas, particularly colostomies, maintaining perfusion to the distal tip of the stoma can be difficult. Often seen in obese patients and those with inflamed or foreshortened mesenteries, there may be a balance between maintaining conduit length in order to avoid stoma retraction and guaranteeing reliable perfusion. In such circumstances, assessing perfusion to the most distal aspect of the stoma is both difficult and essential. Intraoperative gross "naked-eye" optical evaluation of the stoma can be misleading since visible ischemic changes to the mucosa or serosa may take hours to days to develop. Since an error in evaluating stoma perfusion can lead to mucosal sloughing, mucocutaneous separation, stenosis, retraction, and necrosis, assessing stoma perfusion should be a critical step in stoma creation.

Many intraoperative assessments can guide the surgeon to ensure adequate perfusion to the distal aspect of the stoma. Generally, simple measures such as confirming palpable

mesenteric pulses or pulsatile arterial bleeding from the cut edge of the mesentery at the stoma tip are cheap and straightforward. Recently, the advent of near-infrared fluorescence with indocyanine green (ICG) infusion has been used to evaluate intestinal perfusion prior to anastomoses. This technology can also be used to evaluate stomal perfusion. The segment of the colon or ileum to be used for stoma creation is mobilized, and the stoma trephine is created using the aforementioned principles. The bowel is passed through the stoma site and exteriorized. ICG is then infused intravenously while a specialized near-infrared camera is focused on the stomal segment. Well-perfused tissue will fluoresce, while non-perfused tissue will lack enhancement. Any non-perfused segment is excised and the stoma recreated using well-perfused intestine. On occasion, venous congestion may cause the stoma to appear congested and dusky to the naked eye despite ICG fluorescence, whereby indicating venous outflow compression from an overly tight stoma trephine. When venous outflow obstruction is suspected, the trephine can be enlarged slightly, and the perfusion will improve. If ICG fluorescence indicates adequate perfusion, the stoma will very rarely develop any ischemic consequences. Venous congestion may last for several days, and occasionally self-limited inconsequential mucosal sloughing will develop. ICG fluorescence is a fast and highly accurate test but relies on proprietary optical systems that may not be available to all surgeons. Whether simple and cheap methods such as assessing for palpable pulses or pulsatile arterial bleeding at the tip of the mesentery or using specialized technology like ICG fluorescence, the authors recommend that some form of perfusion assessment be used during end stoma creation.

Loop Colostomy

A loop colostomy is typically fashioned from the non-peritonealized sigmoid or transverse colon, although any segment of colon can be used in a loop configuration with adequate mobilization via open or laparoscopic techniques. After identifying the target segment of colon, an assessment of reach and mobilization is performed assuring the colon loop reaches several centimeters above the previously marked stoma site without tension. For open surgery, a narrow Penrose drain is passed through an avascular recess at the junction of the mesentery and colon wall. After creating an approximately 3-cm diameter trephine using the aforementioned techniques, the colon loop is gently pulled through the trephine and delivered over a stoma rod. Following closure and protection of abdominal incisions, the loop colostomy is matured by incising along the long axis of the bowel and maturing the cut edge of bowel to the skin circumferentially (Fig. 54.9). The matured loop colostomy

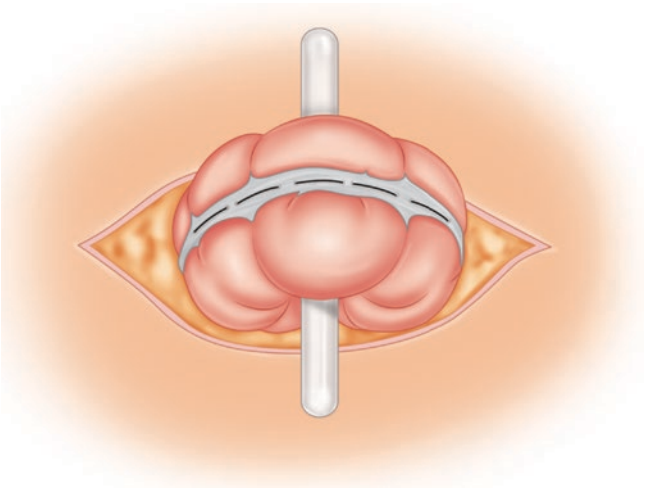

Fig. 54.9 Creating an incision along the long axis of the colon to create a loop colostomy

may be quite large depending upon the bowel caliber, mesenteric thickness, and postoperative edema. As with loop small bowel stomas, loop colostomies may be temporary or permanent and should always be constructed durably if stoma reversal will be inadvisable. Laparoscopic techniques follow similar principles as detailed above. As with loop small bowel stomas, the use of intra-abdominal anti-adhesive products may be considered with temporary loop colostomies to potentially ease future reversal [9].

Postoperative Care for the Stoma

Early Inpatient Postoperative Care

Immediately after creation, the stoma will become edematous and swell to two to three times the original size. The stoma will typically shrink to normal size after approximately 4–6 weeks. The new stoma should be monitored daily and assessed for color, viability, and retraction and should remain pink, moist, and protrude well. If a stoma rod was used, the rod may be removed 3–5 days postoperatively or when centripetal tension decreases and the rod easily slides out. The stoma rod can be left for longer periods of time for difficult or tenuous stomas.

Both small bowel and colonic stomas do not typically function immediately. Stoma outputs initially resemble small volumes of serosanguinous or mildly bilious thin fluid without particulate matter, described as "bowel sweat." Bowel function will recover with time and stoma outputs will increase. Colostomies tend to produce gas first, followed by liquid stool, and ultimately more solid waste as time proceeds – although this cadence can be variable. Small bowel stomas tend to function sooner than colostomies. Even dur-

ing fasting, small bowel stomas will produce significant volumes or dark green bilious outputs. As diet is advanced, particulate materials intensify, and small bowel effluent becomes increasingly thicker.

As described earlier, small bowel stoma outputs can be high leading to profound dehydration and electrolyte abnormalities. As early postoperative bowel function returns, a deluge of backlogged bowel contents may rush out producing initially high stoma outputs. Small bowel stoma outputs generally taper with time but may require dietary and medical management if outputs are persistently high (see Section "Stoma Complications: The High Output Stoma"). Over 30% of new ileostomy patients may experience dehydration with early postoperative readmission rates exceeding 15% [35]. Recent studies show that perioperative stoma care pathways focusing on patient education, standardized discharge criteria, output logs, visiting nurse care, and early follow-up may decrease postoperative readmissions related to dehydration and should be strongly considered for new ostomates [9, 36, 37].

Patient-centered postoperative stoma education should begin as soon as the patient can participate. Since approximately half of stoma care is provided by a spouse and a quarter of stoma care is provided by an offspring, caregiving family members should participate in stoma education [17]. The ultimate goal is to train the patient and caregivers to become proficient in caring for the stoma. Postoperative patients typically follow a graduated program that focuses on both knowledge and skills training for emptying, applying, and troubleshooting common stoma problems. Many new ostomates are only capable of emptying a stoma pouch at time of discharge. As a result, patients are often discharged home lacking knowledge on how to manage common pouch-related issues. Unpublished data from the American College of Surgeons revealed only 53% of homegoing new ostomates were capable of applying a new pouch and only 28% were able to fix pouch leaks. As a result, 45% of all new homegoing ostomates worried about self-care, 40% felt sad and/or depressed, and 62% were uncomfortable leaving home. Accordingly, many institutions bridge inpatient postoperative stoma care and education into the outpatient domain with home nursing.

Postoperative Outpatient Care

Many groups, including ASCRS and the Wound, Ostomy, and Continence Nurses Society (WOCN), believe that optimal care for patients undergoing ostomy surgery includes preoperative and postoperative care by an ostomy nurse specialist, such as a WOCN-certified nurse [9, 13]. Periodic stoma assessment and educational reinforcement should continue following discharge from stoma surgery, particularly in the early postoperative period when stoma-related complications are most frequent. Attention should be paid to stoma outputs and the frequency with which the stoma flange is changed, which is a good surrogate for peristomal skin quality and leakage. Ideally, a flange should last 3–5 days between changes. More frequent appliance changes may indicate improper technique, inappropriate appliance, peristomal skin disease, or a poorly located or constructed stoma. A published survey indicated that on a scheduled postoperative visit with a WOCN nurse, over 60% of new ostomates had peristomal skin irritation that was unrecognized by nearly half of patients of patients. Once identified and treated, stoma-specific quality of life improved [38]. In addition, structured postoperative group sessions may prove beneficial to the ostomate even in the late postoperative period [39]. Ostomy support groups, which are organized online and in person, may provide ongoing support for novice and experienced ostomates alike [40].

Stoma Appliances

Stoma appliances come in a variety of sizes and configurations but generally consist of an adhesive flange (wafer) that seals to the skin and a collecting bag which may come in one- or two-piece models (Fig. 54.10). Two-piece appliances allow the collection bag to completely detach from the flange and allow inspection of the stoma without completely removing the flange and may be advantageous in the early postoperative period while the stoma is examined daily. Stoma flanges are generally comprised of a pectin-like adhesive wafer ring surrounded by waterproof tape-like layer. The inner diameter of the ring comes in various sizes and can often be trimmed with scissors to accommodate larger or irregularly shaped stomas. Generally speaking, the wafer should be trimmed to the exact size of the stoma leaving little to no peristomal skin exposed to bowel contents. Disposable stoma sizing templates are available from most stoma supply manufacturers. Appropriate sizing and trimming of stoma appliances are crucial – particularly during the first 6 weeks as stoma edema subsides. Survey data indicates the average ostomate places a new flange every 4–5 days. The flange should be changed every 3–7 days depending upon peristomal skin care needs [41].

Collection bags come in a variety of sizes in both clear and opaque models based on patient preference. Venting charcoal filter bags may be used to help patients with voluminous gaseous outputs. High output bags may be used to connect to a leg collection system akin to a Foley catheter. Bags should be emptied at the discretion of the patient. New small bowel stoma patients are encouraged to log outputs for the first several weeks and monitor for high outputs.

Specialized stoma appliances may be necessary depending upon the condition of the peristomal skin, stoma morphology, and body habitus. Convex stoma appliances feature

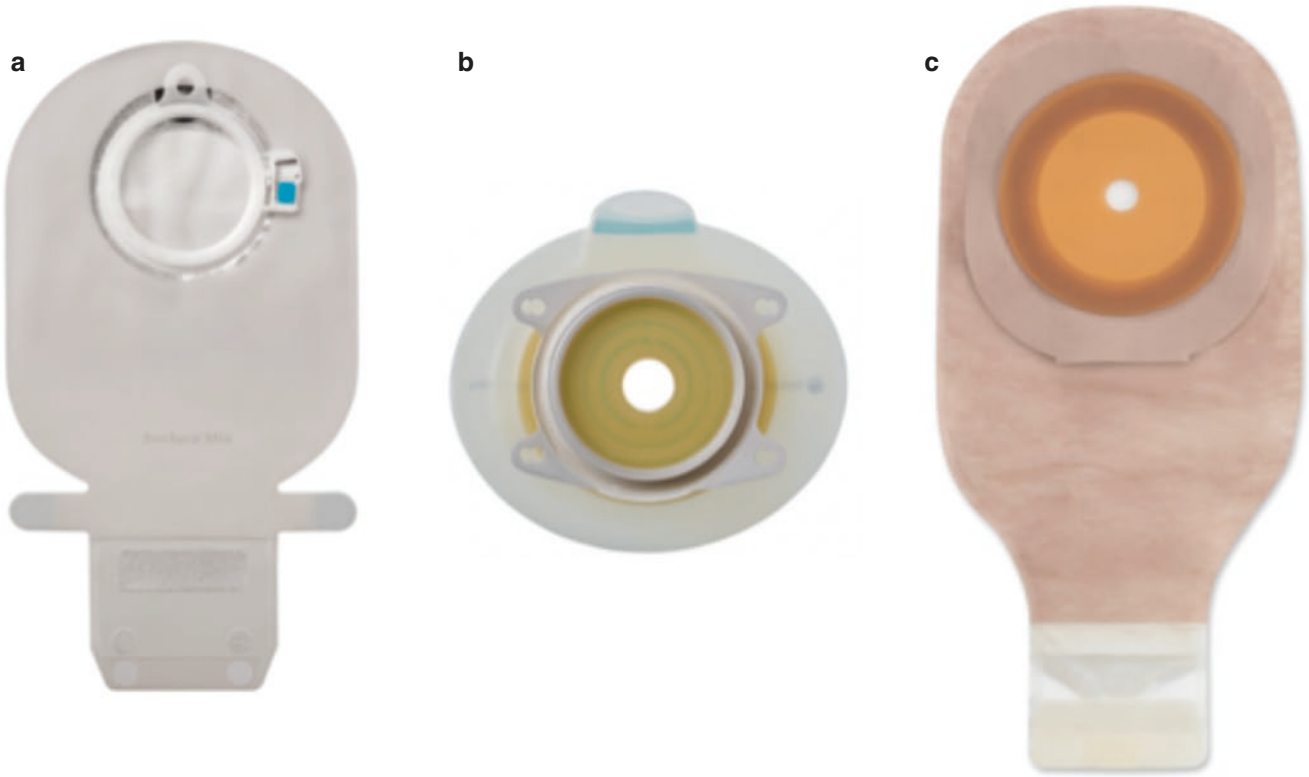

Fig. 54.10 (**a**) and (**b**) Two-piece stoma appliance with flange and pouch. (**c**) One-piece stoma appliance

a bowl-shaped wafer that assists sealing flush or retracted stomas. Elastic stoma belts may be used to bolster skin sealing for leak-prone stomas. Stoma paste and preformed stoma barrier rings may be used to improve sealing between the peristomal skin and wafer and may be particularly useful when skin folds or scars create an uneven peristomal skin surface. A variety of skin adhesives, protectant wipes, adhesive removers, and topical powders are available to assist with difficulties surrounding the peristomal skin.

Table 54.2 Stoma complications

Complication	Incidence rates (%)
Retraction	0–22
Parastomal hernia	0–40
Stoma prolapse	0–10
Stoma necrosis	0–7
Peristomal skin problems	10–42
Total complications	12–72

Adapted from Salvadalena [43]

Stoma Complications

Stoma problems are ubiquitous and profoundly impact ostomate quality of life but can often be mitigated with proper care and education in collaboration with stoma care professionals such as WOCN nurses. American Colloege of Surgeons American College of Surgeons National Surgical Quality Improvement Program data showed a 37% unadjusted complication rate for elective cases involving a stoma and 55% complication rate for emergency operations [42]. Stoma-specific complications are even higher when considering patient-reported outcomes (Table 54.2). Early stoma-related complications such as leakage, peristomal dermatitis, and dehydration tend to arise from stoma management issues that can be remedied with stoma care and education. Prolapse, stenosis, and parastomal hernia are late-term stoma-related complications and may require surgery for definitive correction. Although specialized stoma care nursing is available at many institutions, recognition, care, and management of stoma-related complications are under the purview of the colorectal surgeon.

Stomal Ischemia: Necrosis, Retraction, and Stenosis

Poorly perfused stomas can necrose in the early postoperative period (Fig. 54.11a). Arterial insufficiency is the most common cause of stoma necrosis; however venous ischemia

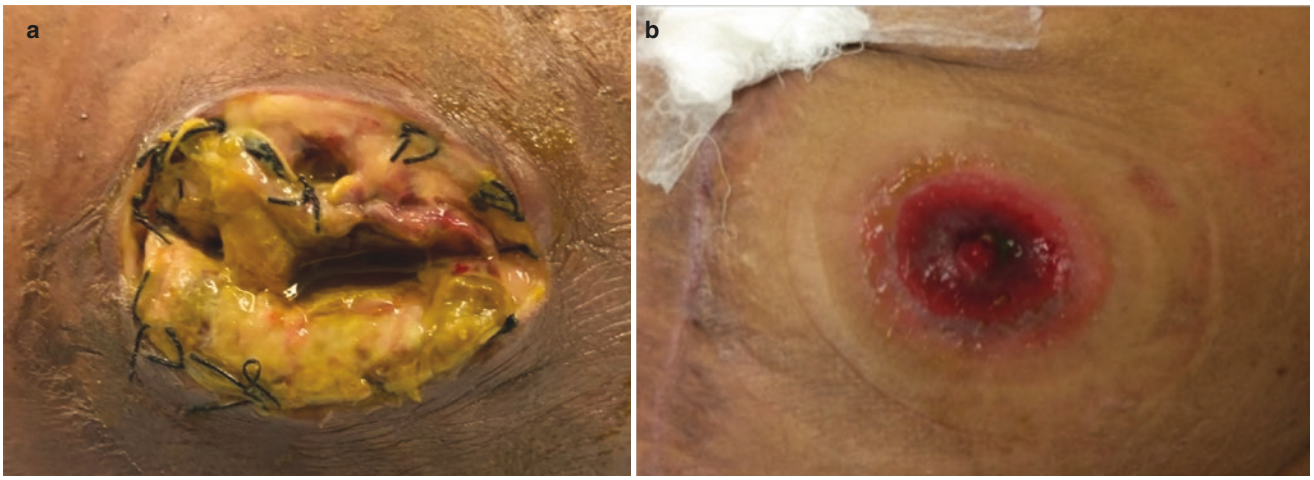

Fig. 54.11 (**a**): Acute postoperative stoma necrosis with mucocutaneous separation [courtesy of Michael McGee]. (**b**) Chronic ileostomy ischemia leading to retraction, stenosis, difficulty pouching, and peristomal erosions. (Courtesy of Adam Stein, MD)

can rarely arise from fascial obstruction within the trephine. Loop stomas, which preserve collateralized mesenteric vasculature proximal and distal to the stoma, are more resistant to ischemia than end stomas, which require mesenteric division and typically rely upon unidirectional arterial flow. Proper stoma creation techniques can help avoid ischemia-related stoma complications by assuring adequacy of bowel perfusion. Intraoperative assessments of mesenteric pulses, pulsatile bleeding from the cut edge of the mesentery, nuisance bleeding from the cut edge of the bowel wall, ICG fluorescence, and mucosal evaluation can mitigate risk of stoma ischemia and related complications.

Akin to ischemic colitis, marginally perfused stomas may demonstrate variable degrees of ischemia with regard to timing, length, and depth of the ischemic bowel segment, rending early postoperative assessment of stoma viability crucial. Stoma ischemia typically begins with mucosal pallor and progresses to petechiae, cyanosis, and purple-black mucosal necrosis. Mild stomal ischemia may cause limited, partial-thickness mucosal necrosis and slough; but deeper bowel wall layers may remain viable. The most distal edge of the stoma, typically matured to the peristomal skin, is the segment most vulnerable to ischemia. As the everted bowel wall courses proximally, a perfusional gradient may be seen where ischemia may transition to a viable bowel wall.

Identification of the proximal extent of the ischemic stoma is crucial and can often be identified with a bedside "test tube" examination. A lubricated clear glass test tube is inserted through the stoma os while a flashlight is directed down the stomal lumen. The illuminated glass permits bedside mucosal evaluation for the length of the tube, allowing the surgeon to assess the proximal extent of mucosal ischemia along the stomal conduit. Management of early postoperative stoma ischemia varies between small bowel and colonic stomas. Any stoma with early evidence of subfascial ischemia (i.e., posterior to abdominal wall fascia) should be revised, since deep ischemia may progress to frank intraperitoneal necrosis and perforation. A colostomy appearing viable anterior to the fascia may be carefully observed without revision, since intraperitoneal perforation is unlikely, and solid colostomy outputs can be reasonably pouched even if distal stoma necrosis renders the stoma flush with the skin. A partially viable permanent end ileostomy with significant ischemia of the muscularis, however, should be revised promptly in the early postoperative period in suitable operative candidates, since distal necrosis may result in a flush ileostomy that is difficult to pouch.

Long-term mild ischemia may result in late-term stoma stenosis and retraction (Fig. 54.11b). Nonischemic stomal retraction can be seen in patients with inadequately mobilized stoma conduits and the obese. Akin to ischemic colitis, necrosis and atrophy of the bowel conduit may cause variable degrees of stomal stricturing and/or retraction that may necessitate surgical revision depending upon symptom severity. Asymptomatic mild stoma stenosis or retraction can be carefully observed provided an adequate seal is maintained with pouching and the peristomal skin remains healthy (Fig. 54.12). Skin-level symptomatic colostomy stenosis can be locally revised provided the majority of the supra-fascial colon is normal. Subfascial stomal stenosis may require intra-abdominal approaches to mobilize a new segment of well-perfused bowel. A chronically retracted colostomy can be observed absent stenosis or pouching problems; however a difficult-to-pouch small bowel stoma may require local revision or complete resection and creation of a new stoma.

Peristomal Skin Disorders

Peristomal skin disorders are the most commonly occurring complication for ostomates [43]. Although skin irritation can occur at any time during the course of the stoma, dermatologic conditions are most commonly seen in the early postoperative period as the ostomate learns proper stoma care techniques. Up to 70% of new ostomates may have peristomal dermatitis, which is often unrecognized by the patient [38, 44–47]. Fortunately, most peristomal skin complications arising from a well-constructed and properly located stoma can be successfully managed with local wound care.

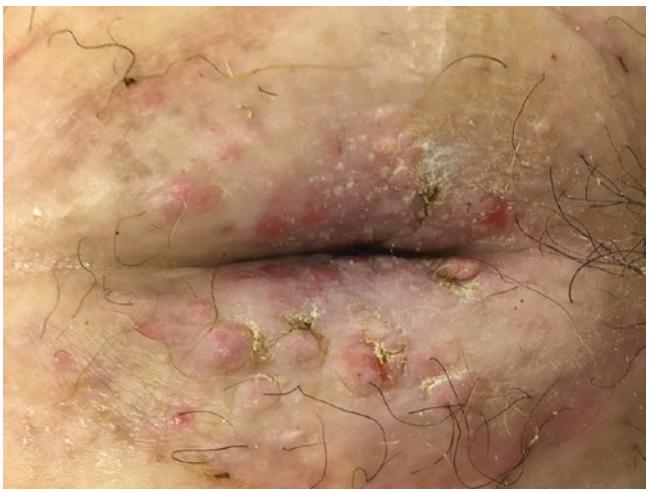

Fig. 54.12 (**a**, **b**) Chronic stoma stenosis. (Courtesy of Michael McGee, MD)

Most peristomal skin irritation arises from poorly fitted or improperly sized appliances that expose vulnerable peristomal skin to potentially caustic stoma effluent (Fig. 54.13) [46]. Leakage begets leakage, as irritated peristomal skin weeps exudative fluids that hinder stoma appliance adhesion; this further worsens leakage, excoriation, and appliance maladhesion. Leakage often requires frequent appliance changes, which inflicts additional mechanical trauma to vulnerable peristomal skin. Pouch leaks and peristomal skin excoriation are best treated with a critical reappraisal of pouching apparatus and sizing. Care should be taken to ensure the stoma flange aperture is sized and trimmed to fit the mucocutaneous junction perfectly, so that no skin is exposed to stoma effluent. Flush or poor-fitting stomas may benefit from a convex pouching system or application of a stoma belt which may improve sealing at the mucocutaneous junction. Protective skin barrier wipes can be used to create a thin polymeric layer to improve and protect skin integrity at the pouch-skin interface. Weeping superficial peristomal skin excoriation can be treated with a thin layer of topical stoma powder. Peristomal contour issues such as peristomal indentations, skin folds, and mucocutaneous separation may be filled with stoma paste or a preformed barrier ring to "caulk" under-the-flange leakage.

Fungal peristomal infections typically appear as reddened, shiny patches with satellite papules involving the skin underlying the stoma appliance flange [45]. *Candida albi-*

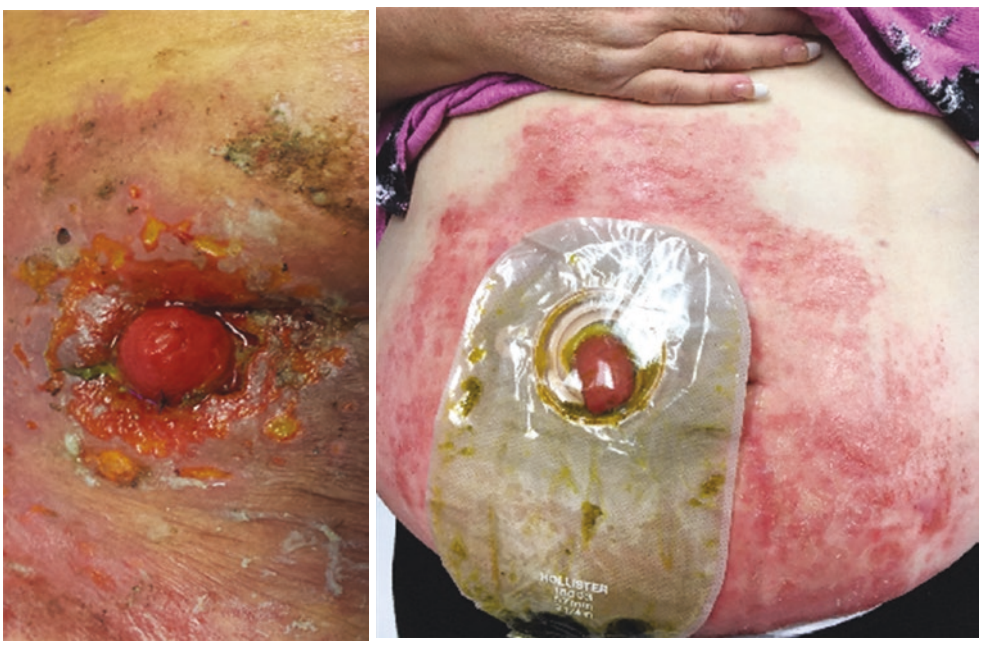

Fig. 54.13 Peristomal skin excoriation and ulceration attributed to an ill-fitting stoma appliance. (Courtesy of Michael McGee, MD)

cans, the most common skin fungus, can proliferate in the warm moist environment at the skin-appliance interface causing itching, irritation, and pain. A fungal infection is first treated by removing and assessing the pouching system for occult leaks that add to skin moisture and irritation. Topical antifungal powder such as nystatin is then applied and rubbed into the irritated peristomal skin. Excess powder is then brushed off, and a skin sealant is typically applied over the powder to enable application of a new stoma appliance. This process is repeated with each appliance change until the rash resolves which usually occurs within 1–2 weeks. In rare cases, topical miconazole and clotrimazole or oral antifungal agents may be required for treatment of resistant fungal dermatitis.

The importance of assessing the peristomal skin cannot be overstressed, particularly in the early postoperative period. High-risk patients, such as those with low health literacy, poor support systems, and emergently created stomas, require special attention. Additionally, obese ileostomy patients are at a higher risk of developing peristomal skin issues owing to the liquid nature of effluent and stoma creation challenges seen in thick abdominal walls [48]. As postoperative stoma edema subsides, the first several postoperative weeks require gradual adaptations in the pouching system to accommodate a shrinking stoma. New homegoing ostomates should be made aware that the stoma diameter will gradually shrink and that the flange aperture should be trimmed smaller over time. Since the majority of peristomal skin disorders can be treated with pouching adjustments, postoperative WOCN support, if available, is an immensely valuable tool for the duration of the patient's stoma. Studies indicate a majority of ostomates do not realize a treatable dermatologic condition exists [44, 48] and, when treated, can expect an improvement in quality of life [38]. To that end, routine postoperative follow-up with a stoma care professional, such as a WOCN-certified nurse, is recommended [9, 41].

Peristomal Pyoderma Gangrenosum

Pyoderma gangrenosum is a rare inflammatory skin disease characterized by painful ulcers with well-defined erythematous or violaceous undermined borders (Fig. 54.14) [49]. Approximately 0.5–5% of patients with inflammatory bowel disease can develop peristomal pyoderma gangrenosum (PPG). Pyoderma gangrenosum is also associated with rheumatoid arthritis, paraproteinemia, or hematologic malignancy in half of patients; PPG appears to be idiopathic in 25–50% of patients [49–51]. Peristomal pyoderma gangrenosum can be seen in approximately 0.6% of ostomates; however some postulate the actual incidence may be higher due to underdiagnosis [50]. For unclear reasons, peristomal pyoderma is associated with female gender, autoimmune disorders, and obesity in IBD patients [50–52]. Nearly 70% of patients presenting with peristomal pyoderma were noted to have reported a concurrent flare of underlying systemic disease in a 2019 meta-analysis [53]. Pyoderma, although poorly understood, is felt to arise from pathergy arising from local skin trauma, which may explain a predilection for the peristomal skin. While peristomal pyoderma is associated with inflammatory bowel disease (IBD), nearly 20% of peristomal pyoderma patients will not have IBD [53].

Diagnosis of PPG is made clinically and requires a high index of suspicion. Lesions characteristically begin spontaneously with a firm, pink, or purple hemorrhagic nodule at the peristomal skin in contact with the stoma appliance. The nodule typically enlarges and ulcerates rapidly, to produce a painful and occasionally purulent ulcer with a raised border [49]. Thin bridges of persisting epidermis may be seen spanning the ulcer. Biopsies of the ulcer margin typically reveal nonspecific epidermal neutrophil infiltration, edema, and perivascular lymphocyte infiltration. Although skin biopsies may exclude other dermatologic processes such as malignancy and infection, biopsies and cultures are usually not helpful in diagnosing pyoderma due to a lack of pathognomonic histologic and microbiologic findings [54, 55].

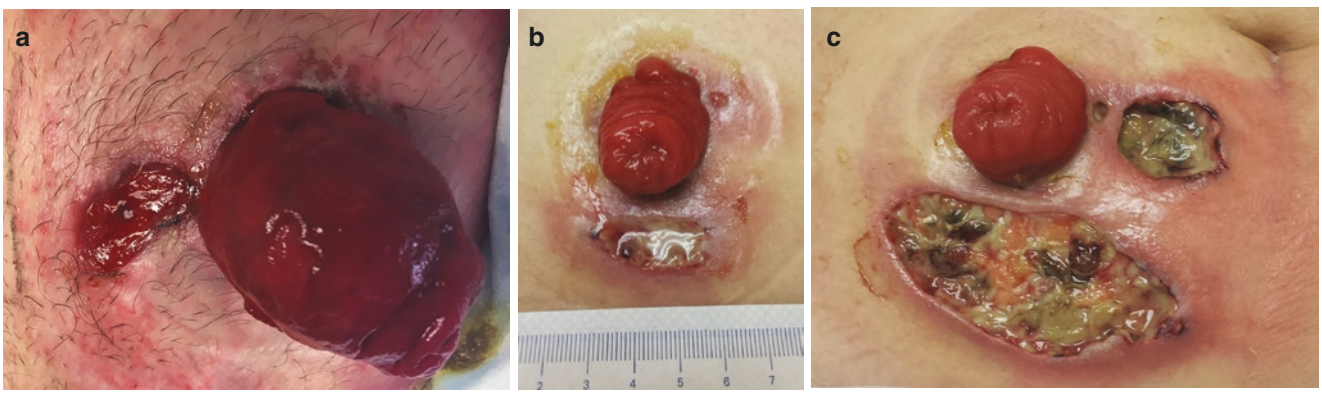

Fig. 54.14 Peristomal pyoderma gangrenosum. (Courtesy of Michael McGee, MD)

There is currently no standard treatment algorithm for pyoderma gangrenosum. Management of peristomal pyoderma utilizes a multidisciplinary approach to treat causative underlying disorders with early and aggressive wound and stoma care [54]. Pyoderma often parallels intestinal IBD activity and may indicate occult intestinal disease activity. Topical, intralesional, and systemic steroids, immunomodulators, and antibiotics have been used to successfully treat peristomal pyoderma [53, 56]. Following a stepwise approach, increasingly powerful systemic immunomodulators and biologics have also successfully healed peristomal pyoderma [54]. Absorbent-type dressings such as protective foam, calcium alginate, and hydrogel dressings covered with an occlusive dressing can be used to create a protective dry barrier over the wound while controlling for wound seepage [55]. Treatment efficacy can be assessed by monitoring the characteristically raised and undermined wound edge that flattens as the wound heals [54].

A combination of intralesional steroid injections and gentle ulcer debridement has been reported to completely heal 40% and partially heal an additional 40% of parastomal pyoderma patients [57]. Some investigators have begun to question if intralesional injections exacerbate pathergy and advocate the use of topical agents such as tacrolimus and steroids while touting healing rates approach 60% [53]. These acceptable results should be interpreted cautiously, since over 50% of treated patients ultimately required stoma resiting for disease control. A 50% healing rate with medical therapy including a combination of topical, intralesional, and systemic steroids and antibiotics, systemic cyclosporine, and infliximab has also been reported [50]. A large case series reported complete healing of peristomal pyoderma with separate surgical resection of nonstomal bowel containing active IBD [53]. Ultimately, stoma resiting may be necessary for treatment refractory peristomal pyoderma; but relocation does not guarantee against pyoderma recrudescence.

Peristomal Varices

Akin to esophageal, gastric, and rectal varices, portosystemic venous shunts may also develop between the stoma and abdominal wall arising to peristomal varices in the setting of chronic portal hypertension. Parastomal varices are identified as a circumferential blue or purple subcutaneous ring extending from the mucocutaneous junction to the peristomal skin (Fig. 54.15). Additional clinical findings of parastomal varices include a raspberry appearance of the stoma, visibly dilated stomal submucosal veins, peristomal caput medusa, and easy bleeding hyperkeratotic skin [58]. Peristomal varices may also be found within the stomal lumen. Commonly seen in IBD patients with concomitant primary sclerosing cholangitis, parastomal varices can also be seen in ostomates with alcoholic cirrhosis and those with an extensive metastatic burden to the liver. The incidence of peristomal varices is unknown but may occur in 27–50% of ostomates with portal hypertension [59, 60].

Peristomal variceal hemorrhage can be heavy and occasionally life-threatening. Approximately 40% of patients with parastomal varices will bleed and require transfusion, with the average time from stoma formation to first hemorrhage being 70 months [58]. Following stabilization and correction of any coagulopathy, hemorrhage can typically be first treated with local measures such as digital pressure, application of epinephrine-soaked gauze, and suture ligation [61]. Suture ligation of the bleeding varix is not typically durable but may temporize heavy bleeding. Approximately 85% of patients will rebleed after local non-

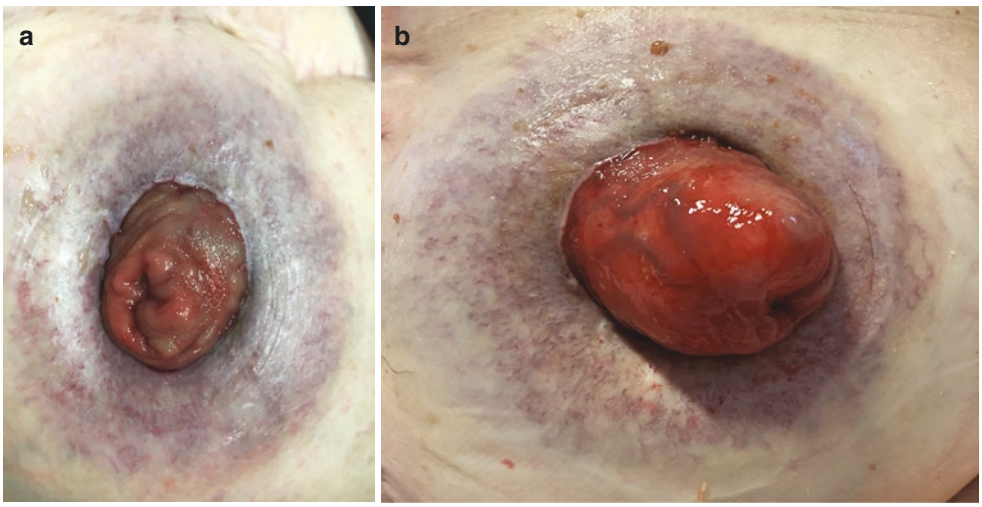

Fig. 54.15 Peristomal varices. (Courtesy of Michael McGee, MD)

operative management of parastomal hemorrhage [58]. Portal decompression, most commonly with a transjugular intrahepatic portosystemic shunt (TIPS), is approximately 5 times more effective than local nonoperative measures in durably treating hemorrhage and cured variceal bleeding in nearly 80% of patients [58, 62, 63]. Moreover, liver transplant may be indicated depending upon the etiology of liver disease but may only be possible for a fraction of patients with stomal varices [58]. Alternative nonoperative treatments using injection sclerotherapy, systemic octreotide, and percutaneous embolization may effectively treat parastomal varices [58, 59, 64–66]. Following local treatments, proper and gentle stoma care with a flexible flange should be employed since the friable varices dwell at the skin-pouch interface [67].

Surgical mucocutaneous disconnection may be employed when local therapy fails and portal decompression is not possible. This local surgery involves a cylindrical incision around the mucocutaneous junction to the level of the anterior fascia with identification and ligation of varices and re-maturation of the stoma. Preoperative peristomal infiltration of dilute epinephrine may assist with hemostasis during this potentially bloody procedure [61]. The surgeon should prepare for significant blood loss, and necessary blood products should be available for transfusion. Varices will recur over time, but the local procedure can be performed repeatedly if needed. Stoma resiting procedures can be carefully considered for suitable variceal patients experiencing concomitant pouching difficulties arising from a parastomal hernia or poorly constructed stoma. The risks of this highly morbid procedure in a high-risk patient need to be thoughtfully balanced with anticipated benefits and life expectancy.

While a stoma is not always avoidable, special situations may arise where portal hypertensives and early cirrhotics can be offered stoma-sparing surgery with the goal of potentially avoiding parastomal varices. Stoma avoidance is particularly germane in the setting of primary sclerosing cholangitis (PSC)-associated inflammatory bowel disease where reports of peristomal variceal hemorrhage can occur in up to 53% of patients within 4 years of total proctocolectomy with end ileostomy [68]. Since patients with ulcerative colitis and PSC can successfully undergo restorative proctocolectomy with an ileal pouch-anal anastomosis (IPAA) and avoid a permanent stoma and varices [69, 70], IPAA is usually the treatment of choice [71]. If necessary, IPAA may be performed safely following TIPS or liver transplant [72, 73]. Although IPAA avoids a permanent stoma, PSC-associated pouchitis can develop in over 50% of patients with PSC within 4 years of pouch creation [70].

Stoma Prolapse

Bowel proximal to an end stoma may intussuscept through the matured stoma, creating stoma prolapse (Figs. 54.16 and

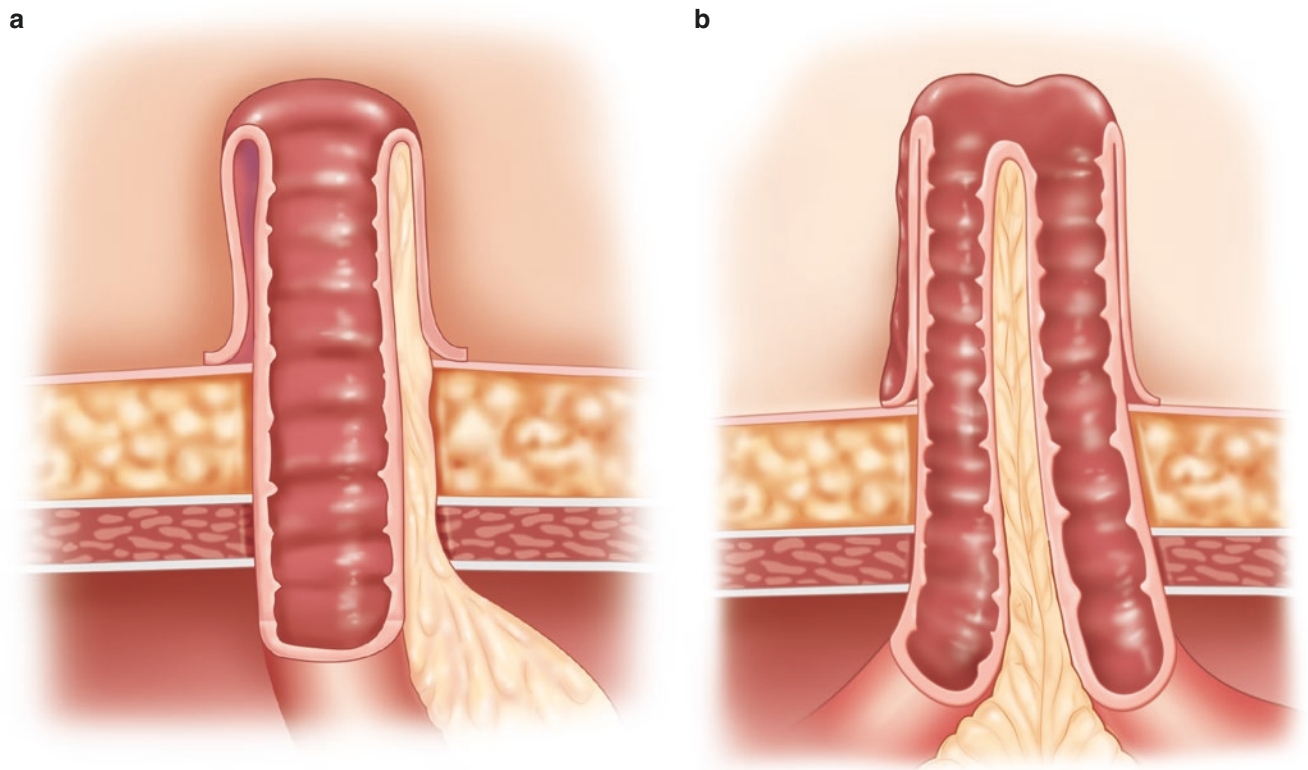

Fig. 54.16 (**a**) Prolapsed end stoma. (**b**) Prolapsed loop stoma

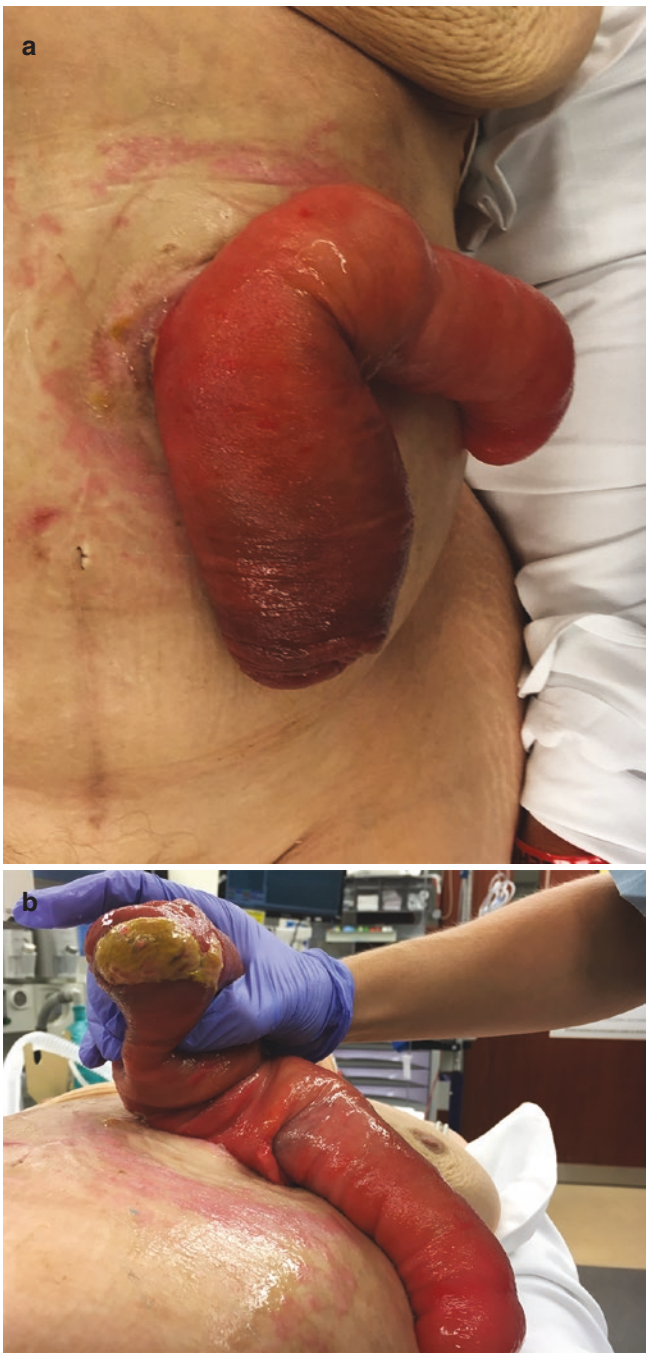

Fig. 54.17 (**a**) Prolapse of a prolapsed loop transverse colostomy (**b**) ischemic mucosa at the tip of the prolapsed stoma. (Courtesy of Michael McGee, MD)

54.17). Loop stomas may prolapse bowel from either limb. Stoma prolapse is categorized as fixed or sliding depending upon the mobility of intussusceptum. A mobile sliding prolapse classically describes the problematic variant that can be seen in up to 8% and 47% of end and loop stomas, respectively [74]. Stoma prolapse is theorized to arise from a combination of a mobile bowel mesentery, increased intra-abdominal pressure, enlarged stoma trephine, or fixation failure of the opposing everted stomal serosa surfaces. Stoma prolapse can cause from mild cosmetic concerns to moderate difficulties pouching to cases of incarceration and strangulation.

Minimally symptomatic stoma prolapse may be managed with reassurance, modification of stoma appliances, and addition of an external fixation device. Significantly symptomatic stoma prolapse may require surgical revision in suitable operative candidates via local parastomal or open abdominal approaches. Anecdotal reports describe various stoma prolapse repair techniques, but no compelling method prevails. In the absence of steadfast evidence, conventional wisdom dictates local procedures are first attempted, relegating more extensive intra-abdominal procedures for recurrent or complicated prolapse. Prolapsing temporary loop stomas are best treated with timely reversal when possible. Prolapsing permanent stomas can be treated with local amputation of the prolapse with reanastomosis, local excision of the stoma and intussusceptum with de novo stoma creation, or prolapse reduction and fixation. Some advocate concomitant seromyotomies to promote serosa-to-serosa bonding along the apposed serosal surface of the everted matured stoma to minimize future prolapse. A series of 10 patients successfully underwent subcutaneous placement of a permanent prosthetic mesh cerclage strip surrounding the peristomal subcutaneous skin without recurrence or infection at a median follow-up of 25 months [75].

Intra-abdominal correction of stoma prolapse has been described using a myriad of techniques, largely focusing on fixation of the intussusceptum and corresponding mesentery. Intra-abdominal techniques may be preferable when prolapse is associated with a concomitant parastomal hernia. Intra-abdominal approaches facilitate suture fixation of prestomal mesentery and/or bowel conduit directly to the peritoneum with variable rates of success. Some propose routing the prestoma conduit through a preperitoneal tunnel lateral to the linea semilunaris prior to exiting through a transrectus trephine, thereby fixating bowel and mesentery; the utility of this technique is debatable (Fig. 54.18a) [76]. Prolapsing permanent loop colostomies commonly are related to prolapse of the distal limb and can be converted to an end or loop-end stoma by dividing the distal limb. Alternatively, the distal limb of a loop colostomy may be sutured to the peritoneum to limit excursion (Fig. 54.18b). Ultimately, a prolapsing stoma can be moved to a new site using any of the above adjuncts to mitigate future prolapse, although isolated stomal prolapse without associated parastomal hernia rarely benefits from stoma relocation.

Rarely, prolapsed stomas will become incarcerated, and reduction may become increasingly difficult to reduce, as cumulative lymphatic and vascular compression worsens stomal engorgement and edema. Beside attempts to reduce a viable incarcerated prolapse may be aided with sedation, anxiolytics, and analgesics, whereas strangulated prolapse mandates immediate surgery. Topical ice and table sugar have been reported to decrease edema within the prolapsed stoma and ease reduction [77]. Incarcerated prolapse may progress to infarction and require immediate surgery (Fig. 54.19).

Transient short-segment stomal "pseudoprolapse" may be seen during pregnancy owing to increased intra-abdominal pressure related to uterine displacement of abdominal vis-

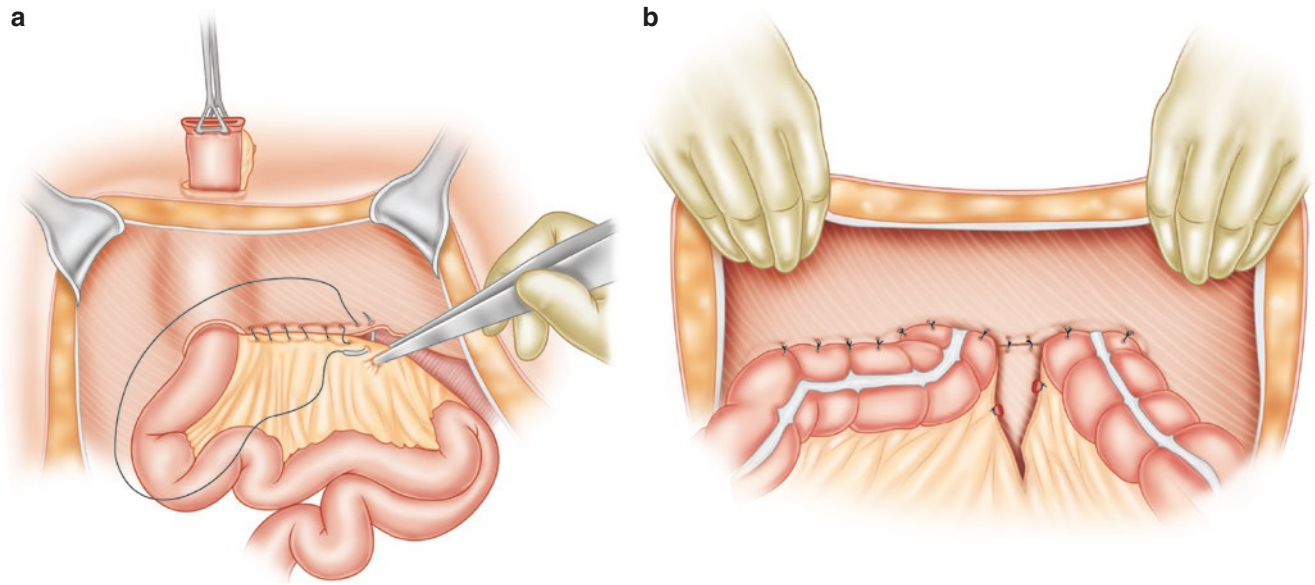

Fig. 54.18 (**a**) Retroperitoneal tunneling of an end ileostomy with suture pexy of the prestomal mesentery to limit prolapse. (**b**) Suture pexy of the distal limb of a loop colostomy to mitigate prolapse of the distal limb

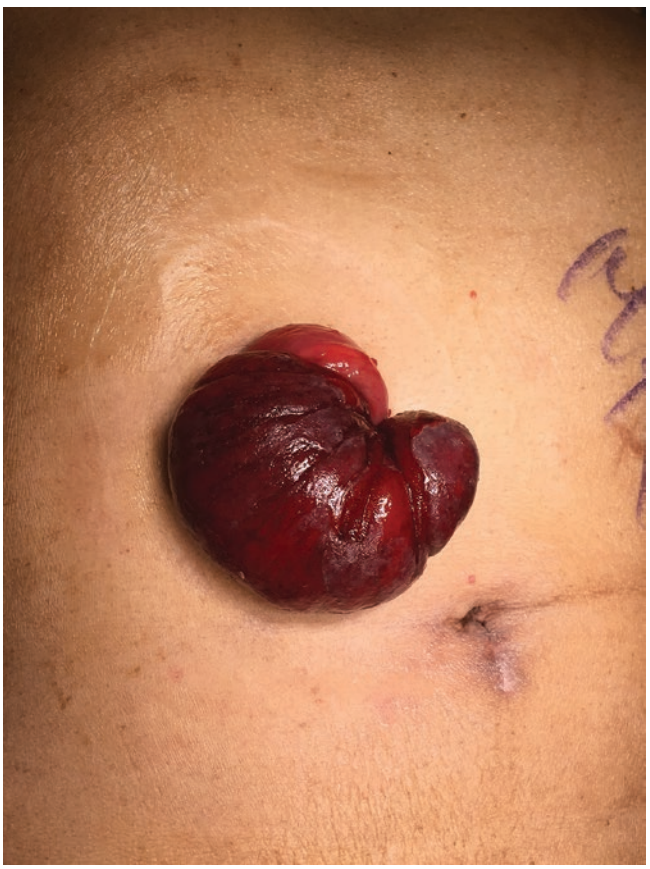

Fig. 54.19 Stomal prolapse with ischemia and infarction. (Courtesy of Michael McGee, MD)

cera. Such prolapse is typically less than 3 cm long and resolves following delivery. Pregnancy-related pseudoprolapse does not typically merit surgical revision unless symptoms persist beyond the postpartum period [78].

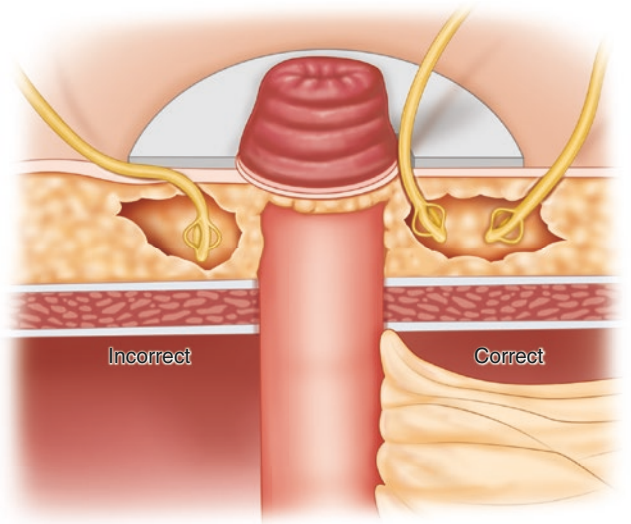

Fig. 54.20 Percutaneous drainage of a parastomal abscess

Peristomal Abscess

Rarely, an ostomate may develop a peristomal abscess. Peristomal tenderness, swelling, and erythema may indicate a subcutaneous collection. Peristomal abscesses are typically seen in the early postoperative period resulting from intraoperative contamination; however late peristomal abscesses can be seen in the setting of penetrating Crohn's disease of the stoma or from an intra-abdominal source. Initial management of a peristomal abscess includes drainage via image-guided or standard operative techniques. To avoid pouching problems, the drainage catheter should either be inserted remote to the peristomal skin-appliance interface or directly through the mucocutaneous junction (Fig. 54.20). If fistuli-

zation from the stoma is suspected following drainage, further endoscopic or radiographic evaluation may determine if the abscess is arising from a diseased stoma.

High Output Small Bowel Stomas

Normal ileostomy outputs are typically between 800 and 1200 mL/day, and outputs exceeding 1200–2000 mL per day are considered to be high [79]. High stoma outputs can cause severe fluid, electrolyte, and nutritional deficiencies and are typically seen with small bowel stomas and rarely proximal (i.e., ascending or proximal transverse) colostomies. High output stomas can be transiently seen in the new ostomate as ileus resolves, and the initial deluge of bowel contents exits the body. Approximately half of postoperative high output stomas will resolve spontaneously within 2 weeks [79]. With time and resumption of a normal diet, stoma outputs typically plateau to a level proportional to the length of remaining proximal bowel; but high outputs can commonly necessitate treatment. This section will focus on small bowel stomas (ileostomy, jejunostomy), the most common culprit in high output situations.

Once postoperative ileus resolves and stomal outputs reach a steady state, daily output assessments determine the need for treatment. Small bowel stomas outputting less than 1200 mL/24 hours are usually well tolerated without clinical derangements and do not typically require treatment. Outputs between 1200 mL and 1500 mL per day are borderline high and may cause problems for some ostomates. Persistently high stoma outputs can be treated with dietary, behavioral, and medical means via a proposed algorithm described in Fig. 54.21. Behavioral alterations include avoidance of large bolus feedings in lieu of smaller, more frequent aliquots. Large meals can be replaced with smaller frequent meals, fluids can be sipped rather than gulped, and solids and liquids can be consumed at different times to minimize bolus effects.

Concentrated sweets including juice, soft drinks, and candy should be limited to decrease the effects of osmotic diarrhea. Breads, crackers, peanut butter, and bananas may naturally thicken stoma outputs and help decrease volumes. Psyllium powder mixed in water helps to absorb excess fluid from the intestinal tract and thicken outputs. Hypotonic oral fluid restriction (500–1000 mL/day) and treatment with the cheap and easily made World Health Organization oral rehydration solution (Table 54.3) [80] help limit sodium loss and may produce a more favorable osmotic intestinal gradient [79]. It has been shown that most high output patients can avoid IV fluid and electrolyte supplementation if oral intake is restricted to 500–1000 ml/24 h of oral rehydration solution [81].

Following dietary and behavioral changes, pharmacotherapy may be required to manage high output stomas. Medical therapy typically begins with stepwise titration of antimotility agents beginning with loperamide and adding diphenoxylate/atropine. It is useful to take such antimotility agents approximately 30 minutes before meals (three times daily) to preemptively slow transit time before eating. Rarely, intestinal transit may be so rapid that tablet medications do not have enough time to completely dissolve; elixir forms of antimotility agents may be preferable in this setting. Antisecretory therapy with either H2 or proton pump blocking agents may be added to decrease stoma outputs by reducing gastric secretions. If dietary, antisecretory, and antimotility therapies fail, oral opium tincture (paregoric, camphorated tincture of opium) or oral codeine phosphate can be added. Paregoric can be costly and can cause sedation and is typically added as a later measure for recalcitrant high output stomas. Common medicines to manage high output stomas are detailed in Table 54.4.

Unexpected and persistently high stoma outputs merit a workup to exclude other potentially treatable causes. Cross-sectional abdominal imaging or a small bowel fluoroscopic series should be performed to exclude partial bowel obstruction, which can cause paradoxically high outputs. High outputs can be caused by small bowel Crohn's disease, which can be evaluated with small bowel enteroscopy through the stoma or cross-sectional imaging. *Clostridium difficile* enteritis is a reported cause of both small and large bowel high output stomas and can be evaluated with stool testing. Steatorrhea may develop in patients with significant ileal resections and can be treated with oral cholestyramine. Pancreatic insufficiency may rarely cause persistently high stoma outputs and can be remedied with a trial of pancreatic enzyme replacements.

During periods of high stoma outputs, fluid, electrolyte, and nutritional support may be necessary. Periodic surveillance of serum electrolytes, daily weights, and strict recording of inputs and outputs guide resuscitation and replacements. Short gut situations with a proximal jejunostomy may not respond to standard therapies and may require parenteral fluids or nutrition. On rare occasions with proximal stomas, patients may require fasting and total parenteral nutrition as a last resort to sustain euvolemia. Octreotide, a somatostatin analogue, teduglutide, a glucagon-like peptide 2 analog, and human growth hormone all show promise in managing the most recalcitrant high output stoma associated with short gut syndrome [82, 83].

Stoma Reversal

Preoperative Preparation

The surgeon should have a clear understanding of the patient's anatomy prior to attempting stoma reversal. For patients with a stoma created by another surgeon, it may be

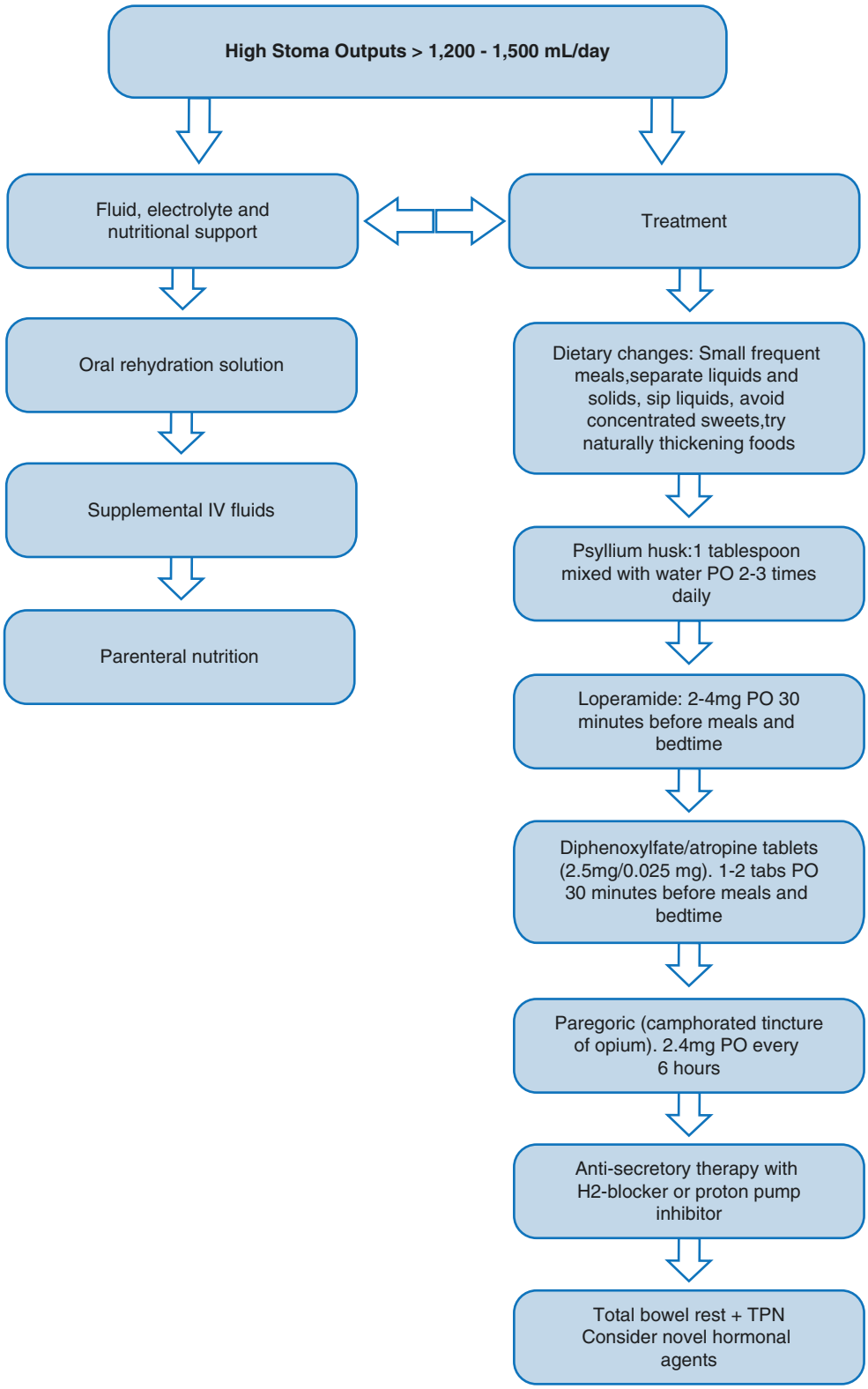

Fig. 54.21 Proposed management algorithm for management of high output small bowel stomas

crucial to review the prior operative and pathology reports to understand the surgical indications, encountered pathology, and remaining anatomy. Record review is particularly important when reversing an end colostomy performed for diverticulitis or malignancy, since additional resection of the rectosigmoid stump, descending colon, and/or splenic flexure mobilization may be needed to complete an adequate resection. Close or threatened margins found on oncologic

Table 54.3 Oral rehydration solution

Ingredients
3/8 tsp. salt (sodium chloride)
¼ tsp. table salt substitute (potassium chloride)
½ tsp. baking soda (sodium bicarbonate)
2 tbsp +2 tsp. sugar (sucrose)
Add tap water to make one (1) liter
Optional: Nutrasweet® or Splenda® based flavoring of choice, to taste

Directions: Mix dry ingredients with water and serve. Best sipped slowly over long periods of time
Contains 27 grams of sucrose, 70 mEq per liter of sodium, 20 mEq per liter of potassium, and 30 mEq per liter of bicarbonate. The final osmolarity is approximately 245 mOsm per liter
tbsp tablespoon, *tsp* teaspoon

Table 54.4 Common medicines for control of high output stomas

Medication	Starting dose	Maximum daily dose
Psyllium	1 tablespoon BID	1 tablespoon TID
Loperamide tab	2–4 mg PO QID	16 mg[a] (4–8 tabs)
Loperamide liquid	2–4 mg PO QID	80 mL (16 mg[a])
Diphenoxylate-atropine tab	2.5–5 mg PO QID	20 mg (4–8 tabs)
Diphenoxylate-atropine liquid	2.5–5 mg PO QID	40 mL (20 mg)
Codeine tab	15–30 mg PO QID	240 mg (60 mg PO QID)
Codeine elixir	15–30 mg PO QID	240 mg (80 mL)
Paragoric 0.4 mg morphine/1 mL paragoric (45% alcohol)	5 mL PO QID	37.5 mL PO QID (150 mL/day)
Opium tincture 10 mg morphine/1 mL opium (19% alcohol)	0.3–1 mL PO QID	1.5 mL PO QID (6 mL/day)

Adapted from Parekh and Seidner [3]
[a]Higher doses have been reported in off-label indications

pathology reports may merit endoscopic anastomotic evaluation to exclude cancer recurrence prior to stoma reversal. Endoscopic evaluation may be helpful prior to reversing stomas in IBD, ensuring that disease activity is controlled in the defunctioned bowel before attempting reversal; but the endoscopist must be aware that diversion colitis may grossly and histologically mimic IBD [84].

If a diverting loop stoma was used to protect a distal anastomosis, the authors prefer to use a lower gastrointestinal fluoroscopic contrast study to exclude anastomotic leak, stricture, and obstruction prior to stoma reversal. Similarly, for patients undergoing reversal of an end stoma, preoperative fluoroscopic and endoscopic studies are important to evaluate the remaining anatomy and quality of both distal and proximal segments of bowel – particularly when reversing another surgeon's stoma. Fluoroscopic abnormalities can be further examined with endoscopy allowing mucosal evaluation, tissue sampling, and anastomotic dilation, if needed. Coloanal, distal colorectal, and ileal pouch-anal anastomoses may be additionally assessed and gently dilated with digital rectal exam and exam under anesthesia, if required. Several groups espouse selective, rather than routine, use of lower GI contrast studies for anastomotic evaluation prior to stoma reversal and note that most anastomotic complications can be diagnosed without imaging [85–89]. Although intra- and postoperative surprises are not completely avoidable, the authors feel preoperative evaluation including record review, imaging, and endoscopy is the best way to avoid unexpectedly complex stoma reversals.

Timing

Timing of stoma reversal may impact the ease of the procedure. Diverting loop stomas are typically reversed within 2–3 months after creation once the surgeon is satisfied with the distal anastomosis (or pathology) that required diversion. Limited evidence over the years has suggested that loop ileostomy reversal performed less than 8.5 weeks following coloanal or ileoanal anastomosis may be associated with increased risk of complications [90]. Recently, several studies have challenged this notion. Most notably, a Scandinavian prospective randomized trial showed that loop ileostomy reversal at 8–13 postoperative days was as safe as late closure at 12 weeks after low anterior resection in selected patients without radiographic or endoscopic evidence of leak [94]. Not only was early closure as safe as late closure, but early closure patients experienced less complications than late closure patients, which largely arose from stoma-related complications.

Intriguingly, there were no differences in health-related quality of life between early and late ileostomy closure patients at 3, 6, and 12 postoperative months [95]. The study, although promising, was limited by the fact that this was a highly selected group of patients where nearly 70% of screened patients were not eligible to participate (13% with suspected leaks, 38% due to medical reasons, 13% due to unwillingness to participate). Until more rigorous evidence is available universally supporting safe early ileostomy closure, the authors recommend defaulting loop ileostomy closure until approximately 8–12 weeks postoperatively as dictated by the clinical situation. The authors concede that early ileostomy closure can be considered in highly selected and motivated patients that are thoroughly evaluated to exclude anastomotic leak.

The use of adjuvant chemotherapy introduces another consideration in the timing of stoma reversal. If adjuvant chemotherapy is planned, conventional wisdom dogmatically dictates keeping a diverting stoma through the duration of treatment to minimize postoperative reversal complications and diarrhea. Conversely, chemotherapy may further compound dehydration resulting in readmission for up to 11% of ileostomy patients [97], and ostomates must be mon-

itored carefully for dehydration during chemotherapy. A small retrospective study and subsequent meta-analysis showed that loop ileostomy reversal in the midst of colorectal cancer chemotherapy had comparable morbidity and cancer-related outcomes in select patients compared to post-chemotherapy reversal [98, 99], although this practice is not widely adopted at this time. Patient choice plays a large role in this situation, and a thorough discussion is helpful in choosing the ideal time for stoma reversal.

The optimal time for end stoma reversal remains a contentious issue with conflicting guidance in the literature [100]. It is generally considered that early postoperative adhesions become less tenacious and vascular with time, which may ease a challenging intra-abdominal dissection. Retrospective comparisons between early (<15 weeks) and late (>15 weeks) end colostomy reversal detail similar morbidity, but increased length of stay, subjective adhesion density scores, and small bowel injuries favor later surgery [101]. An older study associated early Hartmann's reversal (<3 months) with increased leaks, sepsis, and death compared to colostomy reversals took place after 6 months [102]. Although small series have shown no timing-dependent outcome differences [100, 103], the balance of low-level evidence suggests that delaying end stoma reversal for 3–6 months eases future surgery in patients having undergone open end colostomy creation.

Technical Consideration of Loop Stoma Reversal

Once the surgeon is satisfied with the quality of the protected distal anastomosis (or pathology) (see section "Stoma Reversal: Pre-operative Preparation"), loop colostomy or ileostomy reversal can typically be performed as a local procedure through a peristomal circular incision under general anesthesia. The entire abdominal midline should be included and prepared in the operative field, in the event an unplanned laparotomy is required. A circumferential skin incision is made just outside the mucocutaneous junction and sharply deepened until subcutaneous fat is seen (Fig. 54.22). Clamps may be placed on the skin rim to retract the stoma anteriorly to expose the interface between the serosal surfaces of the bowel limbs and the subcutaneous tissues. A cylindrical sharp dissection is performed on the serosal surfaces of the bowel limbs heading posteriorly until the anterior rectus sheath is encountered. If the patient is obese and the fascia is deep, clamps can be used to grasp and elevate the fascia; alternatively, radial 1–2 cm counter-incisions extending from the cut skin edge may allow better exposure. The rectus muscle is dissected from the bowel serosa and can be distinguished from the bowel by the longitudinal orientation of muscle fibers. Circumferential dissection continues until the abdomen is entered. Limited intra-abdominal adhesiolysis is performed to enable adequate mobilization of the bowel loop for eventual anastomosis and fascial closure. Care should be taken to avoid injury to the stoma mesentery during dissection, especially during loop colostomy reversal, since marginal artery injury can result in distal colonic ischemia.

If the stoma is everted, sharp adhesiolysis may be used to flip the everted bowel wall back into a normal configuration. The skin disk and mucocutaneous junction are excised and debrided back circumferentially to soft and supple bowel suitable for closure. Partial and full-thickness bowel injuries can rarely occur during loop stoma closure. Bowel assessment can be performed by injecting dilute povidone-iodine solution via a bulb syringe while digitally occluding each

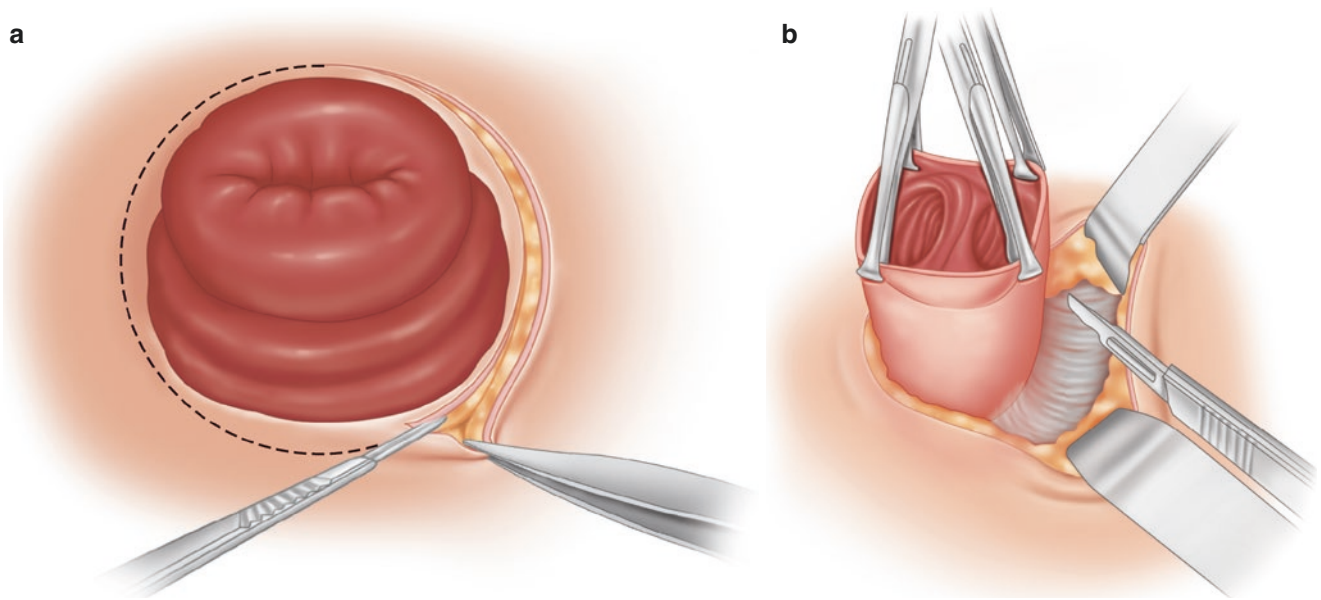

Fig. 54.22 (**a**) Incision of the stomal mucocutaneous junction. (**b**) Elevating the stoma with clamps to expose the subcutaneous stomal dissection performed assistance of clamps

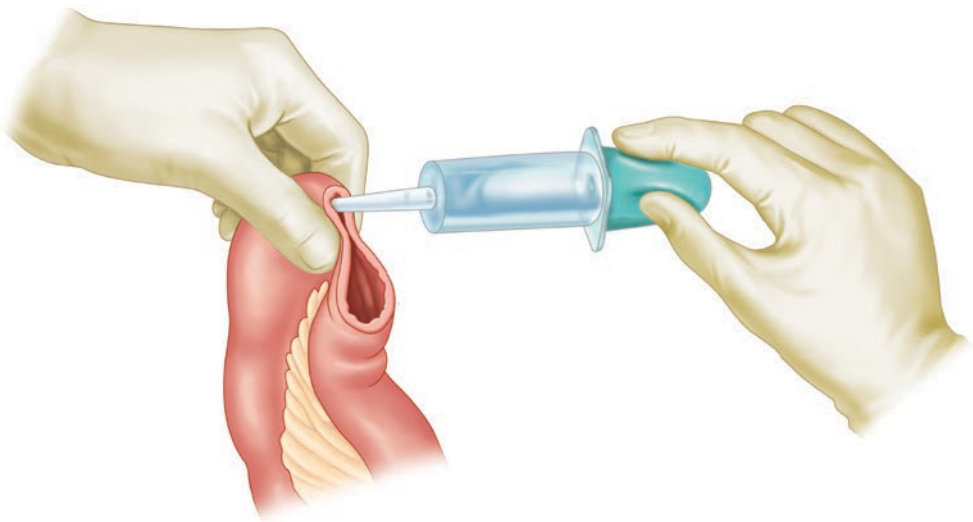

Fig. 54.23 Pressurized leak testing of injured bowel during loop stoma closure

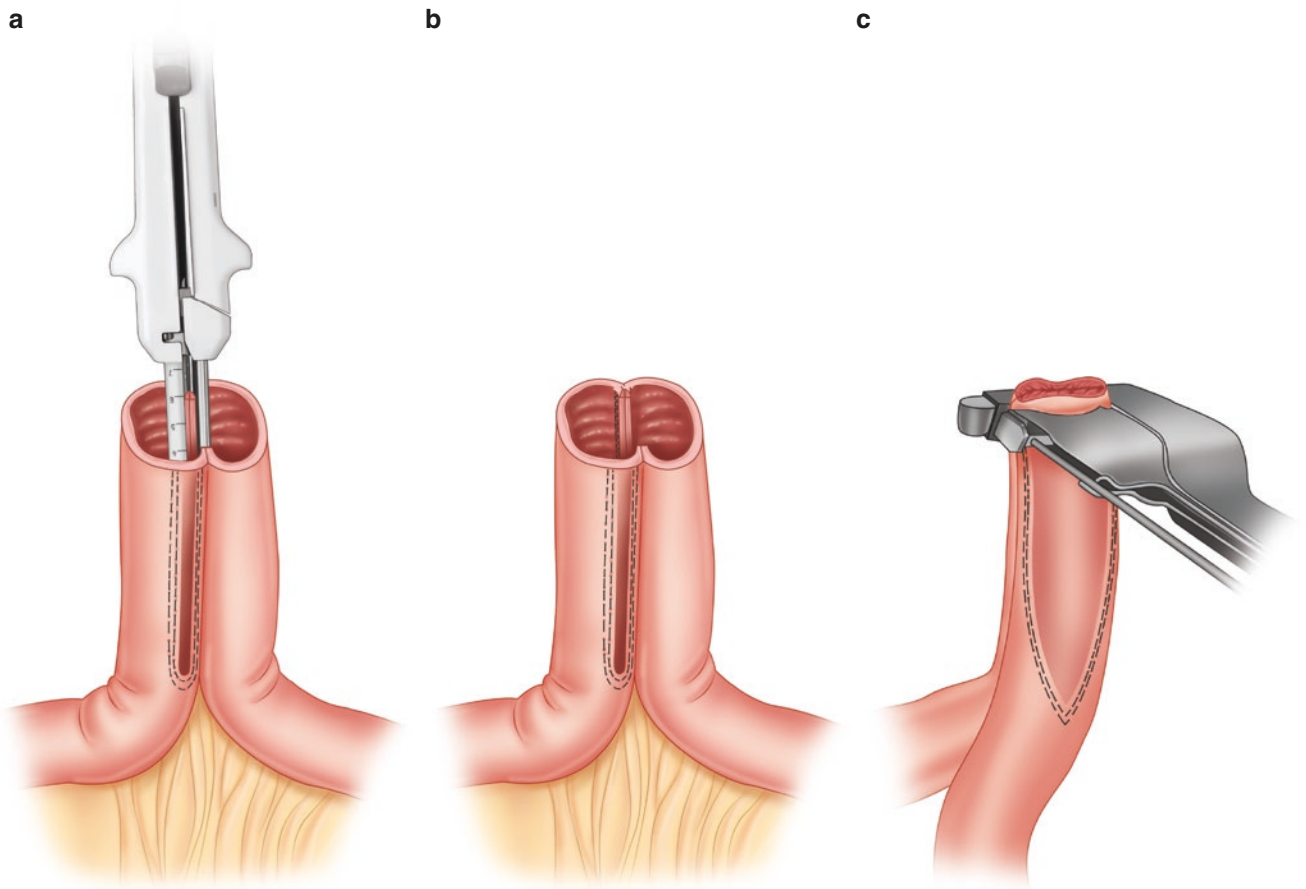

Fig. 54.24 (**a**–**c**) A stapled side-to-side anastomosis

bowel limb to pressurize the dissected bowel limbs and evaluate for injury (Fig. 54.23). Injuries can be suture repaired or resected depending upon the nature and location of injury. Rarely, tenacious adhesions or deep bowel injury may require a laparotomy for repair. The bowel portions that comprised the stoma can be resected or left in situ at the surgeon's discretion. Once the bowel is adequately mobilized and inspected, a stapled or handsewn closure is performed.

A side-to-side (functional end-to-end) stapled closure is performed by inserting the limbs of a linear cutter stapler (GIA type) into each limb of the loop stoma (Fig. 54.24). Care is taken to ensure the limbs are opposed along the anti-mesenteric surfaces prior to firing the stapler. The common portion of bowel

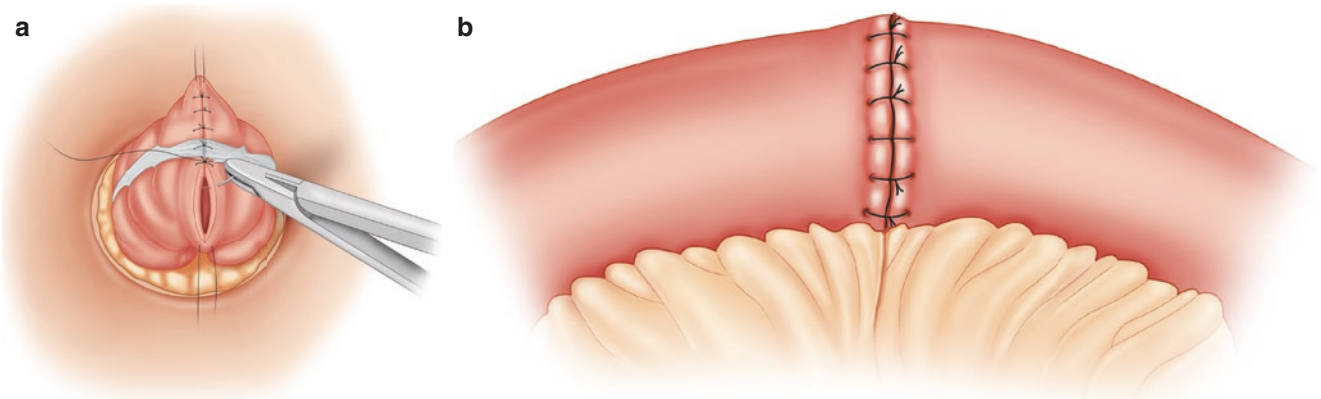

Fig. 54.25 Handsewn loop closure for (**a**) colostomy (**b**) ileostomy

wall that connects both bowel limbs may be divided or resected to improve antimesenteric opposition. The common enterotomy is then closed with either suture or an intersecting fire of another GIA or TA type stapler. The completed anastomosis may be oversewn at the discretion of the surgeon, and a suture may be placed at the confluence of the bowel limbs ("crotch stitch").

Alternatively, a handsewn anastomosis is performed with either running or continuous suture, in one or two layers to longitudinally close the defect (Fig. 54.25). The completed anastomosis is then reduced into the abdomen. Adequate intra-abdominal adhesiolysis must be completed prior to fascial closure to avoid injury to bowel adherent to peritoneum. The fascia is closed with interrupted or running suture. The skin can be closed with or without a drain, left partially open with wicks, or left completely open to heal secondarily.

Mode of loop ileostomy closure has long been a source of debate amongst surgeons based largely on preference and training pedigree. Several meta-analyses and three single-center prospective randomized control trials have shown that stapled and loop closures are equivalent with regard to anastomotic leakage, wound infection, overall complications, and cost; however, stapled closure was faster, caused less postoperative bowel obstruction, and was associated with shorter hospital stays [104–108]. It is postulated that the narrow luminal diameter produced with handsewn closure techniques is prone to edema and early obstruction compared to widely patent stapled anastomoses. Recently, a large multicenter trial showed stapled and handsewn anastomoses to have similar rates of postoperative bowel obstruction [109]. As a result, ASCRS Clinical Practice Guidelines (CPG) state that stapled and hand-sutured techniques are both acceptable for loop ileostomy closure [9].

Wound closure at the former stoma site is also a contentious issue that has been studied extensively. Several studies have compared various techniques including traditional linear wound closure, closure over a suction drain, and skin-level purse-string cerclage technique (which leaves a small opening at the center of the wound). Purse-string techniques are shown to have significantly lower wound infection rates and improved patient satisfaction [110, 111]. ASCRS CPG recommends stoma site skin reapproximation should be performed when feasible, and purse-string skin closure may have advantages compared with other techniques [9].

Technical Considerations of End Stoma Reversal

Undoubtedly, reversal of an end stoma can be a substantial surgical undertaking and may be a larger operation than the initial stoma creation. The patient and surgeon should be prepared for an extensive and potentially hostile operation. In addition to the preoperative preparation described above, the surgeon may selectively use ureteral stents to aid in identification of the ureters in a potentially hostile operative field. A fully prepared surgeon should have pelvic retractors, proctoscopes, EEA sizers, and vaginal retractors available in the operating room. Lastly, the surgeon should note the adequacy of the current stoma and site. If the current stoma site is in a poor location, the patient can be marked for a new stoma site should a temporary loop ileostomy be required.

Once the surgeon is satisfied with the quality of the protected distal anastomosis (or pathology), an end stoma can be reversed using open or laparoscopic approaches [112, 113]. The patient is typically placed in modified Lloyd-Davis (low lithotomy) or split-leg position allowing access to the anus. For open reversal of an end stoma, the stoma is prepared in the surgical field. A sterile, countable, gauze sponge, and adherent plastic drape can be used to limit colostomy contamination of the midline wound. The abdomen is entered sharply, and adhesions are lysed to identify the bowel conduit leading to the end stoma. The distal bowel conduit is identified, mobilized if necessary, and inspected for anastomotic suitability. In the case of a rectal stump, scarring and retraction may rarely require mobilization and resection of the previous rectal closure line; however, the anastomosis should be to the rectum and not sigmoid (see below). Once adequate intra-abdominal adhesiolysis is performed, the stoma is mobilized back into the abdomen by incising the stomal mucocutaneous junction and cylindrically dissecting

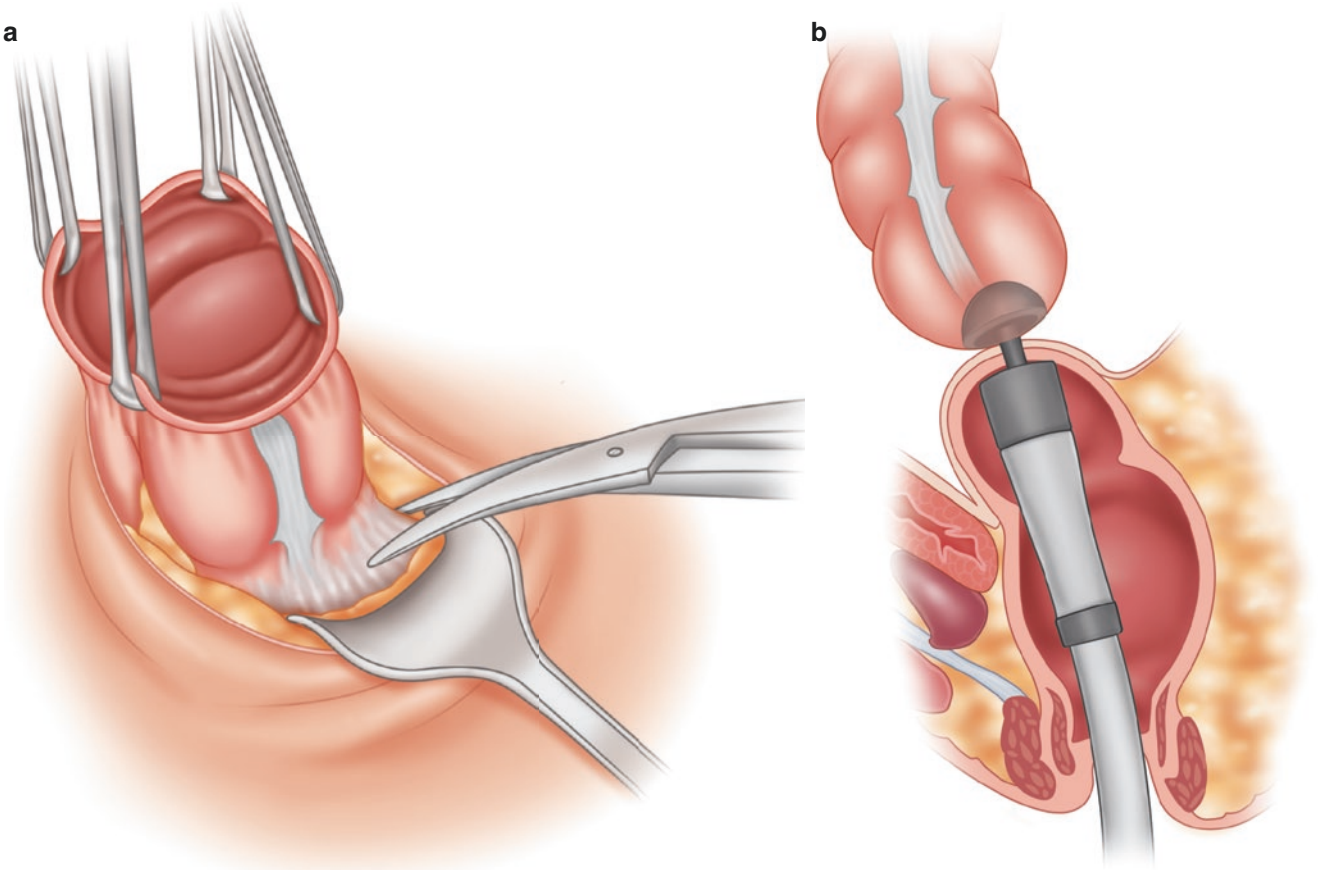

Fig. 54.26 (**a**) Mobilization of an end colostomy. (**b**) Stapled end-to-end colorectal anastomosis

subcutaneous adhesions until the abdominal dissection is met (Fig. 54.26a). Care is taken to avoid mesenteric injury and devascularization of the stoma since bowel length preservation may aid in creating low pelvic anastomoses.

After the end stoma is reduced into the abdomen, the surgeon may need to perform additional mobilization of the former stoma to obtain tension-free reach to the target distal bowel. For end ileostomy reversals, generous small bowel mobility does not typically require much additional mobilization. Colorectal anastomoses may require additional lengthening maneuvers including mobilization of the flexures and high vascular ligation to obtain tension-free reach into the pelvis. For an end colostomy reversal following sigmoid diverticulitis, the surgeon must ensure the adequacy of the initial resection at time of stoma reversal, with particular attention paid to previous resection margins. A surgeon may have left a sigmoid rather than a rectal stump during emergency surgery, and a completion sigmoid colectomy may be necessary at time of stoma reversal to ensure an adequate diverticular resection. Similarly for cancer, the oncologic adequacy of the initial resection must be assessed and remedied at time of stoma reversal, which may require additional bowel resection or lymphadenectomy.

Once the distal and proximal bowel conduits are adequately mobilized and prepared, an anastomosis is created with either stapled or handsewn techniques at the surgeon's discretion. For colorectal anastomoses following Hartmann's procedure, a stapled end-to-end anastomosis (EEA) is commonly performed (Fig. 54.26b). For stapled anastomoses, the surgeon must ensure the stapler can easily be passed to the transected rectal staple line. This may not always be easy or possible since the rectal stump can become corrugated, contracted, filled with clay-like desiccated mucus, entrapped, or lost in a hostile pelvis. Lighted deep pelvic retractors, proctoscopes, vaginal retractors, EEA-sizers, and copious lubrication may aid in identification of the rectal stump. If the stapler is unable to be advanced fully to the proximal rectal transection line, the end of the colon can be anastomosed to the side of the anterior rectal wall, but the end-to-side anastomosis must be several centimeters from the proximal rectal margin to avoid ischemia to the remaining bridge of rectal wall. Moreover, if an anterior end-to-side rectal anastomosis is performed, the surgeon must assure the vagina, and bladder is fully mobilized away from the intended rectal anastomotic site to avoid iatrogenic fistulas. An anastomotic air-leak test should be performed to interrogate anas-

tomotic quality. If a leak is discovered, the anastomosis can be resected and recreated, revised, or protected with a diverting loop ileostomy at the surgeon's discretion.

Laparoscopic and robotic end stoma reversal with colorectal or ileorectal anastomosis is predicated upon the same principles and techniques described above but are modified to reflect the nuisances of minimally invasive surgery. After similar preoperative workup and positioning, surgery typically commences with incision of the mucocutaneous stomal junction and subcutaneous stomal dissection. Once the stoma is completely freed from peritoneal attachments and un-everted, the anvil to an EEA stapler is secured in place, and the anvil-stoma combination is reduced into the abdomen. The former stoma site is occluded with an airtight, twisted plastic wound retractor or plugged with a balloon-tipped Hasson trocar as pneumoperitoneum is generated. Additional laparoscopic working ports are placed to complete the necessary adhesiolysis, pelvic dissection, and rectal mobilization exactly as performed for an open procedure. An intracorporeal EEA stapled rectal anastomosis is then completed as described above.

Stoma Reversal Complications

Loop stoma reversal is often considered a minor procedure when compared to the index operation; however complications may occur more frequently than most surgeons acknowledge (Table 54.5). Regardless of technique, loop ileostomy reversal is generally well tolerated with low risk of anastomotic leakage; however, early wound infections and late-term incisional hernias may occur. Reversal of an end stoma is associated with high morbidity, and stoma reversal is often more challenging than the initial operation. Given the gravity of some end stoma reversals, proper surgical planning is essential to assure the best surgical outcomes, while preoperative patient counseling can best manage perioperative patient expectations.

Table 54.5 Select published complications rates for stoma reversal [100, 109, 113, 114, 117, 126–128]

Stoma reversal type	Loop ileostomy reversal (%)	Loop colostomy reversal (%)	End colostomy reversal with colorectal anastomosis (%)
Superficial surgical site infection	3–13.5	5–20	14–43.8
Deep space infection/leak	2–4	2–4	1.5–21
Bowel obstruction/ileus	5–16	4	23
Hernia (clinically diagnosed)	0–50	2–38	3–31

Special Considerations

The Difficult Stoma

Increasing rates of obesity present a particular challenge to the colorectal surgeon. Unfortunately, obesity is associated with an increased risk of stoma-related complications [15]; as such, the patients who require the highest quality stomas paradoxically can have the most challenging stomas to create. Acutely inflamed and chronically foreshortened bowel mesentery also may hinder stoma creation, even in thin patients. Special tips and tricks can help the surgeon create difficult stomas in complex situations. Since stoma height has been identified as an independent risk factor for problematic stomas, it is not surprising that the majority of tips involve means of obtaining adequate, tension-free reach of an adequate length of the stoma conduit.

Simple measures are first employed when dealing with the difficult stoma. In obese patients with a thick abdominal wall, the surgeon will usually find the supraumbilical abdominal wall to be thinner, easing reach and minimizing tension on a stoma (Fig. 54.27). In the super morbidly obese, a subxiphoid loop transverse colostomy may be the easiest stoma to create if temporary diversion is necessary. If upper abdominal stoma sites are not plausible and the surgeon still strug-

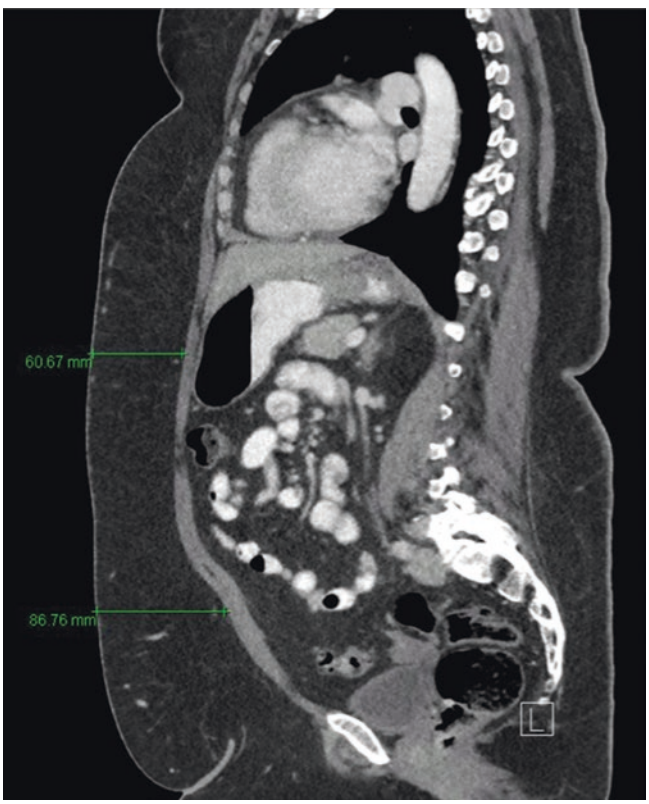

Fig. 54.27 The abdominal wall may be thinner above the umbilicus in the obese patient, easing creation of a potentially difficult stoma

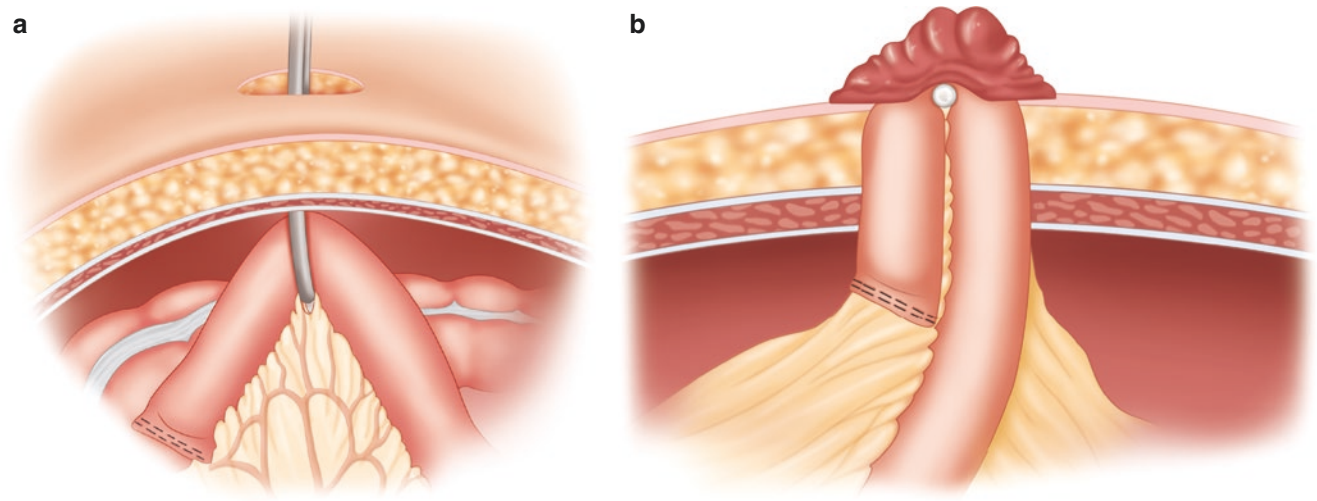

Fig. 54.28 (**a**, **b**) Loop-end ileostomy

gles to deliver bulky bowel through a thick abdominal wall, the stoma can be delivered in a stepwise fashion. First, the subcutaneous tissues can be completely elevated off of the anterior rectus sheath and the stoma delivered completely through the muscular layer. The stoma can then be delivered through the subcutaneous tissues and skin in a second step. Alternatively, the use of a plastic sleeve wound retractor with or without water soluble lubricant may provide a slick conduit to help deliver thickened bowel and mesentery through a challenging trephine. Some advocate performing subcutaneous lipectomy to minimize abdominal wall distance; however this may lead to a recessed stoma that is difficult to pouch and should be used judiciously, if at all.

A loop-end stoma is a unique ostomy configuration that may allow additional reach of an end ileostomy (Fig. 54.28) or colostomy (Fig. 54.29) in obese patients or those with a foreshortened mesentery. The loop-end stoma configuration is useful when the tip of the intended stoma conduit is tethered by the mesentery and the bowel immediately proximal to the end is more mobile. The loop-end arrangement preserves the mesentery to the entire stoma, assuring adequate perfusion. A loop-end stoma is created similar to a loop stoma, which is aided by passing a narrow Penrose drain through a mesenteric defect at the mesentery bowel interface to deliver the loop. The stoma is matured as a loop ileostomy or colostomy as detailed previously (see section "Technical Considerations of Stoma Creation").

Two to three centimeters of additional bowel reach can be obtained by sequentially scoring the peritoneal surface of the stoma mesentery perpendicular to the course of the vessels (Fig. 54.30). Such "pie crusting" should be carefully performed by only dividing the peritoneum while protecting the underlying vessels. In the case of a small bowel stoma, both peritonealized mesenteric surfaces may need to be scored to obtain maximum reach.

In the acute setting when it may be inadvisable to create an anastomosis, both segments of bowel may be exteriorized in a Prasad-style end-loop stoma (Fig. 54.31). This configuration is most commonly used when there is a bowel perforation related to diverticulitis or trauma but may be employed in any situation when primary anastomosis is inadvisable. The unique aspect of this stoma is that both bowel limbs are exteriorized and eventual reanastomosis may often be performed with a local procedure, without the need for laparotomy.

Challenging situations may require the surgeon to compromise on the tenets of stoma creation, and the ideal stoma at the ideal location with the ideal bowel segment may not be possible. If a surgeon is forced to decide between making a poor stoma in a good location versus making a good stoma in a poor location, a general consensus among stoma care professionals is that a poor stoma in a good location is the lesser of two evils [19]. Rarely, thickened bowel and mesentery may prohibit stoma eversion and maturation. In these cases where eversion and maturation are not possible, the stoma can be simply opened without maturation and secured to the skin well above skin level. While reactive serositis and late-term "bishop's collar" stricture may develop, this temporizing measure may get the patient through until the bowel is suitable for stomal revision or reversal.

Seldom, a remarkably hostile abdomen may prohibit stoma delivery through a traditional stoma trephine despite exhausting all lengthening maneuvers. In these rare situations, a stoma may be fashioned through the midline incision. Although a stoma placed in an incision is prone to wound infection and hernia, it may temporize or palliate an otherwise unsustainable surgical situation. Infrequently, a heavy mesentery or friable bowel may cause a stoma support rod to tear through the mesenteric aspect of a loop stoma. Instead, the bowel can be supported by two stoma rods placed alongside one another to distribute the tension over a

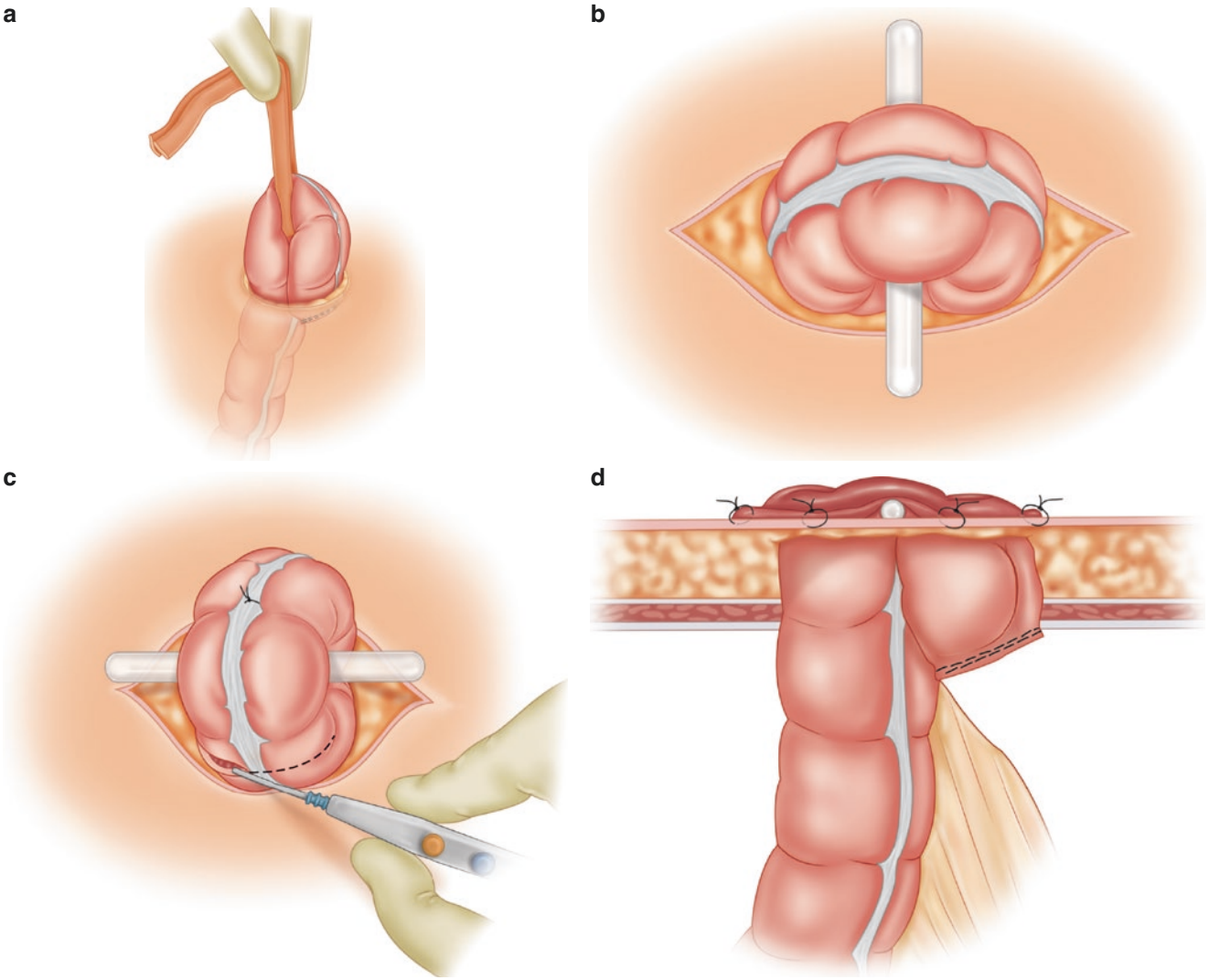

Fig. 54.29 (**a**–**d**) Creation of a loop-end colostomy

greater surface area. Alternatively, the mesentery can be braced at the fascia level rather than the skin level. In this method, a long malleable or pliable tube (e.g., thin chest tube, filiform, follower, plastic vascular tunneling device) is passed through a skin incision remote from the stoma site down to the anterior fascia of the abdominal wall where it pierces an avascular portion of the stoma mesentery before rising through the skin on the opposite side of the stoma (Fig. 54.32). This tube is subsequently removed in several days when the stoma and mesentery have adhered to the subcutaneous tissues and are at minimal risk for retraction.

Temporary Fecal Diversion: Loop Ileostomy Versus Loop Colostomy

The ideal level of temporary protective fecal diversion following colorectal or coloanal anastomosis has long been debated by colorectal surgeons. It is generally acknowledged that loop ileostomy and loop colostomy have similar complication rates but different complication profiles [9]. Clinical and patient-reported outcomes between temporary loop ileostomy versus loop colostomy have been compared in several recent trials and meta-analyses with inconsistent results [114–116]. Loop ileostomies, although more prone to dehydration, readmission, and post-reversal obstruction, are found to have less post-closure sepsis and less pre- and postoperative hernias and may offer improved quality of life compared to loop colostomy [117–119]. ASCRS CPG recommends loop ileostomy preferentially over transverse loop colostomy for temporary fecal diversion in most cases but acknowledges that there may be particular circumstances favoring a loop transverse colostomy [9]. For instance, a distal colorectal obstruction may best be treated with a transverse loop colostomy that allows both afferent diversion with efferent retrograde venting. Additionally, a transverse loop colostomy may be easier to fashion in the obese than a loop ileostomy (see section "Special Considerations: The Difficult Stoma").

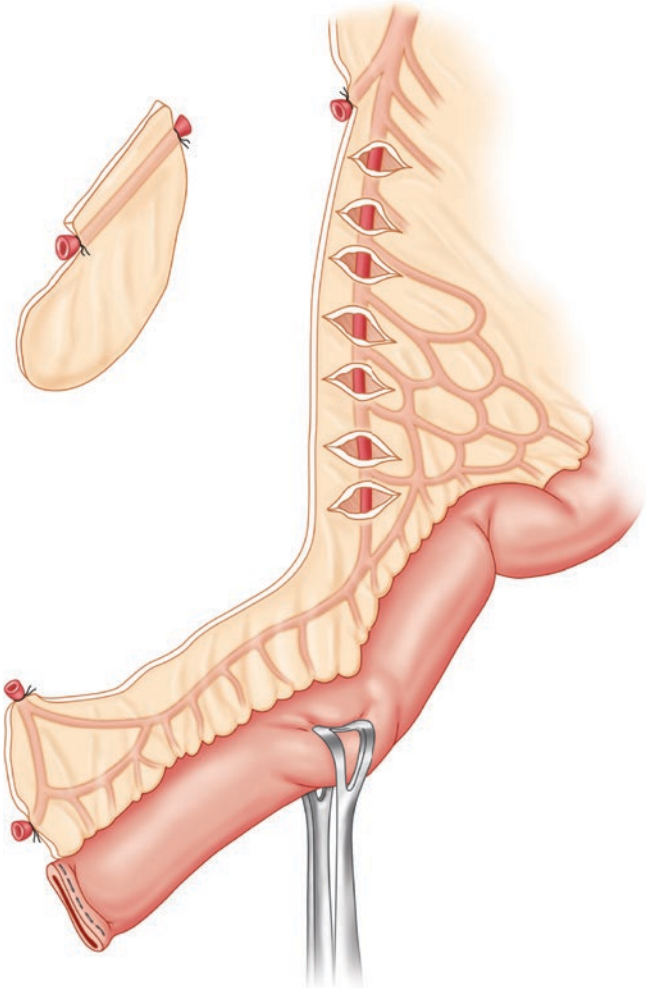

Fig. 54.30 "Pie crusting" of the bowel mesentery to obtain additional length prior to stoma creation. If a difficult end ileostomy is fashioned from the terminal ileum, the surgeon may find it helpful to ligate the ileocolic artery proximally to obtain reach

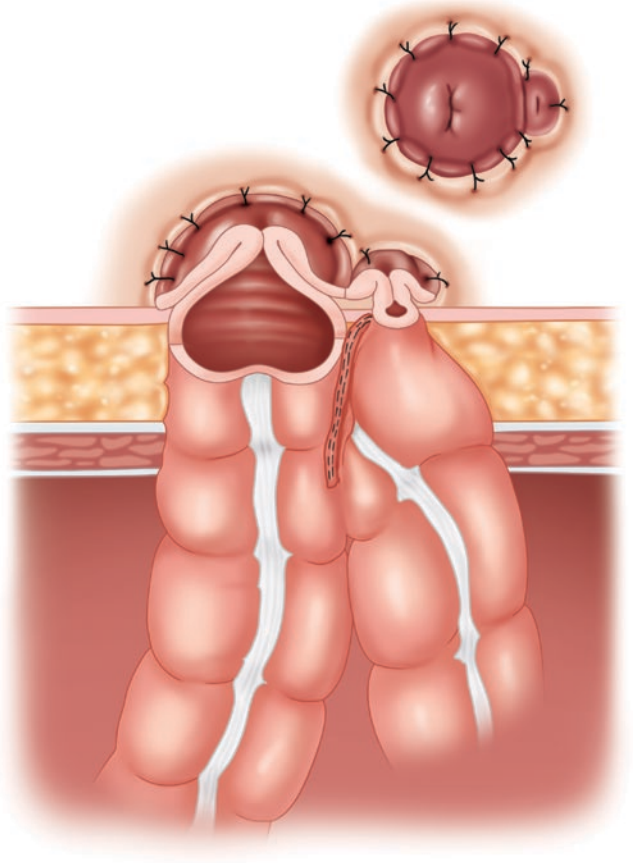

Fig. 54.31 A Prasad-type end-loop colostomy

Genitourinary Stomas

Although colorectal surgeons do not typically perform reconstructive genitourinary procedures, familiarity with such procedures is important for several reasons. First, a colorectal surgeon may be asked to help with stoma care and complications and assist with urinary stoma revisions. Additionally, a thorough understanding of urinary stoma construction and anatomy can prove invaluable during urgent and emergent reoperations on patients with previous genitourinary reconstructions. Moreover, genitourinary reconstruction may be necessary for patients with locally advanced pelvic malignancies that require multivisceral resection. Lastly, patients with neurogenic bowel and bladder may require synchronous urinary and fecal diversion, so understanding of the urologic aspects of a synchronous operation may be crucial.

The simplest reconstructive urinary diversion is the ileal conduit (Fig. 54.33) [120]. This procedure typically harvests a 10–15 cm segment of the ileum (typically at least 15–20 cm proximal to the ileocecal valve) to serve as a conduit between ureters and the skin. Enteric continuity is restored with an ileo-ileostomy, and the left ureter is tunneled through a sigmoid mesenteric defect. Both left and right ureters may be anastomosed separately (in a "Bricker" fashion) or sewn together and a single uretero-ileal performed ("Wallace" anastomosis). The proximal end of the conduit is usually oversewn to limit stone formation. The open end of the conduit is delivered through a stoma trephine and matured to the skin. The stoma is matured in either an end or loop-end configuration. The surgeon must be keenly aware of the left ureter's aberrant course during reoperation and left colon mobilization. Moreover, the tenuous ileal conduit mesentery must be preserved during reoperation, since inadvertent injury can result in conduit infarction and convert a simple adhesiolysis to an extensive and complex urinary reconstruction. The mesentery for the conduit will be inferior to the new ileo-ileostomy.

Urologic surgeons may augment or replace urinary bladders with harvested ileal segments for a myriad of indica-

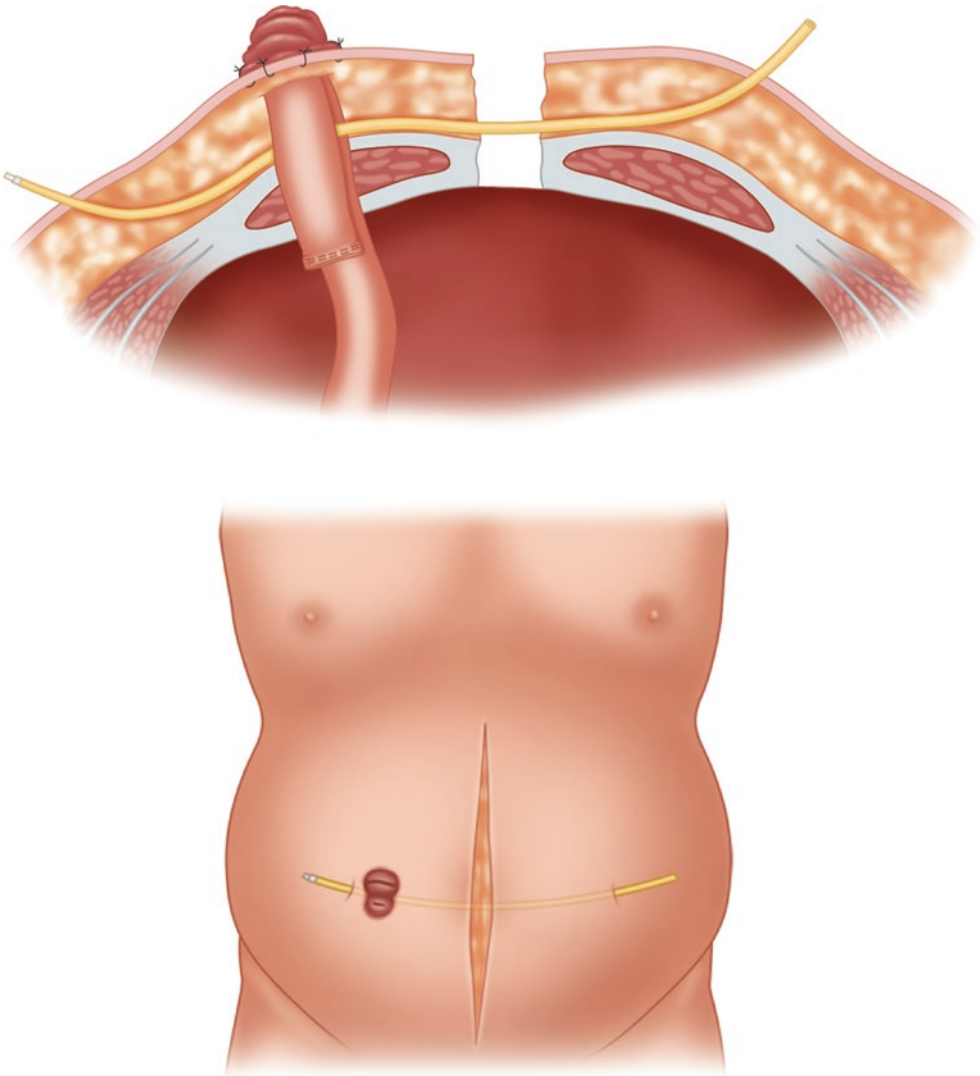

Fig. 54.32 Supporting a difficult loop enterostomy at the fascial level with a filiform catheter

tions [121]. Akin to the ileal conduit, a similar segment of mid ileum is harvested and configured as either a panel or pouch to augment or reconstruct the bladder and increase its capacity. Regardless of the ileal configuration, enteric continuity is restored with an ileo-ileostomy, and a mesenteric pedicle spans from the closed mesenteric defect to the pelvis. This ileal mesentery pedicle can be a nidus for obstruction and internal herniation, and extreme care should be taken to preserve the mesentery to avoid devascularization of the reconstructed urinary bladder.

Several types of catheterizable urinary stomas may provide appliance-free urinary continence to patients in need of genitourinary diversion. These catheterizable stomas are brought to the umbilicus or the right lower quadrant. Most pouches are created from the right colon with the appendix or the terminal ileum serving as the channel for catheterization. An Indiana pouch follows similar principles as the ileal conduit; however the right colon and ileum are harvested en bloc to create a large intra-abdominal urinary reservoir (Fig. 54.34) [122]. The ileocolic segment is anastomosed to the ureters, and a narrow, skin-level stoma is created that serves as a valve and permits intermittent catheterization. A Mitrofanoff appendicovesicostomy utilizes an appendiceal conduit to create a catheterizable stoma for the bladder or neobladder (Fig. 54.35) [123]. A Monti conduit is similar to the Mitrofanoff appendicovesicostomy but utilizes a pedicled segment of tubularized ileum to create a narrow, catheterizable urostomy (Fig. 54.36) [124].

The Turnbull Blowhole Colostomy

Rarely, difficult situations may arise where colectomy or proper fecal division is inadvisable due to prohibitively high operative risk. For example, gravid patients with fulminant colitis may be unsuitable for colectomy out of concern for patient or fetal demise. Occasionally, profound comorbidities such as sepsis or cardiovascular collapse may make a

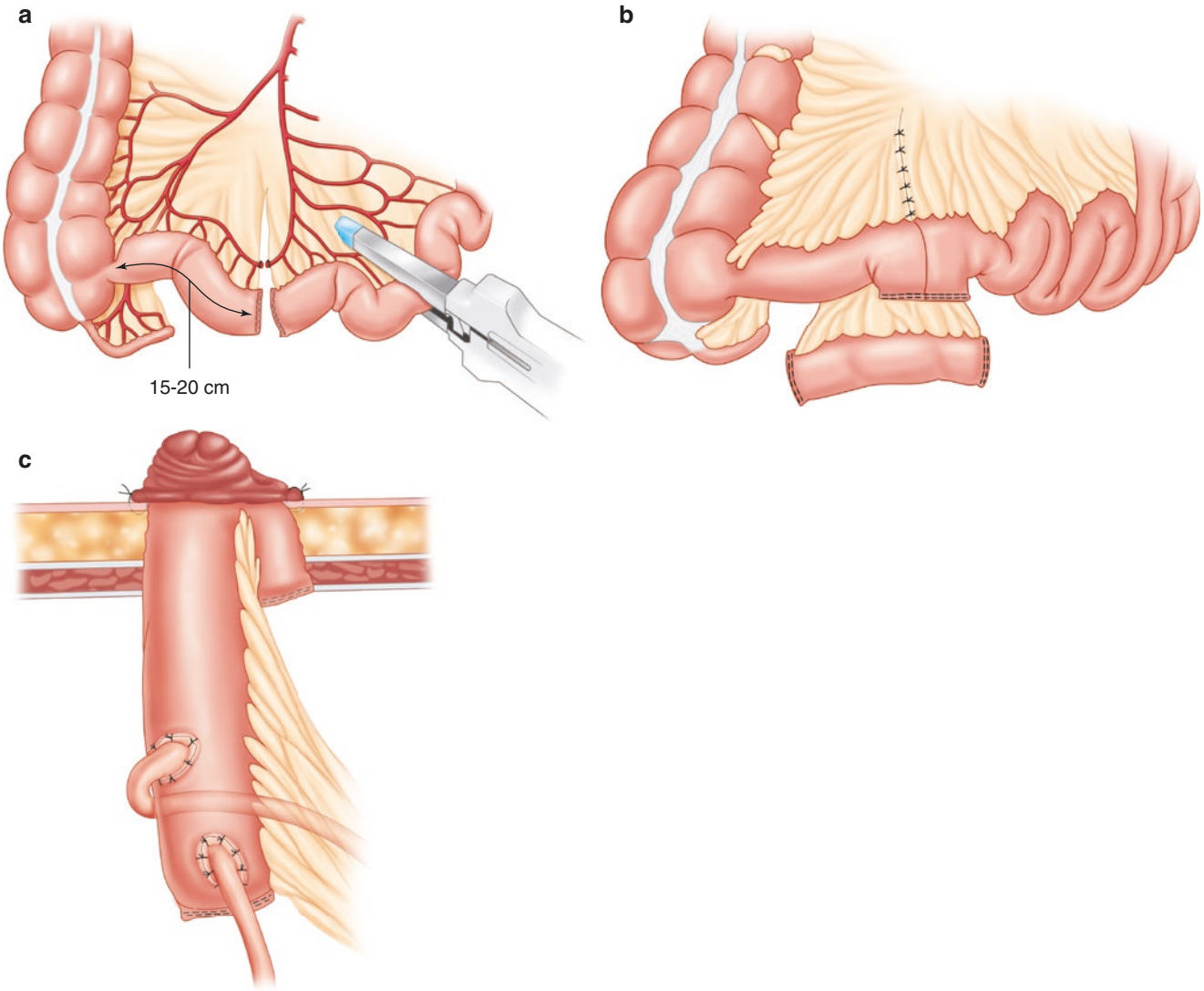

Fig. 54.33 The ileal urinary conduit: (**a**) A segment of mid ileum is resected, (**b**) an ileo-ileostomy is created, and (**c**) the harvested ileal conduit is anastomosed to the ureters and matured as a stoma

total colectomy inadvisable. In these situations, a limited upper midline laparotomy with loop ileostomy and Turnbull blowhole colostomy can be fashioned quickly to divert and decompress a toxic colon until the patient can sustain a proper resection (Fig. 54.37) [125]. In these challenging situations, a limited 10-cm supraumbilical laparotomy can be made to accommodate a hand to explore the abdomen. A loop ileostomy can be made through a separate stoma trephine, and the loop of transverse colon can be brought out through the midline incision. The midline fascia is closed around the bulge of the transverse colon loop and then a watertight seal is created between the seromuscular surface of the colon and the surrounding peritoneum with one or two layers of continuous suture (Fig. 54.38). Once the peritoneal cavity is sequestered from potential bowel spillage, the colon is incised, and the bowel edge is sutured to the skin. The ileostomy is then matured. The blowhole stoma is suboptimal due to prolapse and pouching difficulties owing to the flat nature of the stoma, but it can be a useful temporizing adjunct when no other options exist.

For rare patients too ill to tolerate a general anesthetic, the Turnbull blowhole colostomy can be performed under local anesthesia. A fluoroscopic projection of the upper abdomen is obtained with the patient supine on the operating table. The colon is identified by its characteristic bowel gas pattern, and a metallic coin is then used to mark the intersection of the transverse colon and the midline. The spot is then marked, and local anesthetic is infiltrated through the subcutaneous tissues, and a 4 cm midline incision is made directly over the colon. Local anesthetic is infiltrated layer by layer as the fas-

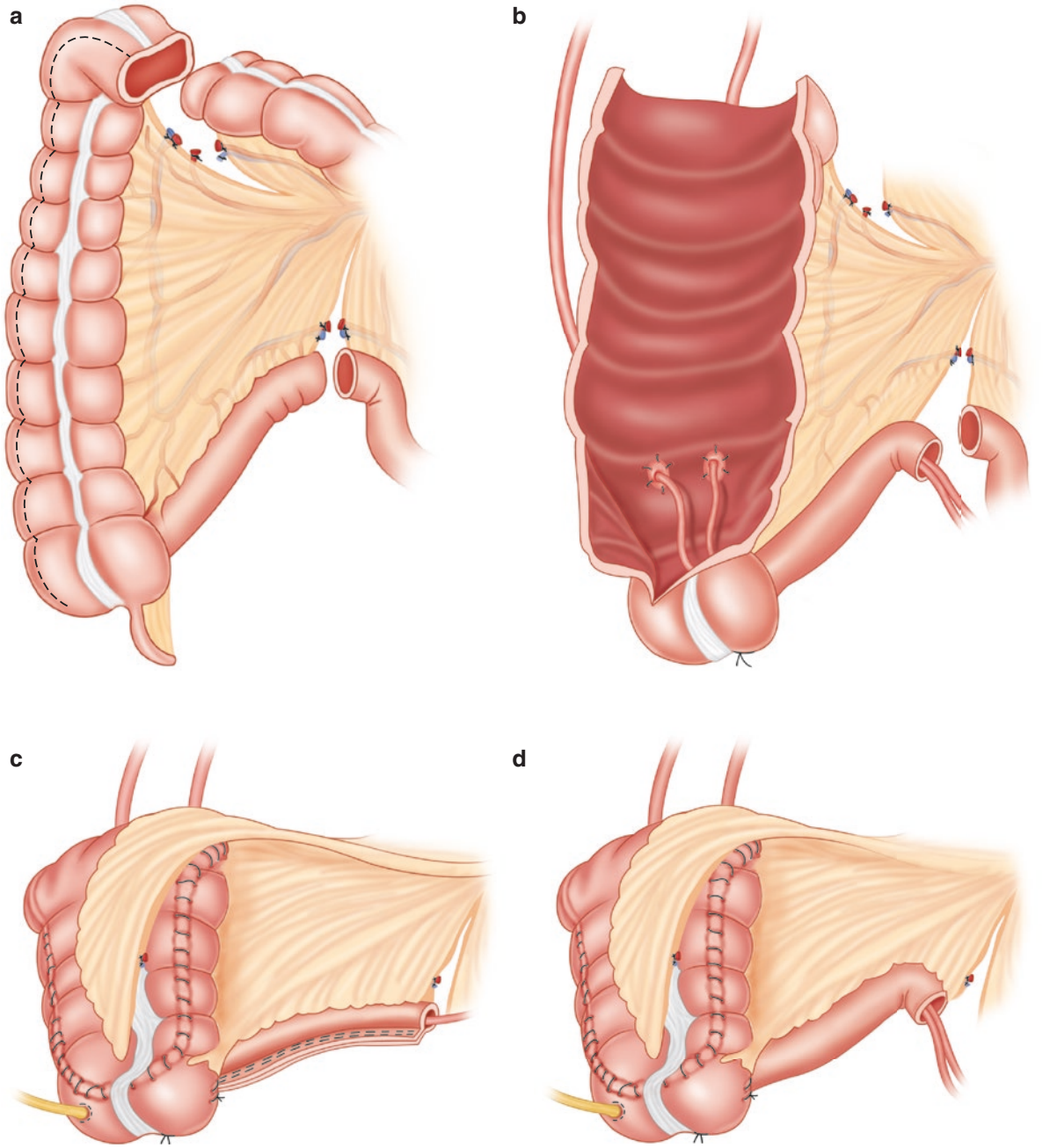

Fig. 54.34 (**a**–**d**) The Indiana pouch

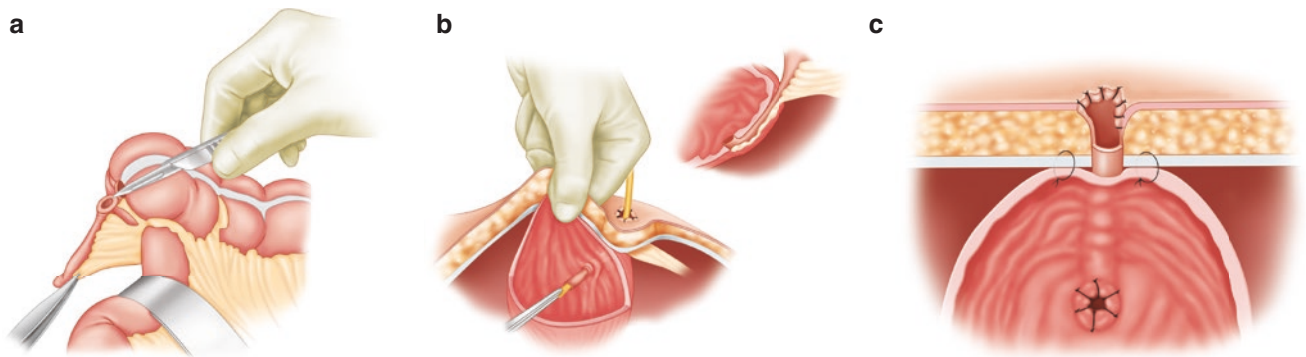

Fig. 54.35 (**a**–**c**) Mitrofanoff appendicovesicostomy

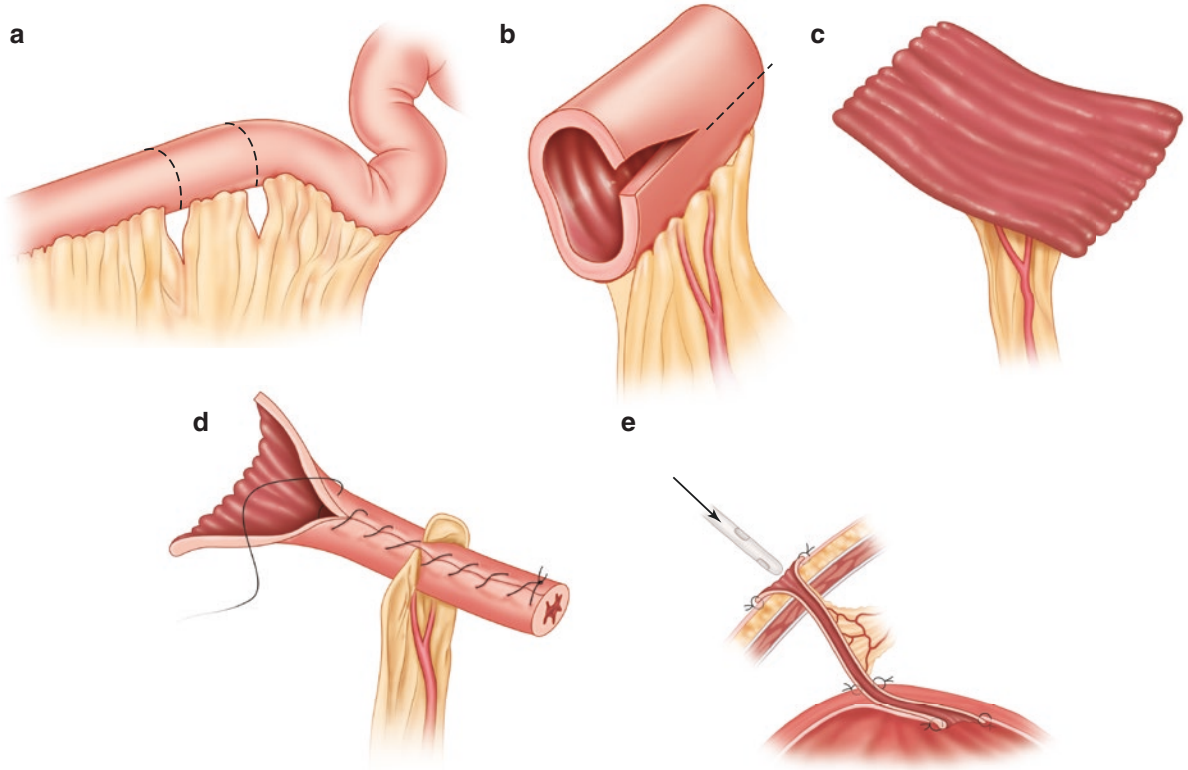

Fig. 54.36 (**a**–**e**) The Monti procedure

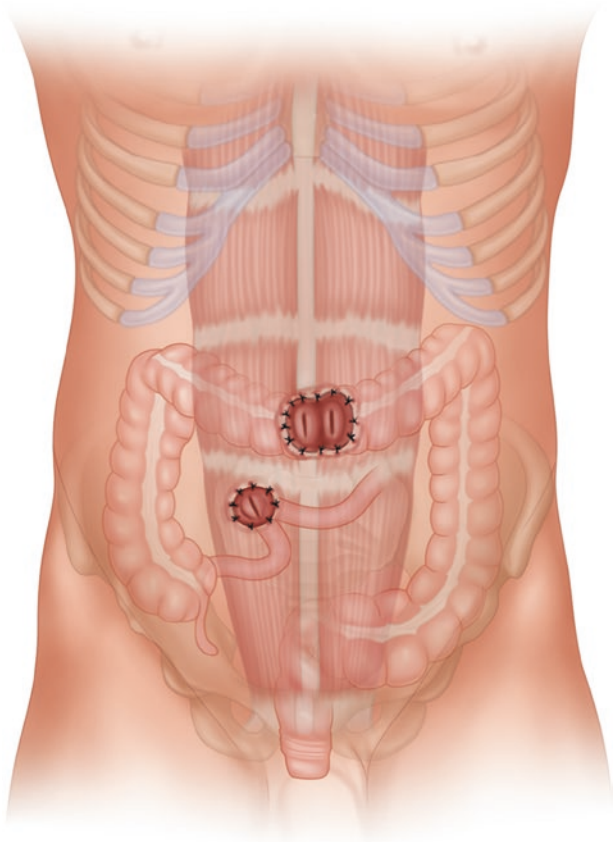

Fig. 54.37 The completed Turnbull blowhole colostomy and loop ileostomy

cia and peritoneum are carefully divided and the abdomen is entered. The anterior seromuscular surface of the colon is grasped through the incision and sutured circumferentially to the peritoneum to limit intra-abdominal stool contamination. A colotomy is made, and the stoma is sutured to the skin as described above.

Ileostomy and Foodstuff Bolus Obstruction

Early postoperative edema may cause transient ileostomy obstruction at the level of the rectus fascia. Such edema typically subsides before return of bowel function, but lasting edema can cause an obstruction. In the setting of obstructive symptoms, ileostomy obstruction may be suspected when there is peristomal pain with either thin, non-bilious, hydrops-type fluid ileostomy effluent or no output at all. Cross-sectional imaging may reveal an abrupt transition in bowel caliber as the stoma traverses the abdominal wall. If acute postoperative ileostomy obstruction is suspected, a 14–18-French Foley (or red rubber) catheter can be gently placed at the bedside to bypass the level of obstruction and decompress the bowel proximal to the ileostomy. To place a catheter, a two-piece stoma appliance should be used.

With the stoma flange in place and bag removed, a well-lubricated catheter is inserted into the stomal os as small aliquots of water are gently injected through the catheter with a Toomey syringe to create a water cushion ahead of the catheter tip. The catheter is advanced as long as resistance is not

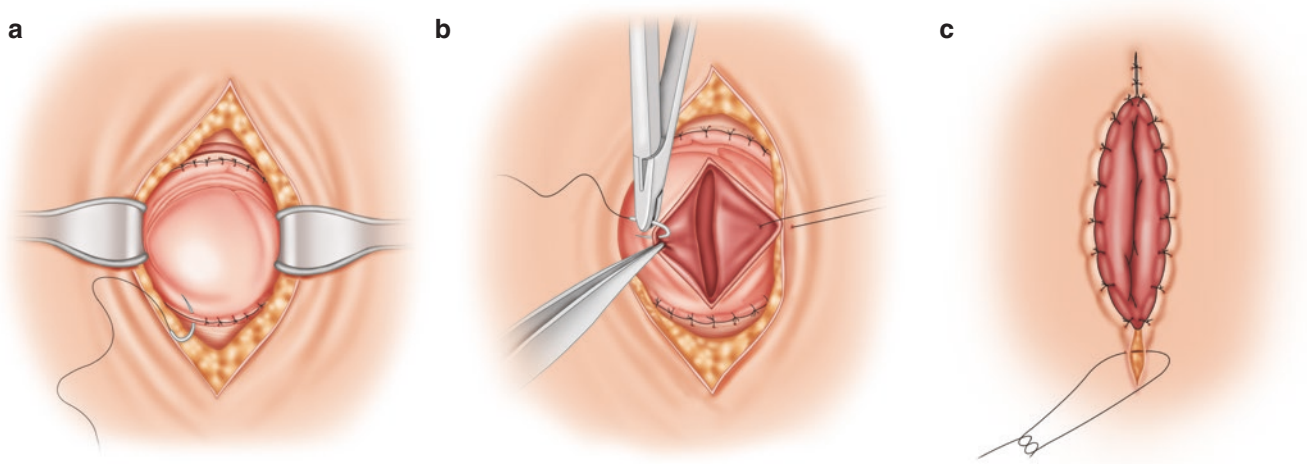

Fig. 54.38 (**a**–**c**) Creation of a Turnbull blowhole colostomy

met beyond the fascial obstruction and secured to the stoma appliance with suture or dental floss to hold the catheter in place. If a Foley catheter is used, the balloon should not be blown up out of concern of injuring the bowel. The catheter should be used cautiously, as both short- and long-term use of indwelling stoma catheters, can cause bowel perforation.

The relatively narrow luminal diameter of an ileostomy may occasionally cause bolus obstruction by nondigestible foodstuffs. High-residue foods such as nuts, seeds, shellfish, sausage casings, and raw produce are poorly digested and may pass through the ileostomy in large chunks. Rarely, such foodstuffs may become lodged within the ileostomy and require ileostomy irrigation to disimpact the food bolus. To irrigate an ileostomy, a Foley (or red rubber) catheter is placed as described above to a distance just beyond the fascia (typically <6 inches from the skin surface). A Toomey syringe is then used to slowly irrigate out the bolus obstruction with 30–50 mL aliquots of water until the bolus is dislodged. This process may take 1–2 hours.

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References

1. Turnbull GB. Ostomy statistics: the $64,000 question. Ostomy Wound Manage. 2003;49(6):22–3.
2. Rombeau J. Physiologic and metabolic effects of intestinal stomas. In: Fazio VW, Church JM, Wu JS, editors. Atlas of intestinal stomas: Springer; 2012. p. 59–67.
3. Parekh N, Seidner DL. Medical management of the high output enterostomy and enterocutaneous ffistula. In: Fazio VW, Church JM, Wu JS, editors. Atlas of intestinal stomas: Springer; 2012. p. 97–109.
4. Kent DJ, Arnold Long M, Bauer C. Revisiting colostomy irrigation: a viable option for persons with permanent descending and sigmoid colostomies. J Wound Ostomy Continence Nurs. 2015;42(2):162–4.
5. Kent DJ, Long MA, Bauer C. Does colostomy irrigation affect functional outcomes and quality of life in persons with a colostomy? J Wound Ostomy Continence Nurs. 2015;42(2):155–61.
6. Nightingale J, et al. Guidelines for management of patients with a short bowel. Gut. 2006;55(Suppl 4):iv1–12.
7. Purandare A, Phalgune D, Shah S. Variability of length of small intestine in Indian population and its correlation with type 2 diabetes mellitus and obesity. Obes Surg. 2019;29(10):3149–53.
8. Teitelbaum EN, et al. Intraoperative small bowel length measurements and analysis of demographic predictors of increased length. Clin Anat. 2013;26(7):827–32.
9. Hendren S, et al. Clinical practice guidelines for ostomy surgery. Dis Colon Rectum. 2015;58(4):375–87.
10. Salvadalena G, Hendren S, McKenna L, Muldoon R, Netsch D, Paquette I, Pittman J, Ramundo J, Steinberg G. WOCN Society and ASCRS Position Statement on Preoperative Stoma Site Marking for Patients Undergoing Colostomy or Ileostomy Surgery. J Wound Ostomy Continence Nurs. 2015;42(3):249–52. https://doi.org/10.1097/WON.0000000000000119. PMID: 25695929.
11. Burch J. Stoma care: an update on current guidelines for community nurses. Br J Community Nurs. 2017;22(4):162–6.
12. Ferrara F, et al. Italian guidelines for the surgical management of enteral stomas in adults. Tech Coloproctol. 2019;23(11):1037–56.
13. WOCN society clinical guideline: management of the adult patient with a fecal or urinary ostomy-an executive summary. J Wound Ostomy Continence Nurs. 2018;45(1):50–8.
14. Bass EM, et al. Does preoperative stoma marking and education by the enterostomal therapist affect outcome? Dis Colon Rectum. 1997;40(4):440–2.
15. Parmar KL, et al. A prospective audit of early stoma complications in colorectal cancer treatment throughout the Greater Manchester and Cheshire colorectal cancer network. Color Dis. 2011;13(8):935–8.
16. Burch J. Research and expert opinion on siting a stoma: a review of the literature. Br J Nurs. 2018;27(16):S4–s12.
17. Person B, et al. The impact of preoperative stoma site marking on the incidence of complications, quality of life, and patient's independence. Dis Colon Rectum. 2012;55(7):783–7.
18. Wasserman MA, McGee MF. Preoperative considerations for the ostomate. Clin Colon Rectal Surg. 2017;30(3):157–61.
19. Whitehead, A., A. Seah, and P. Cataldo, Technical tips for difficult stomas, in Complexities in colorectal surgery: decision-making and management, S. Steele, et al., Editors. 2014, Springer: New York p 147-156.

20. Erwin-Toth, P., B. Hocevar, and S. LJ, Wound, ostomy, and continence/enterostomal therapy (WOC/ET) nursing, in Atlas of intestinal stomas, V.W. Fazio, J.M. Church, and J.S. Wu, Editors. 2012, Springer. p. 75–84.
21. Sjodahl R, Anderberg B, Bolin T. Parastomal hernia in relation to site of the abdominal stoma. Br J Surg. 1988;75(4):339–41.
22. Hardt J, et al. Lateral pararectal versus transrectal stoma placement for prevention of parastomal herniation. Cochrane Database Syst Rev. 2013;11:CD009487.
23. Hardt J, et al. A pilot single-centre randomized trial assessing the safety and efficacy of lateral pararectus abdominis compared with transrectus abdominis muscle stoma placement in patients with temporary loop ileostomies: the PATRASTOM trial. Color Dis. 2016;18(2):O81–90.
24. Hardt J, et al. Lateral pararectal versus transrectal stoma placement for prevention of parastomal herniation. Cochrane Database Syst Rev. 2019;4:CD009487.
25. Chaudhri S, et al. Preoperative intensive, community-based vs. traditional stoma education: a randomized, controlled trial. Dis Colon Rectum. 2005;48(3):504–9.
26. Younis J, et al. Focused preoperative patient stoma education, prior to ileostomy formation after anterior resection, contributes to a reduction in delayed discharge within the enhanced recovery programme. Int J Color Dis. 2012;27(1):43–7.
27. Stocchi L. Ileostomy. In: Fazio VW, Church JM, Wu JS, editors. Atlas of intestinal stomas: Springer; 2012. p. 85–95.
28. Sier MF, et al. Randomized clinical trial of intracutaneously versus transcutaneously sutured ileostomy to prevent stoma-related complications (ISI trial). Br J Surg. 2018;105(6):637–44.
29. Cottam J, et al. Results of a nationwide prospective audit of stoma complications within 3 weeks of surgery. Color Dis. 2007;9(9):834–8.
30. Speirs M, et al. Ileostomy rod--is it a bridge too far? Color Dis. 2006;8(6):484–7.
31. Mohan HM, et al. Stoma rods in abdominal surgery: a systematic review and metaanalyses. Tech Coloproctol. 2019;23(3):201–6.
32. Salum M, et al. Does sodium hyaluronate- and carboxymethylcellulose-based bioresorbable membrane (Seprafilm) decrease operative time for loop ileostomy closure? Tech Coloproctol. 2006;10(3):187–90. discussion 190-1
33. Tang CL, et al. Bioresorbable adhesion barrier facilitates early closure of the defunctioning ileostomy after rectal excision: a prospective, randomized trial. Dis Colon Rectum. 2003;46(9):1200–7.
34. Tjandra JJ, Chan MK. A sprayable hydrogel adhesion barrier facilitates closure of defunctioning loop ileostomy: a randomized trial. Dis Colon Rectum. 2008;51(6):956–60.
35. Hayden DM, et al. Hospital readmission for fluid and electrolyte abnormalities following ileostomy construction: preventable or unpredictable? J Gastrointest Surg. 2013;17(2):298–303.
36. Hignett S, et al. Ileostomy formation does not prolong hospital length of stay after open anterior resection when performed within an enhanced recovery programme. Color Dis. 2011;13(10):1180–3.
37. Nagle D, et al. Ileostomy pathway virtually eliminates readmissions for dehydration in new ostomates. Dis Colon Rectum. 2012;55(12):1266–72.
38. Erwin-Toth P, Thompson SJ, Davis JS. Factors impacting the quality of life of people with an ostomy in North America: results from the Dialogue Study. J Wound Ostomy Continence Nurs. 2012;39(4):417–22; quiz 423–4.
39. Altuntas YE, et al. The role of group education on quality of life in patients with a stoma. Eur J Cancer Care (Engl). 2012;21(6):776–81.
40. America, U.O.A.o.; Available from: http://www.ostomy.org/Home.html#.
41. Ostomy Guidelines Task F, et al. Management of the patient with a fecal ostomy: best practice guideline for clinicians. J Wound Ostomy Continence Nurs. 2010;37(6):596–8.
42. Sheetz KH, et al. Complication rates of ostomy surgery are high and vary significantly between hospitals. Dis Colon Rectum. 2014;57(5):632–7.
43. Salvadalena G. Incidence of complications of the stoma and peristomal skin among individuals with colostomy, ileostomy, and urostomy: a systematic review. J Wound Ostomy Continence Nurs. 2008;35(6):596–607; quiz 608–9.
44. Herlufsen P, et al. Study of peristomal skin disorders in patients with permanent stomas. Br J Nurs. 2006;15(16):854–62.
45. Alvey B, Beck DE. Peristomal dermatology. Clin Colon Rectal Surg. 2008;21(1):41–4.
46. Colwell JC, McNichol L, Boarini J. North America wound, ostomy, and continence and enterostomal therapy nurses current ostomy care practice related to peristomal skin issues. J Wound Ostomy Continence Nurs. 2017;44(3):257–61.
47. Steinhagen E, Colwell J, Cannon LM. Intestinal stomas-postoperative stoma care and peristomal skin complications. Clin Colon Rectal Surg. 2017;30(3):184–92.
48. Nybaek H, et al. Skin problems in ostomy patients: a case-control study of risk factors. Acta Derm Venereol. 2009;89(1):64–7.
49. Lyon CC, et al. Parastomal pyoderma gangrenosum: clinical features and management. J Am Acad Dermatol. 2000;42(6):992–1002.
50. Poritz LS, et al. Management of peristomal pyoderma gangrenosum. J Am Coll Surg. 2008;206(2):311–5.
51. Weizman AV, et al. Pyoderma gangrenosum among patients with inflammatory bowel disease: a descriptive cohort study. J Cutan Med Surg. 2015;19(2):125–31.
52. Wu XR, et al. Risk factors for peristomal pyoderma gangrenosum complicating inflammatory bowel disease. J Crohns Colitis. 2013;7(5):e171–7.
53. Afifi L, et al. Diagnosis and management of peristomal pyoderma gangrenosum: a systematic review. J Am Acad Dermatol. 2018;78(6):1195–1204 e1.
54. Miller J, et al. Pyoderma gangrenosum: a review and update on new therapies. J Am Acad Dermatol. 2010;62(4):646–54.
55. Hanley J. Effective management of peristomal pyoderma gangrenosum. Br J Nurs. 2011;20(7):S12–S14-7.
56. Ratnagobal S, Sinha S. Pyoderma gangrenosum: guideline for wound practitioners. J Wound Care. 2013;22(2):68–73.
57. Kiran RP, et al. Management of peristomal pyoderma gangrenosum. Dis Colon Rectum. 2005;48(7):1397–403.
58. Pennick MO, Artioukh DY. Management of parastomal varices: who re-bleeds and who does not? A systematic review of the literature. Tech Coloproctol. 2013;17(2):163–70.
59. Pabon-Ramos WM, Niemeyer MM, Dasika NL. Alternative treatment for bleeding peristomal varices: percutaneous parastomal embolization. Cardiovasc Intervent Radiol. 2013;36(5):1399–404.
60. Gordon P, Nivatvongs S, editors. Principles and practices of surgery of colon, rectum, and anus; 2006. p. 1059.
61. Beck DE, Fazio VW, Grundfest-Broniatowski S. Surgical management of bleeding stomal varices. Dis Colon Rectum. 1988;31(5):343–6.
62. Morris CS, Najarian KE. Transjugular intrahepatic portosystemic shunt for bleeding stomal varices associated with chronic portal vein occlusion: long-term angiographic, hemodynamic, and clinical follow-up. Am J Gastroenterol. 2000;95(10):2966–8.
63. Ryu RK, et al. Treatment of stomal variceal hemorrhage with TIPS: case report and review of the literature. Cardiovasc Intervent Radiol. 2000;23(4):301–3.
64. Samaraweera RN, et al. Stomal varices: percutaneous transhepatic embolization. Radiology. 1989;170(3 Pt 1):779–82.

65. Wolfsen HC, et al. The role of endoscopic injection sclerotherapy in the management of bleeding peristomal varices. Gastrointest Endosc. 1990;36(5):472–4.
66. Selby D, Jackson LD. Octreotide for control of bleeding peristomal varices in palliative care. J Pain Symptom Manag. 2015;49(3):e2–4.
67. De Ocampo ML. WOC nurse consult: peristomal varices. J Wound Ostomy Continence Nurs. 2012;39(2):178–9.
68. Wiesner RH, et al. Peristomal varices after proctocolectomy in patients with primary sclerosing cholangitis. Gastroenterology. 1986;90(2):316–22.
69. Poritz LS, Koltun WA. Surgical management of ulcerative colitis in the presence of primary sclerosing cholangitis. Dis Colon Rectum. 2003;46(2):173–8.
70. Kartheuser AH, et al. Complications and risk factors after ileal pouch-anal anastomosis for ulcerative colitis associated with primary sclerosing cholangitis. Ann Surg. 1993;217(4):314–20.
71. Kartheuser AH, et al. Comparison of surgical treatment of ulcerative colitis associated with primary sclerosing cholangitis: ileal pouch-anal anastomosis versus Brooke ileostomy. Mayo Clin Proc. 1996;71(8):748–56.
72. Grucela AL, Steinhagen RM. Restorative proctocolectomy and ileal pouch-anal anastomosis for ulcerative colitis after liver transplant for primary sclerosing cholangitis: case report and review of literature. Am Surg. 2005;71(4):362–5.
73. Lian L, et al. Inflammatory bowel disease complicated by primary sclerosing cholangitis and cirrhosis: is restorative proctocolectomy safe? Dis Colon Rectum. 2012;55(1):79–84.
74. Szmulowicz U, Hull T. Stoma prolapse. In: Fazio VW, Church JM, Wu JS, editors. Atlas of intestinal stomas: Springer; 2012. p. 249–72.
75. Sobrado Junior CW, et al. Local treatment of colostomy prolapse with the MESH STRIP technique: a novel and highly efficient day hospital technique. Clinics (Sao Paulo). 2020;75:e1353.
76. Kroese LF, et al. Systematic review and meta-analysis of extraperitoneal versus transperitoneal colostomy for preventing parastomal hernia. Dis Colon Rectum. 2016;59(7):688–95.
77. Theofanis G, et al. Avoiding emergency stoma surgery with the use of sugar. Br J Nurs. 2017;26(22):S24–6.
78. Wu JS, Fazio VW. Difficult stomas. In: Schrock TR, editor. Perspectives in colon and rectal surgery, vol. 33-60. St. Louis: Quality Medical Publishing; 1998.
79. Baker ML, Williams RN, Nightingale JM. Causes and management of a high-output stoma. Color Dis. 2011;13(2):191–7.
80. Avery ME, Snyder JD. Oral therapy for acute diarrhea. The underused simple solution. N Engl J Med. 1990;323(13):891–4.
81. Nightingale JM, et al. Oral salt supplements to compensate for jejunostomy losses: comparison of sodium chloride capsules, glucose electrolyte solution, and glucose polymer electrolyte solution. Gut. 1992;33(6):759–61.
82. Nightingale JM, et al. Octreotide (a somatostatin analogue) improves the quality of life in some patients with a short intestine. Aliment Pharmacol Ther. 1989;3(4):367–73.
83. Jeppesen PB. Pharmacologic options for intestinal rehabilitation in patients with short bowel syndrome. JPEN J Parenter Enteral Nutr. 2014;38(1 Suppl):45S–52S.
84. Geraghty JM, Talbot IC. Diversion colitis: histological features in the colon and rectum after defunctioning colostomy. Gut. 1991;32(9):1020–3.
85. Hong SY, et al. Routine barium enema prior to closure of defunctioning ileostomy is not necessary. J Korean Surg Soc. 2012;83(2):88–91.
86. Kalady MF, et al. Routine contrast imaging of low pelvic anastomosis prior to closure of defunctioning ileostomy: is it necessary? J Gastrointest Surg. 2008;12(7):1227–31.
87. Khair G, et al. Routine use of gastrograffin enema prior to the reversal of a loop ileostomy. Dig Surg. 2007;24(5):338–41.
88. da Silva GM, et al. Is routine pouchogram prior to ileostomy closure in colonic J-pouch really necessary? Color Dis. 2004;6(2):117–20.
89. Selvaggi F, et al. Is omitting pouchography before ileostomy takedown safe after negative clinical examination in asymptomatic patients with pelvic ileal pouch? An observational study. Tech Coloproctol. 2012;16(6):415–20.
90. Perez RO, et al. Loop ileostomy morbidity: timing of closure matters. Dis Colon Rectum. 2006;49(10):1539–45.
91. Krand O, et al. Early vs. delayed closure of temporary covering ileostomy: a prospective study. Hepato-Gastroenterology. 2008;55(81):142–5.
92. Omundsen M, et al. Early ileostomy closure: is there a downside? ANZ J Surg. 2012;82(5):352–4.
93. Worni M, et al. Early closure of ileostomy is associated with less postoperative nausea and vomiting. Dig Surg. 2011;28(5–6):417–23.
94. Danielsen AK, et al. Early closure of a temporary ileostomy in patients with rectal cancer: a multicenter randomized controlled trial. Ann Surg. 2017;265(2):284–90.
95. Park J, et al. Quality of life in a randomized trial of early closure of temporary ileostomy after rectal resection for cancer (EASY trial). Br J Surg. 2018;105(3):244–51.
96. Danielsen AK, et al. Early closure of temporary ileostomy--the EASY trial: protocol for a randomised controlled trial. BMJ Open. 2011;1(1):e000162.
97. Phatak UR, et al. Impact of ileostomy-related complications on the multidisciplinary treatment of rectal cancer. Ann Surg Oncol. 2014;21(2):507–12.
98. Tulchinsky H, et al. Should a loop ileostomy closure in rectal cancer patients be done during or after adjuvant chemotherapy? J Surg Oncol. 2014;109(3):266–9.
99. Hajibandeh S, et al. Meta-analysis of temporary loop ileostomy closure during or after adjuvant chemotherapy following rectal cancer resection: the dilemma remains. Int J Color Dis. 2019;34(7):1151–9.
100. Fleming FJ, Gillen P. Reversal of Hartmann's procedure following acute diverticulitis: is timing everything? Int J Color Dis. 2009;24(10):1219–25.
101. Keck JO, et al. Reversal of Hartmann's procedure: effect of timing and technique on ease and safety. Dis Colon Rectum. 1994;37(3):243–8.
102. Pearce NW, Scott SD, Karran SJ. Timing and method of reversal of Hartmann's procedure. Br J Surg. 1992;79(8):839–41.
103. Roe AM, et al. Reversal of Hartmann's procedure: timing and operative technique. Br J Surg. 1991;78(10):1167–70.
104. Gong J, et al. Stapled vs hand suture closure of loop ileostomy: a meta-analysis. Color Dis. 2013;15(10):e561–8.
105. Hull TL, Kobe I, Fazio VW. Comparison of handsewn with stapled loop ileostomy closures. Dis Colon Rectum. 1996;39(10):1086–9.
106. Leung TT, et al. Comparison of stapled versus handsewn loop ileostomy closure: a meta-analysis. J Gastrointest Surg. 2008;12(5):939–44.
107. Hasegawa H, et al. Stapled versus sutured closure of loop ileostomy: a randomized controlled trial. Ann Surg. 2000;231(2):202–4.
108. Markides GA, et al. Meta-analysis of handsewn versus stapled reversal of loop ileostomy. ANZ J Surg. 2015;85(4):217–24.
109. Loffler T, et al. HAnd suture versus STApling for closure of loop ileostomy (HASTA trial): results of a multicenter randomized trial (DRKS00000040). Ann Surg. 2012;256(5):828–35; discussion 835–6
110. Camacho-Mauries D, et al. Randomized clinical trial of intestinal ostomy takedown comparing pursestring wound closure vs conventional closure to eliminate the risk of wound infection. Dis Colon Rectum. 2013;56(2):205–11.

111. Reid K, et al. Randomized clinical trial of short-term outcomes following purse-string versus conventional closure of ileostomy wounds. Br J Surg. 2010;97(10):1511–7.
112. Mazeh H, et al. Laparoscopic and open reversal of Hartmann's procedure--a comparative retrospective analysis. Surg Endosc. 2009;23(3):496–502.
113. Haughn C, et al. Complication rates after Hartmann's reversal: open vs. laparoscopic approach. Dis Colon Rectum. 2008;51(8):1232–6.
114. Guenaga KF, et al. Ileostomy or colostomy for temporary decompression of colorectal anastomosis. Cochrane Database Syst Rev. 2007;1:CD004647.
115. Gooszen AW, et al. Quality of life with a temporary stoma: ileostomy vs. colostomy. Dis Colon Rectum. 2000;43(5):650–5.
116. Sakai Y, et al. Temporary transverse colostomy vs loop ileostomy in diversion: a case-matched study. Arch Surg. 2001;136(3):338–42.
117. Edwards DP, et al. Stoma-related complications are more frequent after transverse colostomy than loop ileostomy: a prospective randomized clinical trial. Br J Surg. 2001;88(3):360–3.
118. Klink CD, et al. Diversion stoma after colorectal surgery: loop colostomy or ileostomy? Int J Color Dis. 2011;26(4):431–6.
119. Rullier E, et al. Loop ileostomy versus loop colostomy for defunctioning low anastomoses during rectal cancer surgery. World J Surg. 2001;25(3):274–7; discussion 277–8.
120. Colombo R, Naspro R. Ileal conduit as the standard for urinary diversion after radical cystectomy for bladder cancer. Eur Urol Suppl. 2010;9(10):736–44.
121. Gakis G, Stenzl A. Ileal neobladder and its variants. Eur Urol Suppl. 2010;9(10):745–53.
122. Rowland RG, et al. Indiana continent urinary reservoir. J Urol. 1987;137(6):1136–9.
123. Harris CF, et al. Appendicovesicostomy: the mitrofanoff procedure-a 15-year perspective. J Urol. 2000;163(6):1922–6.
124. Cain MP, Casale AJ, Rink RC. Initial experience using a catheterizable ileovesicostomy (Monti procedure) in children. Urology. 1998;52(5):870–3.
125. Ooi BS, Remzi FH, Fazio VW. Turnbull-Blowhole colostomy for toxic ulcerative colitis in pregnancy: report of two cases. Dis Colon Rectum. 2003;46(1):111–5.
126. Bhangu A, et al. Systematic review and meta-analysis of the incidence of incisional hernia at the site of stoma closure. World J Surg. 2012;36(5):973–83.
127. Aydin HN, et al. Hartmann's reversal is associated with high postoperative adverse events. Dis Colon Rectum. 2005;48(11):2117–26.
128. Law WL, Chu KW, Choi HK. Randomized clinical trial comparing loop ileostomy and loop transverse colostomy for faecal diversion following total mesorectal excision. Br J Surg. 2002;89(6):704–8.

Abdominal Wall Reconstruction and Parastomal Hernia Repair

55

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Key Concepts

- The precise incidence of parastomal herniation is largely based on criteria for diagnosis.
- A selective approach to repair of parastomal hernias is warranted owing to the high recurrence rates associated with surgical repair.
- Repair should generally be restricted to highly symptomatic patients with parastomal hernia.
- Laparoscopic Sugarbaker repair is the procedure of choice for most patients requiring surgery for parastomal hernias.
- Advanced abdominal wall reconstruction techniques may be indicated in complex defects.

Introduction

Parastomal hernias are a ubiquitous problem for both the general and colorectal surgeon alike. Experienced surgeons will admit that their repair is a humbling endeavor, and a thorough review of the literature for guidance reveals only anecdotal cohorts often with limited follow-up. As with all incisional hernias, repair of parastomal defects is impacted by the patient's comorbidities, the characteristics of the hernia itself, and the surgeons' experience or comfort level with various repair techniques. Here we review the available literature on repair options and attempt to provide a practical approach to surgical decision-making when presented with these difficult patients.

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Incidence, Risk Factors, and Diagnosis

Conservatively, 120,000 ostomies are created yearly in the United States, and at any given time, approximately 800,000 Americans are living with a stoma [1]. Subsequent development of a parastomal hernia (PSH) – defined as an incisional hernia at the site of an ostomy – is one of the most common complications thereof [2]. The reported rates of PSH formation vary widely depending on the type of stoma, patient characteristics, the duration of follow-up, and definition or method of detection. Generally, rates are approximately 30% by 1 year and 40% by 2 years and can be greater than 50% with longer follow-up [3]. Some would even pessimistically contend that with long enough follow-up, PSH development is inevitable [4]. In addition to pain and potential obstructive symptoms akin to all incisional hernias, PSH bulging can also cause pouching dysfunction with a devastating impact on these patients' quality of life (QoL), not to mention the financial burden of additional supplies and frequent need for hospital readmission to break the cycle of appliance leakage and worsening skin excoriation [5, 6]. Consequently, both the American Society of Colon and Rectal Surgeons and the Association of Coloproctology of Great Britain and Ireland have identified PSH prevention and repair as a top research priority [7, 8].

As was previously alluded to, the precise incidence of PSH is a function of several important factors. Most rudimentary is the stoma type with the incidence ranges listed in Table 55.1 [9, 10]. In general, end colostomies have a higher incidence of PSH formation compared to the relatively similar rates identified in end ileostomies and loop colostomies.

Table 55.1 Parastomal hernia incidence

End ileostomy	2–28%
Ileal conduit [10]	17%
End colostomy	4–48%
Loop ileostomy	0–6%
Loop colostomy	0–31%

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Loop ileostomies have the lowest incidence, likely owed to their transient presence. As was mentioned in the previous chapter, an enlarged trephine size at the time of creation has been associated with PSH formation and therefore minimizing the muscle defect without causing ischemia to the trespassing bowel is a delicate balance the surgeon hopes to achieve [11]. To account for some of the wide variability in PSH reporting, inconsistent definitions and variable patient characteristics often play a significant role. A review of the literature by Israelsson points out the frequent absence of parastomal definitions in clinical reports as well as the hindrance of this weakness on comparing repair techniques. In addition to emphasizing the importance of following stoma patients at least 1 year to monitor for PSH occurrence, he proposed the following definition that provides some practical specifics during clinical assessment – "any palpable defect or bulge adjacent to the stoma detected when the patient is supine with legs elevated or while coughing or straining when the patient is erect" [12]. Still, inter-observer reliability among staff surgeons is more disappointing that one would expect [13]. Regarding patient characteristics, advanced age, diabetes, surgical site infection, malnutrition, immunosuppression, malignancy, and emergent presentation have all been implicated as risk factors for PSH development. That said, obesity and waist circumference seem to carry the strongest association supported by clinical data [14–16]. While not entirely reflective of an American patient population, the Swedish National Colorectal Cancer Registry and National Patient Register of over 6300 patients with a permanent colostomy identified body mass index (BMI) >30 kg/m^2 as the only risk factor for PSH development [13]. Furthermore, the patient's particular body habitus may be an even more specific predictor, as a waist circumference > 100 cm has a 75% probability of budding a PSH [15]. For this reason, preoperative weight loss before embarking on PSH repair is something that should be taken seriously whenever possible.

Next, the timing and methodology of diagnosis deserve some additional discussion. Data from large prospective series tend to demonstrate that PSH occurrences start to plateau after the first two postoperative years [3, 17, 18]. Specifically, a large cohort of 202 parastomal hernias analyzed by the French federation of ostomy patients found a median time of 18 months until presentation but with a range of up to 27 years [19]. The aforementioned diagnoses were self-reported by those patients who were educated on the signs and symptoms of a PSH. The authors acknowledge that self-observation could underestimate the true rate of PSH in their patients. However, 76% of the PSH patients identified by patients themselves had symptoms, and 56% had undergone operative repair (Table 55.2) suggesting that self-observation is at least a good way to identify a clinically significant PSH. Alternatively, while CT scan findings can be useful to identify a concomitant incisional hernia, PSH interpretation can be challenging. Some have suggested that CT scans can overestimate the presence of a clinically significant PSH bulge by misinterpreting redundant bowel in the subcutaneous tissue, while others have found that a traditional supine image with reduced hernia contents may not adequately demonstrate a clinically significant parastomal bulge that would be present in the standing/prone position or with Valsalva [20, 21]. So while CT scans can provide a lot of useful information for operative planning – specifically the presence of a concomitant incisional hernia, bowel obstruction, or size of a PSH defect that may dictate the need for re-siting – the importance of the patient's self-assessment in non-urgent scenarios should not be underrated as their symptoms correlate with required operative intervention more often than not [19].

Table 55.2 Parastomal hernia symptoms and complications

Symptom	
Pain	35%
Appliance difficulty	28%
Leakage	27%
Skin irritation	22%
Irrigation difficulty	24%
Complications	
Prolapse	18%
Obstruction	15%
Hemorrhage	2%

Classification

Several PSH classification schemes have been proposed, though none has been validated or gained wide adoption. While their systems have less clinical value in regard to operative decision-making, colorectal surgeons should at least be familiar with the historical definitions by Rubin, Bailey and Devlin summarized in Table 55.3A [22, 23]. The definitions proposed by the European Hernia Society (EHS) in 2014 reflect multinational collaboration and somewhat formalized the systems proposed by Gil, Szczepkowski and Moreno-Matias (Table 55.3B). Modern pragmatic systems incorporate two of the most important variables that impact surgical decision-making – the size of the parastomal defect and the presence of a concomitant incisional hernia.

Operative Indications

Before we discuss repair techniques and strategies, we should set the stage by discussing the implications of operative endeavors in the context of a PSH. First, data from the Abdominal Core Health Quality Collaborative (ACHQC)

Table 55.3 Parastomal hernia classifications

Rubin and Bailey		
I: "True" parastomal hernia	Hernia sac penetrates a dilated stomal canal	
II: Intrastomal hernia	Stomal sac formed by serous membrane of prolapsed intestine	
III: Subcutaneous prolapse	Excess bowel forms a loop in the subcutaneous tissue	
IV: Pseudohernia	Enervation of the lateral abdominal wall	
Devlin		
I: Interstitial hernia	Hernia sac between layers of the abdominal wall	
II: Subcutaneous hernia	Hernia sac penetrating into the subcutaneous layers	
III: Intrastomal hernia		
IV: Peristomal hernia	Associated with stomal prolapse	
Gil and Szczepkowski		
Parastomal hernia w/o coexisting cicatricial hernia and w/o abdominal wall deformation		
Parastomal hernia with cicatricial hernia w/o abdominal wall deformation		
Large, isolated parastomal hernia w/o coexisting cicatricial hernia w/ abdominal wall deformity		
Large parastomal and coexisting cicatricial hernias with abdominal wall deformity		
Moreno-Matias		
Ia	Bowel forming the colostomy with a sac <5 cm	
Ib	Bowel forming the colostomy with a sac >5 cm	
II	Sac containing omentum	
III	Intestinal loop other than bowel forming the stoma	
EHS parastomal hernia classification		
I	<5 cm parastomal hernia, no concomitant incisional hernia	Primary or recurrent
II	<5 cm incision hernia, yes, concomitant incisional hernia	
III	>5 cm parastomal hernia, no concomitant incisional hernia	
IV	>5 cm parastomal hernia, yes, concomitant incisional hernia	

found that only 22% of stomas were reversible at the time of their hernia repair [24]. So while reversal of a temporizing stoma simplifies reconstruction techniques akin to an incisional hernia, in the vast majority of situations, the surgeon is going to have to deal with the trespassing bowel again. Second, while the success of each technique is somewhat variable and will be discussed in more detail shortly, no PSH repair is tremendously successful. Recurrences again depend on risk factors, the length of follow-up, and diagnostic technique, but can still be >50% when long-term follow-up is available, even when a mesh reinforcement is utilized [19, 25]. Finally, with each additional repair that includes prosthetic reinforcement, the next operation typically becomes more complex, with reports of sobering complication rates >50% and re-operation rates of 12% [26]. So in the absence of symptoms that warrant repair, it is not surprising that up to 70% of patients living with a PSH do not pursue an operation, a preference no doubt shared by their surgeon [27]. While there is no good evidence to describe the consequence of watchful waiting, the results of operative intervention are certainly not celebrated enough to appeal to the asymptomatic or minimally symptomatic patient, and there are at least anecdotal reports of safe non-operative practices by surgeons [28]. Unlike descriptions of pain that can be widely variable, patients with pouching issues or intermittent obstruction typically have an impaired QoL sufficient enough to pursue surgical repair – *see incidence in* Table 55.3. A standardized QoL measure – Patient-Reported Outcomes after Parastomal HErnia tReatment (PROPHER Study) – is in the midst of development by the European Society of Coloproctology to help guide this discussion and give patients feedback on realistic expectations after their operation [26]. To date, repair should be offered to those patients with a history of PSH complications – most commonly bowel obstruction and prolapse – or symptoms causing significant limitation in their QoL. An honest discussion should be had about the real risk of recurrence and the optimization techniques that can help prevent both recurrence and wound morbidity discussed next.

Preoperative Optimization and Planning

Given the tenuous results of surgical repair, every effort should be made to optimize these patients before their operation. In the absence of an emergent presentation, an emphasis should be placed on weight loss, smoking cessation, and diabetes control. In addition to the association of BMI with wound morbidity and an increased length of stay, the aforementioned association of PSH recurrence with BMI and waist circumference underscores the importance of preoperative weight loss specifically in this context [29, 30]. Most experts agree on the extremes – that surgery should be offered to those with a BMI <30 kg/m^2 and that a BMI >50 kg/m^2 should be considered prohibitive [31]. However, recommendations on those patients between a BMI of 30 and 50 mg/m^2 are ambiguous, and prospective evidence on the benefits of weight loss in this setting is lacking. Intuitively, retrospective data from the AHSQC regarding incisional hernias found that surgical site infection and those requiring an intervention progressively decreased with a lower BMI, but a safe "cutoff" could not be determined [32]. The authors suggest that the surgeon counsel patients on weight loss and monitor the patient's progress in 3-month intervals [33]. We typically aim for a BMI <35 kg/m^2, or < 40 kg/m^2 if a sincere attempt has been made and the severity of the patient's symptoms is escalating. Likewise, active smoking and poorly controlled diabetes have similar correlations with wound morbidity [34–36]. Data supports the effectiveness of smok-

Table 55.4 Parastomal hernia repair preoperative optimization

BMI	<35–40 kg/m^2
Smoking cessation	≥4 weeks
Hemoglobin A1C	<7–8
Stoma marking	All patients
Bowel prep	No

ing cessation for at least 4 weeks before surgery and a hemoglobin A1C <7–8 [36, 37].

Briefly, there are two additional points to discuss regarding preoperative planning – the importance of stoma marking and role of a bowel prep. Preoperative stoma marking of a PSH patient should be done even when not planning to re-site a stoma in the uncommon case where it is necessary. Certainly the insight of an enterostomal therapist has been found to be helpful in regard to reducing postoperative adverse events and improving patients' postoperative quality of life and independence [38, 39]. Finally, there is actually not evidence to support the use of a routine bowel prep during PSH repair [2]. Practically, this can increase the leakage of watery stool during a repair that may require manipulation of the bowel. Furthermore, data from the ACHQC has found that a routine bowel prep does not impact wound morbidity and may increase the impact of wound morbidity requiring a procedural intervention in contaminated cases [40].

The outlined optimization approaches – summarized in Table 55.4 – seem straightforward. However, some of the most challenging and emotional discussions with patients are those without an urgent operative indication who resist the recommended optimization efforts, most typically weight loss and smoking cessation. Often surgeons feel compelled to intervene when a patient "gives up," concerned that an emergent presentation would be viewed as their failure to intervene in an elective setting. Here, the authors encourage strict adherence to the aforementioned optimization efforts at all costs, emphasizing to the patient that they too are responsible for the consequences of non-adherence that include potential emergent presentation and a non-definitive primary repair.

Repair Techniques and Associated Outcomes

To date there are no randomized controlled trials comparing repair techniques for parastomal hernias with mesh reinforcement. As such we will summarize the findings of large or significant series for each approach.

Primary Repair

Primary repair has mostly fallen out of favor due to unacceptable recurrence rates as high as 80% [12, 41–43]. Relocation of the stoma without mesh reinforcement – typically requiring a midline laparotomy – likewise has recurrence rates as high as 86% with the added risk of a midline incisional hernia or hernia at the previous stoma site, again as high as 52% [44, 45]. Additionally, ipsilateral and multiple re-siting procedures further potentiate these recurrences [44, 46]. These maneuvers should be reserved for patients in extremis or for sub-optimized patients presenting for urgent repair – typically for an associated bowel obstruction.

Onlay Mesh Repair

Using an incision at least 10 cm away from the stoma to avoid interactions with the appliance, an extraperitoneal dissection is achieved in the anterior rectus sheath, external oblique aponeurosis, hernia sac, and stoma circumferentially to allow for sufficient mesh overlap (5–10 cm) [12]. Next the hernia sac can either be excised or reduced. The fascial edges are then approximated with permanent suture, working toward the stoma to create a desired aperture of two finger breaths. Next uncoated polypropylene is placed in the onlay position and fixated with either suture or a skin stapler [47, 48]. If the stoma is left in situ, a keyhole slit can be made in the mesh and the tails secured around the bowel with permanent suture. If the stoma is mobilized from the skin and subcutaneous tissue, then a cruciate incision can be made in the mesh sufficient for the bowel caliber. Benefits are the avoidance of a laparotomy for high-risk patients with small- to medium-sized defects. Disadvantages are that concomitant incisional hernias will not be addressed and the raising of skin flaps poses potential wound ischemia and subcutaneous seroma formation, though most authors acknowledge this can be managed with the use of closed suction drains [49].

Using the aforementioned keyhole technique, Ho et al. report 1 recurrence (7%) in 15 patients over the span of 19 years with an average follow-up of 15 months [50]. De Ruiter et al. supplemented the onlay technique with a solid polypropylene ring reinforcement in 46 patients. While their 15% recurrence rate at 51 months appears favorable, 26% of patients ultimately required removal of the prosthetic – two for infection, five for recurrence, and five during another operation [51]. Steele and colleagues subsequently described another modification to the cruciate mesh repair – the "stove pipe hat" – in which an additional piece of polypropylene mesh is secured to the bowel circumferentially and then separately to a piece of onlay polypropylene. They reported a more modest 26% recurrence rate at 51 months. While 16% of patients had complications, only one patient developed a mesh erosion with this modification [52]. Pooled analysis by Hansson et al. in 2012 of these 3 trials and 3 other small series of onlay PSH repair culminates in 149 patients with at least 1-year follow-up (median 3 years) and an overall recurrence rate of 19%. Importantly, they also summarized rela-

Table 55.5 Onlay parastomal hernia repair: key reports

	n	Technique	F/U (month)	Recurrence
Ho	15	Keyhole PP	15*	7%
DeRuiter	46	Cruciate PP + PP ring	51*	15%
Steele	58	Cruciate PP + stove pipe hat	51*	26%
Warwick	30	Keyhole porcine dermis	36^	90%

PP Polypropylene, * mean, ^ median

Table 55.6 Open intraperitoneal mesh parastomal hernia repair

	n	Technique	F/U (month)	Recurrence
Byers [77]	9	Keyhole PP	13*	0
Morris-Stiff [78]	7	Keyhole PP	78*	29%
Hofstetter [79]	13	Keyhole ePTFE	NR	0
Van Sprundel [80]	16	Keyhole ePTFE	28*	6%
Stelzner [55]	20	Sugarbaker ePTFE	42*	15%

PP Polypropylene, * mean

tively low rates of surgical site infection (2%) and mesh infection (2.6%), tempering theoretical concerns regarding devascularized skin flaps [43]. Since that analysis, Warwick and colleagues have provided an important addition to the literature, describing the high failure rate of keyhole biologic mesh as a supplement for polypropylene in this setting. With a median follow-up of 3 years, 26/30 (90%) patients developed a recurrence, and the median time to that event was 10 months (Table 55.5) [53].

Open Intraperitoneal Mesh Repair

In the setting of an open PSH repair – following closure of the parastomal defect – intraperitoneal mesh with at least 5 cm of overlap can be placed in one of two orientations relative to the bowel leaving the peritoneal cavity. One is a keyhole or cruciate mesh reinforcement and like the onlay description depends on whether the bowel is left in situ or re-sited respectively [43]. Alternatively, Sugarbaker described lateralizing the bowel as it exits the peritoneal cavity, placing a mesh reinforcement directly over the hernia site and allowing the loop of intestine to drape between the abdominal wall and the prosthetic, creating a "valve" effect with increased abdominal pressure. Sugarbaker's initial description of seven patients resulted in no recurrences after an average of 5 years [54]. While the Sugarbaker technique allows for more of an interface between the exiting bowel and the prosthetic, raising concern for erosion, this alternative overcomes a limitation of cruciate and keyhole repairs that are subject to mesh shrinkage and enlargement of the orifice leaving these patients more prone to recurrence [55]. While some of the initial descriptions were with uncoated polypropylene, contemporary repairs utilize anti-adhesive/barrier-coated synthetic mesh or expanded polytetrafluoroethylene (ePTFE).

Five series exist for these repairs, none with more than 20 patients. Pooled analysis by Al Shakarchi and Williams totaled 65 patients with a 9% recurrence rate at a mean follow-up of 38 months, as well as a 3% surgical site infection rate and 1 report of mesh infection [56]. The largest single study consisted of 20 repairs with ePTFE in the Sugarbaker orientation, reporting a 15% recurrence rate with a mean follow-up of 42 months [55]. The keyhole repairs totaled a slightly lower recurrence rate (7%) but with less follow-up (median 28 months) (Table 55.6) [43].

Laparoscopic Intraperitoneal Mesh Repair

The paucity of literature on open intraperitoneal mesh repair is likely because of the rapid adoption of laparoscopic intraperitoneal mesh repair. The principles of repair are similar to an open approach with use of three or four trocars for peritoneal access, reduction of the hernia contents, optional closure of the parastomal defect, and placement/fixation of mesh in either the keyhole (Fig. 55.1) or Sugarbaker orientation (Fig. 55.2) [43]. When technically feasible, the benefits of most laparoscopic alternatives remain true for these repairs compared to their open counterparts in regard to reduced pain, morbidity, length of stay, and earlier return to work [57]. Given the need for 5 cm of fascial overlap in all directions, small- to medium-sized defects without a concomitant fascial defect are ideal candidates for a minimally invasive approach.

A meta-analysis by DeAsis et al. pooled 15 studies from 2005 to 2015 with at least 5 patients and a minimum 1-year follow-up. There was no difference in morbidity rates among techniques. Specifically, rates of surgical site infection (4%), infected mesh (1.7%), and obstruction requiring re-operation (1.7%) were relatively low. The overall recurrence rate was 17–10% for the 191 laparoscopic Sugarbaker repairs and 28% for the 231 laparoscopic keyhole repairs [58]. This comprehensive analysis would suggest that the laparoscopic Sugarbaker is the more durable repair compared to the keyhole technique (Table 55.7).

Open Retromuscular Repair and Abdominal Wall Reconstruction

While technically challenging, the versatility of open retromuscular repair with sublay mesh placement offers numerous benefits. When attempted, the surgeon should first consider whether a retrorectus dissection alone will suffice. This technique involves dissection of the posterior rectus sheath from the rectus muscle to the semilunar line bilater-

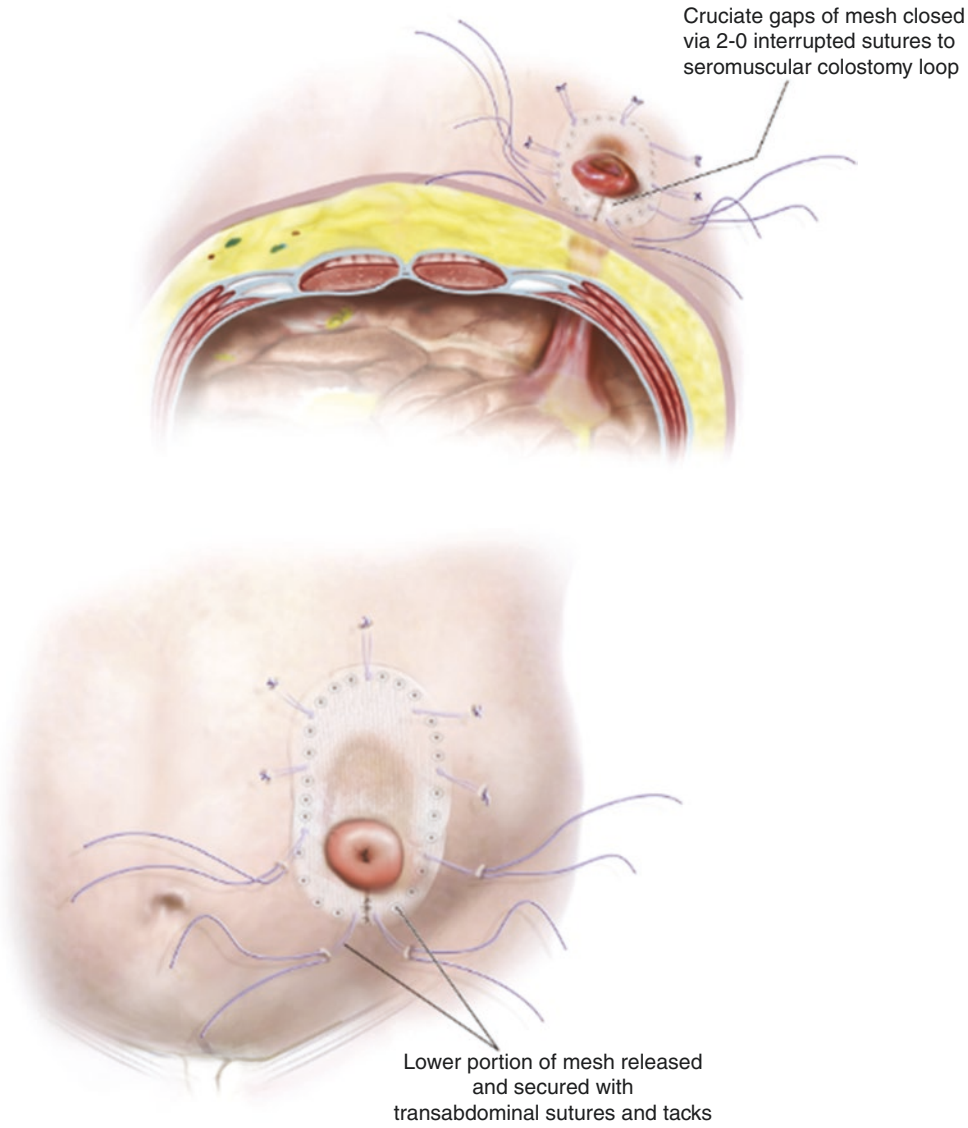

Fig. 55.1 Intraperitoneal mesh repair – keyhole (Reused with permission from Rosen [81]. Copyright © 2017 Elsevier)

ally. When possible, the stoma should be re-sited to the contralateral side before approximating the posterior rectus sheaths to isolate the viscera from the retrorectus pocket. Placement of mesh in the retrorectus position not only allows for prophylactic mesh reinforcement of the new stoma site, but mesh repair of the prior stoma site and reinforcement of the midline when necessary [27]. This technique is favorable when a concomitant midline defect is present or after several alternate methods have failed. It also allows for the usage of uncoated polypropylene, which is less expensive than its intraperitoneal barrier mesh alternatives. Early reports of retromuscular repair with polypropylene mesh have shown favorable results. The pooled analysis of 4 studies including 76 patients found an 8% recurrence rate with a mean follow-up of 24 months [56]. While they also report an overall infection rate of 4%, there were no mesh infections or reports of mesh excision (Table 55.8).

Often, a large parastomal defect or concomitant large midline defect makes re-approximation of the posterior rectus sheaths impossible after an isolated retrorectus dissection. Furthermore, with large lateral parastomal defects, a retrorectus dissection to the semilunar line will often not allow for sufficient mesh overlap to prevent a recurrence. It is in these cases where an abdominal wall reconstruction with a posterior component separation/transversus abdominis release (TAR) allows for several additional advantages. At the lateral extent of either retrorectus dissection, division of the transversus abdominis muscle just medial to the laterally perforating neurovascular bundles allows for extension of the retrorectus dissection to the lateral preperitoneal plane above the arcuate line. This preperitoneal plane can be matured bilaterally to the psoas muscles, cephalad to the central tendon of the diaphragm, and inferiorly to the space of Retzius. Liberation of the peritoneum from its surround-

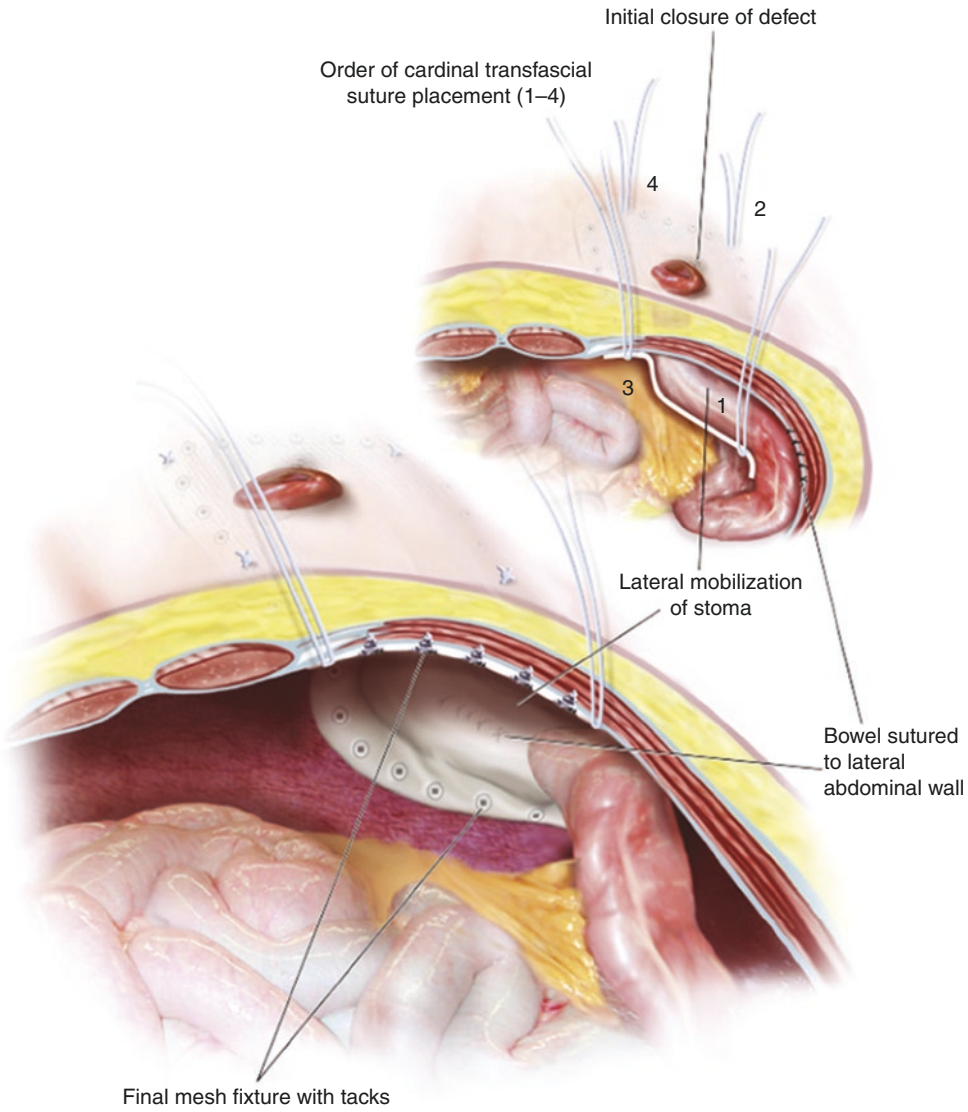

Fig. 55.2 Intraperitoneal mesh repair – Sugarbaker (Copyright © 2017 Elsevier)

Table 55.7 Laparoscopic intraperitoneal mesh parastomal hernia repair [58]

	n	Technique	F/U (month)	Recurrence
11 studies 2004–2012	231	Laparoscopic keyhole	Minimum 12 months	28%
9 studies 2005–2013	191	Laparoscopic Sugarbaker		10%

Table 55.8 Open retromuscular repairs

	n	Technique	F/U (month)	Recurrence
Early reports				
4 studies 2000–2010	76	Sublay PP	24	8%
Concomitant AWR				
Raigani	46	TAR/keyhole	13	11%
Beffa	46	Retrorectus ± TAR/keyhole	22	22%
Pauli	44	TAR/Sugarbaker	10	4.5%

ing attachments allows for a large visceral sac and even wider retromuscular pocket for prosthetic reinforcement with wide overlap in all directions. Again, a large mesh placement allows for reinforcement of the previous stoma site, midline, and stoma – which is typically brought through the mesh in a keyhole or cruciate orientation (Fig. 55.3).

Several cohorts exist of parastomal hernia repair with an abdominal wall reconstruction and keyhole/cruciate mesh reinforcement. Raigani et al. report our experience with 46 repairs using this technique, and we found a 46% surgical site infection rate but with only 1 re-operation for mesh erosion. At a mean follow-up of 13 months, five (11%) patients developed a recurrence, and three required repair. In a separate report of 46 retromuscular PSH repairs, Beffa et al. required the addition of a TAR in 2/3 of cases. Their overall surgical site infection rate was lower (17%) but increased dramatically (40%) when the stoma was re-sited. Their recurrence rate was 22% with a more meaningful follow-up

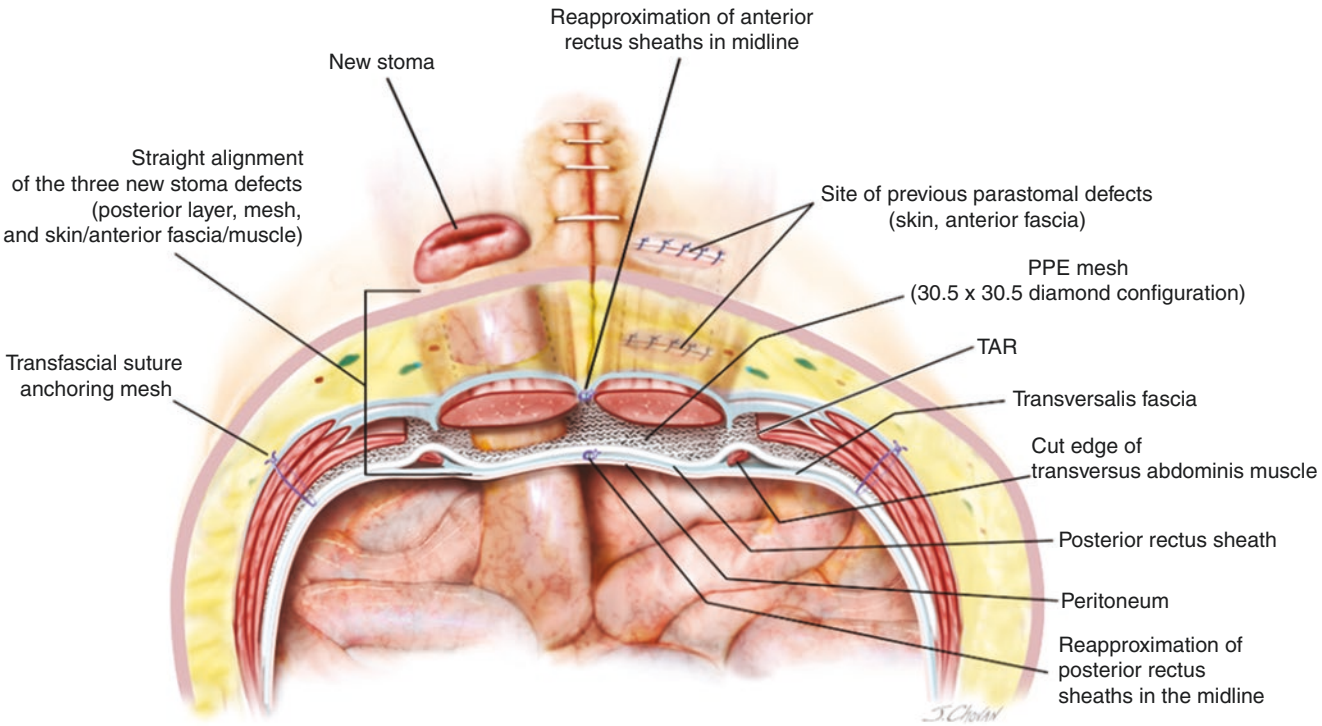

Fig. 55.3 Retromuscular mesh repair – keyhole (Copyright © 2017 Elsevier)

of 22 months [59]. Several descriptions of an adjunct to retromuscular keyhole mesh have also been described – both of which use a 28 mm EEA stapler to secure the retromuscular mesh to both the anterior and posterior rectus sheaths. The use of Stapled Transabdominal Ostomy Reinforcement with Retromuscular Mesh (STORRM) in 12 patients identified 2 (17%) recurrences with a mean follow-up of 13 months [60]. Likewise, a report of the Stapled Mesh stomA Reinforcement Technique (SMART) procedure identified four (18%) recurrences with a median follow-up of 21 months [61].

Recently, Pauli and colleagues reported their results of a novel technique for parastomal hernia repair at the 2018 International Hernia Congress with exciting early results. As was previously described, they utilized a bilateral transversus abdominis release and placement of a retromuscular mesh reinforcement. However, rather than bringing the stoma through a keyhole or cruciate defect in the mesh, it is draped over the mesh in the retromuscular space akin to a Sugarbaker repair (Fig. 55.4). Six surgeons reported their results of 44 patients with a mean follow-up of 10 months, and they currently have a 4.5% ($n = 2$) recurrence rate, with no reports of mesh erosion or stoma necrosis [62]. Our institution's experience with the technique was humbling, as early results demonstrated mesh erosion into the bowel in 3/38 (8%) patients [63]. We have since modified the technique to no longer fixate the mesh adjacent to the stoma and are currently enrolling patients in a randomized controlled trial of open retromuscular PSH repair with either keyhole/cruciate or Sugarbaker mesh reinforcement (NCT03972553).

Algorithm

Each of the abovementioned repairs has advantages and disadvantages and should be part of the armamentarium of the surgeon attempting to make PSH repair part of their routine practice. While there is certainly room for variability based on the surgeon's comfort level with each technique, we propose the following algorithm to utilize in surgical decision-making (Fig. 55.5).

Mesh Options

While a comprehensive discussion of mesh options is beyond the scope of this chapter, surgeons choosing from an ever-expanding menu of synthetic, biosynthetic, and biologic prosthetics should have a basic understanding of what evidence exists, particularly due to the cost implications. Despite the almost exclusive use of permanent synthetic mesh in the aforementioned studies with low rates of mesh-associated complications – findings supported by numerous randomized controlled trials of prophylactic mesh reinforcement of stomas – the use of synthetic mesh in contaminated

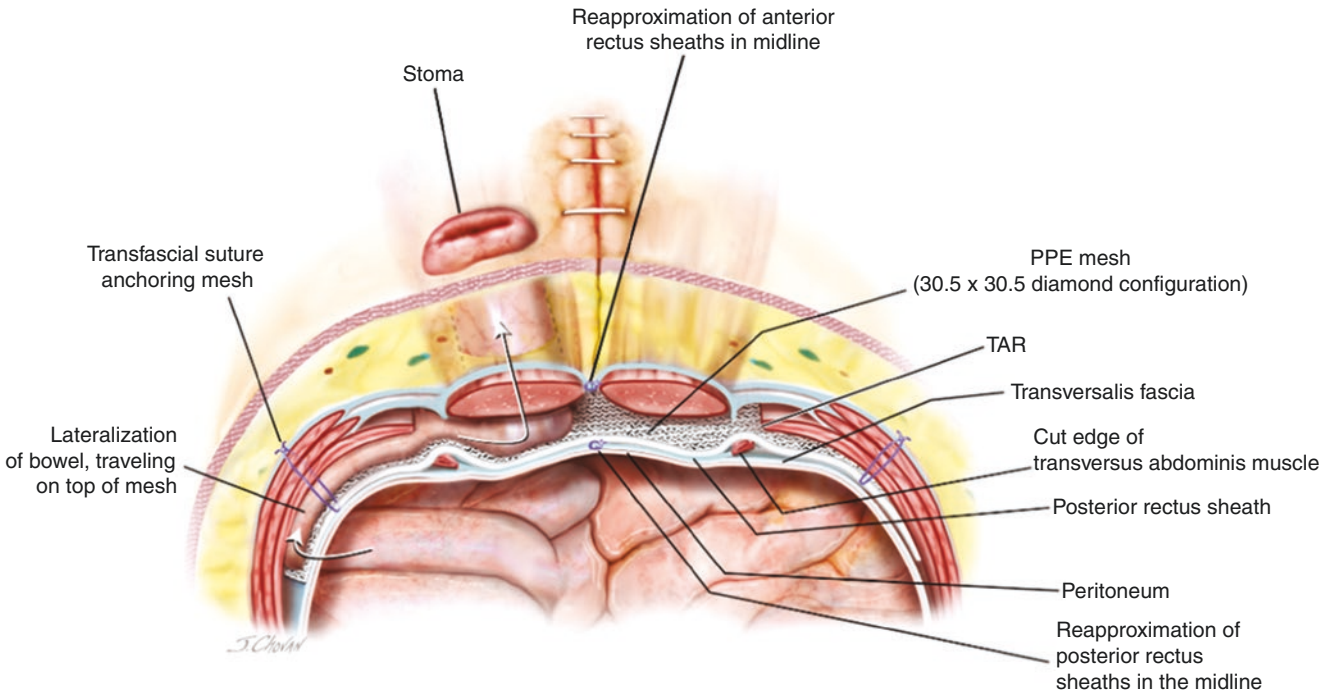

Fig. 55.4 Retromuscular mesh repair – Sugarbaker (Copyright © 2017 Elsevier)

fields remains a surgical faux pas, and use of non-synthetic alternatives remains commonplace [64–67]. Several factors have tempered the concern of using permanent mesh in these scenarios, and an understanding of these concepts can help to demystify why such an evolution in this thinking has occurred in the past 10 years. First, a contemporary understanding of favorable mesh characteristics has taught surgeons to avoid multifilament or barrier-coated meshes in contaminated settings, as animal studies have demonstrated that macroporous, monofilament, uncoated polypropylene is most resilient to a bacterial burden [68, 69]. This fact underscores the importance of minimizing contamination when using a barrier-coated mesh for intraperitoneal repairs and explains why uncoated polypropylene was the mesh of choice for prophylactic stoma reinforcement studies. Next, a better understanding of patient optimization techniques outlined earlier has narrowed the usage of synthetic mesh in contaminated fields to optimized patients in an elective setting (Centers for Disease Control and Prevention {CDC} wound classes II–III), as opposed to early reports of synthetic mesh in damage control laparotomies where staged mesh excision was essentially planned [70, 71]. Finally, popularization of retromuscular techniques including TAR has allowed for a large retromuscular pocket with well-vascularized tissue at each interface to accommodate the ideal polypropylene prosthetic without concern for interaction with the underlying viscera or exposure of the prosthetic to potential superficial wound morbidity [72]. So to summarize, usage of the right mesh, in the right myofasciocutaneous plane, and in the right patient, offers a much more thoughtful utilization of synthetic mesh in contaminated scenarios than what promulgated most of the negative conceptions among surgeons.

The largest series to date of synthetic mesh in contaminated fields was recently published by Warren et al. in 2020. They describe a complex group of 402 patients with a 30% active smoking history, moderate-sized defects (mean 9 cm), and significant levels of contamination (CDC II 53%, III 42%, IV 6%). With a median follow-up of 21 months, they were able to overcome a 14% surgical site infection rate with mesh excision in 2.4% of cases and recurrences in 10% [73]. Regarding biologic and biosynthetic alternatives, there actually only exist three prospective series in which any of these materials were studied and none had a control arm. The RICH study evaluated the effectiveness of porcine dermis collagen matrix in a very complex group of 80 patients with large hernias (mean width 16 cm) and a 9% rate of enterocutaneous fistula (ECF) takedown. While 19% of these patients had a bridged repair, they were able to overcome a 35% surgical site infection rate with no mesh excisions. At 2 years their recurrence rate was 28% [74]. The COBRA study evaluated the long-active resorbable mesh Bio-A (GORE®) in a group of patients with moderate-sized hernias (mean width 9 cm) but with high degrees of contamination (CDC II 23%, CDC III 77%). They overcame a surgical site infection rate of 18%, again with no

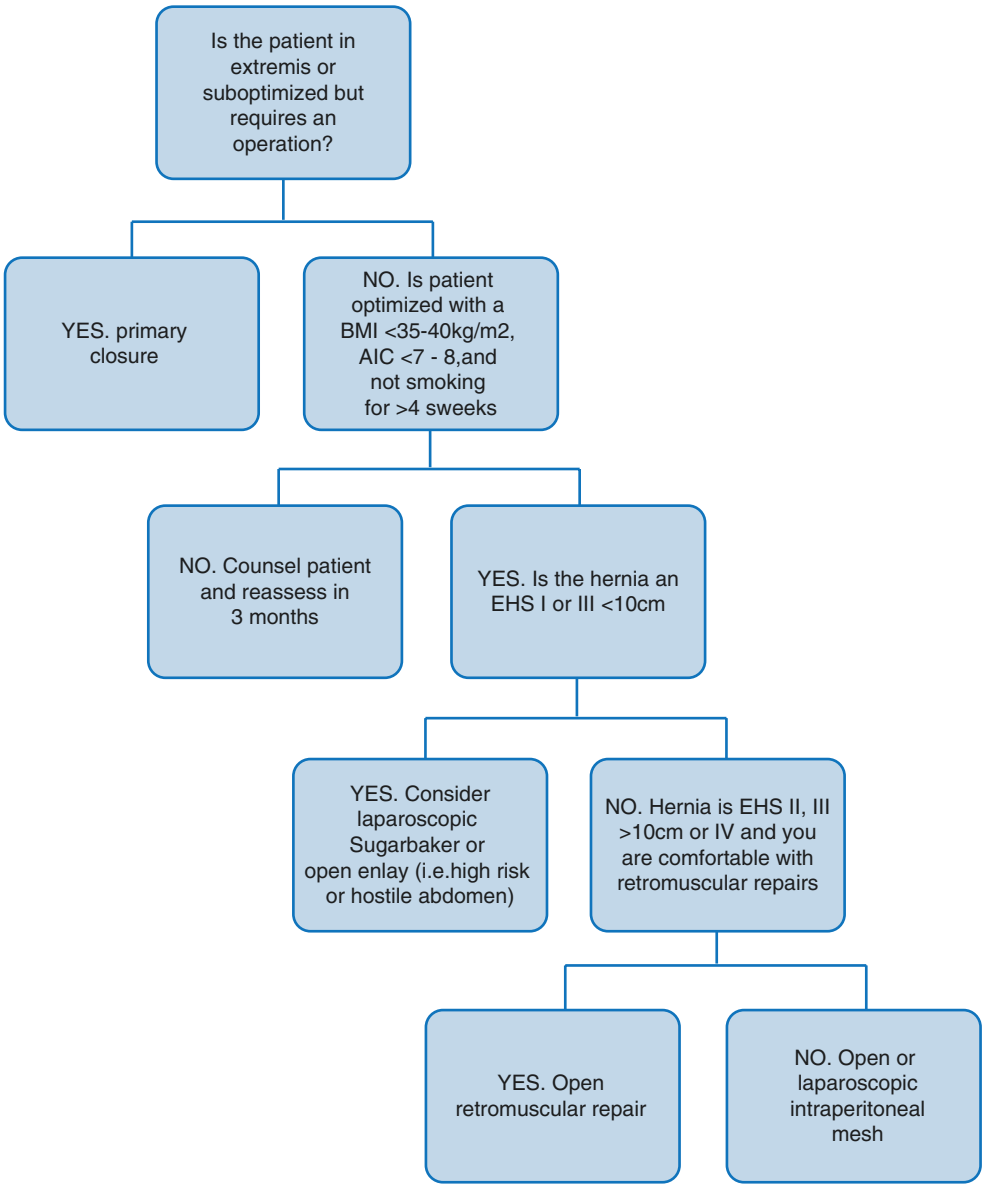

Fig. 55.5 Parastomal hernia surgical decision-making

mesh excisions, but ultimately had a recurrence rate of 17% at 2 years [75]. Finally, a study by Roth et al. evaluated poly-4-hydroxybutyrate mesh – another long-active resorbable mesh (Phasix – Bard) – in a relatively less complex cohort of comorbid patients with medium-sized defects in clean cases. They reported a 9% surgical site infection rate and no mesh excision, with a 9% recurrence rate at 18 months [76].

Taken together, the results summarized in Table 55.9 demonstrate that biologic and biosynthetic prosthetics appear to have rates of wound morbidity that correlate with long-term recurrence. That said, mesh excision is an exceedingly rare event for those patients. Alternatively, while synthetic mesh still allows for relatively acceptable wound morbidity and a seemingly durable repair with lower long-term recurrence, the tradeoff is a slightly higher risk of mesh excision.

Table 55.9 Significant mesh trials

	RICH study *N* = 80	COBRA study *N* = 104	Phasix study *N* = 121	Synthetic mesh Warren et al. *N* = 402
Patient complexity	BMI > 30–25% DM – 21% Smoking – 18% ECF – 9%	Mean BMI 28 DM – 18% Smoking – 19% ECF – 24%	Mean BMI 32 DM – 33% Smoking – 23% ECF – 0	Mean BMI 32 DM – 27% Smoking – 30% ECF – 0
Hernia size	Mean width – 16 cm Size – 236cm^2	Mean width – 9 cm Size – 137cm^2	Size – 115cm^2	Mean width – 9 cm
Contamination	CDC II – 49% CDC III – 49% CDC IV – 2%	CDC II – 23% CDC III – 77%	CDC I – 100%	CDC II – 53% CDC III – 42% CDC IV – 6%
Wound morbidity	SSI – 35% SSOPI – 6% Mesh excision – 0 ECF – 3%	SSI – 18% SSOPI – 3% Mesh excision – 0 ECF – 2%	SSI – 9% SSOPI – 6% Mesh excision – 0 ECF – 0	SSI – 14% SSOPI – 13% Mesh excision – 2.4% ECF – 0
Recurrence	2 year – 28% Non-bridge – 23%	2 year – 17% Midline – 14%	18 months – 9%	Median 21 montha – 10%

Conclusion

Parastomal hernia repair is a humbling endeavor with little evidence-based guidance. Surgeons should make every effort to optimize their patients preoperatively and familiarize themselves with the repair techniques that have a place in the operative armamentarium. While advanced abdominal wall reconstruction techniques utilizing a posterior component separation have promising results and are growing in popularity, open onlay, as well as both open and laparoscopic use of intraperitoneal mesh, also has very reasonable results and should not be dismissed.

References

1. Turnbull GB. Ostomy statistics: the $64,000 question. Ostomy Wound Manage. 2003;49(6):22–3.
2. Sylla P, Kaiser AM, Popowich D. The SAGES manual of colorectal surgery. 1 online resource.
3. Antoniou SA, et al. European Hernia Society guidelines on prevention and treatment of parastomal hernias. Hernia. 2018;22(1):183–98.
4. Goligher JC, Duthie HL, Nixon HH. Surgery of the anus, rectum, and colon. 4th ed. London: Bailli©·re Tindall; 1980. xii, 968 p.
5. Naverlo S, et al. Quality of life after end colostomy without mesh and with prophylactic synthetic mesh in sublay position: one-year results of the STOMAMESH trial. Int J Color Dis. 2019;34(9):1591–9.
6. Taneja C, et al. Risk and economic burden of peristomal skin complications following ostomy surgery. J Wound Ostomy Continence Nurs. 2019;46(2):143–9.
7. Tiernan J, et al. Use of a modified Delphi approach to develop research priorities for the association of coloproctology of Great Britain and Ireland. Color Dis. 2014;16(12):965–70.
8. Burt CG, et al. Developing a research agenda for the American Society of Colon and Rectal Surgeons: results of a delphi approach. Dis Colon Rectum. 2009;52(5):898–905.
9. Carne PW, Robertson GM, Frizelle FA. Parastomal hernia. Br J Surg. 2003;90(7):784–93.
10. Narang SK, et al. Parastomal hernia following cystectomy and ileal conduit urinary diversion: a systematic review. Hernia. 2017;21(2):163–75.
11. Hong SY, et al. Risk factors for parastomal hernia: based on radiological definition. J Korean Surg Soc. 2013;84(1):43–7.
12. Israelsson LA. Parastomal hernias. Surg Clin North Am. 2008;88(1):113–25. ix
13. Gurmu A, et al. The inter-observer reliability is very low at clinical examination of parastomal hernia. Int J Color Dis. 2011;26(1):89–95.
14. Arumugam PJ, et al. A prospective audit of stomas--analysis of risk factors and complications and their management. Color Dis. 2003;5(1):49–52.
15. De Raet J, et al. Waist circumference is an independent risk factor for the development of parastomal hernia after permanent colostomy. Dis Colon Rectum. 2008;51(12):1806–9.
16. Londono-Schimmer EE, Leong AP, Phillips RK. Life table analysis of stomal complications following colostomy. Dis Colon Rectum. 1994;37(9):916–20.
17. Sajid MS, et al. Parastomal hernia as a consequence of colorectal cancer resections can prophylactically be controlled by mesh insertion at the time of primary surgery: a literature based systematic review of published trials. Minerva Chir. 2012;67(4):289–96.
18. Tam KW, et al. Systematic review of the use of a mesh to prevent parastomal hernia. World J Surg. 2010;34(11):2723–9.
19. Ripoche J, et al. Parastomal hernia. A study of the French federation of ostomy patients. J Visc Surg. 2011;148(6):e435–41.
20. Cingi A, et al. Enterostomy site hernias: a clinical and computerized tomographic evaluation. Dis Colon Rectum. 2006;49(10):1559–63.
21. Janes A, Weisby L, Israelsson LA. Parastomal hernia: clinical and radiological definitions. Hernia. 2011;15(2):189–92.
22. MacKeigan JM, et al. Intestinal stomas: principles, techniques, and management. St. Louis: Quality Medical Publishing; 1993. xvi, 414 p.
23. Devlin HB, Elcoat C. Alimentary tract fistula: stomatherapy techniques of management. World J Surg. 1983;7(4):489–94.
24. Gavigan T, et al. Patients undergoing parastomal hernia repair using the Americas Hernia Society quality collaborative: a prospective cohort study. J Am Coll Surg. 2018;227(4):393–403 e1.
25. Shah NR, Craft RO, Harold KL. Parastomal hernia repair. Surg Clin North Am. 2013;93(5):1185–98.

26. Blackwell S, Pinkney T. Quality of life and parastomal hernia repair: the PROPHER study. Hernia. 2020;24:429.
27. Israelsson LA. Preventing and treating parastomal hernia. World J Surg. 2005;29(8):1086–9.
28. Cevese PG, et al. Peristomal hernia following end-colostomy: a conservative approach. Ital J Surg Sci. 1984;14(3):207–9.
29. Kaoutzanis C, et al. Risk factors for postoperative wound infections and prolonged hospitalization after ventral/incisional hernia repair. Hernia. 2015;19(1):113–23.
30. Desai KA, et al. The effect of BMI on outcomes following complex abdominal wall reconstructions. Ann Plast Surg. 2016;76(Suppl 4):S295–7.
31. Liang MK, et al. Ventral hernia management: expert consensus guided by systematic review. Ann Surg. 2017;265(1):80–9.
32. Tastaldi L, et al. The effect of increasing body mass index on wound complications in open ventral hernia repair with mesh. Am J Surg. 2019;218(3):560–6.
33. Rosen MJ, et al. A multidisciplinary approach to medical weight loss prior to complex abdominal wall reconstruction: is it feasible? J Gastrointest Surg. 2015;19(8):1399–406.
34. Sorensen LT. Wound healing and infection in surgery. The clinical impact of smoking and smoking cessation: a systematic review and meta-analysis. Arch Surg. 2012;147(4):373–83.
35. Finan KR, et al. Predictors of wound infection in ventral hernia repair. Am J Surg. 2005;190(5):676–81.
36. Dronge AS, et al. Long-term glycemic control and postoperative infectious complications. Arch Surg. 2006;141(4):375–80; discussion 380.
37. Thomsen T, Villebro N, Moller AM. Interventions for preoperative smoking cessation. Cochrane Database Syst Rev. 2014;3:CD002294.
38. Person B, et al. The impact of preoperative stoma site marking on the incidence of complications, quality of life, and patient's independence. Dis Colon Rectum. 2012;55(7):783–7.
39. Bass EM, et al. Does preoperative stoma marking and education by the enterostomal therapist affect outcome? Dis Colon Rectum. 1997;40(4):440–2.
40. Krpata DM, et al. Does preoperative bowel preparation reduce surgical site infections during elective ventral hernia repair? J Am Coll Surg. 2017;224(2):204–11.
41. Horgan K, Hughes LE. Para-ileostomy hernia: failure of a local repair technique. Br J Surg. 1986;73(6):439–40.
42. Rieger N, et al. Parastomal hernia repair. Color Dis. 2004;6(3):203–5.
43. Hansson BM, et al. Surgical techniques for parastomal hernia repair: a systematic review of the literature. Ann Surg. 2012;255(4):685–95.
44. Rubin MS, Schoetz DJ Jr, Matthews JB. Parastomal hernia. Is stoma relocation superior to fascial repair? Arch Surg. 1994;129(4):413–8; discussion 418–9
45. Kingsnorth AN, LeBlanc KA, Devlin HB. Management of abdominal hernias. 3rd ed. London: Arnold; 2003. 356 p
46. Allen-Mersh TG, Thomson JP. Surgical treatment of colostomy complications. Br J Surg. 1988;75(5):416–8.
47. Amin SN, et al. Lateral repair of parastomal hernia. Ann R Coll Surg Engl. 2001;83(3):206–8.
48. Haskins IN, et al. Onlay with adhesive use compared with sublay mesh placement in ventral hernia repair: was Chevrel right? An Americas hernia society quality collaborative analysis. J Am Coll Surg. 2017;224(5):962–70.
49. Hotouras A, et al. The persistent challenge of parastomal herniation: a review of the literature and future developments. Color Dis. 2013;15(5):e202–14.
50. Ho KM, Fawcett DP. Parastomal hernia repair using the lateral approach. BJU Int. 2004;94(4):598–602.
51. de Ruiter P, Bijnen AB. Ring-reinforced prosthesis for paracolostomy hernia. Dig Surg. 2005;22(3):152–6.
52. Steele SR, et al. Is parastomal hernia repair with polypropylene mesh safe? Am J Surg. 2003;185(5):436–40.
53. Warwick AM, et al. Onlay parastomal hernia repair with cross-linked porcine dermal collagen biologic mesh: long-term results. Hernia. 2016;20(2):321–5.
54. Sugarbaker PH. Peritoneal approach to prosthetic mesh repair of paraostomy hernias. Ann Surg. 1985;201(3):344–6.
55. Stelzner S, Hellmich G, Ludwig K. Repair of paracolostomy hernias with a prosthetic mesh in the intraperitoneal onlay position: modified Sugarbaker technique. Dis Colon Rectum. 2004;47(2):185–91.
56. Al Shakarchi J, Williams JG. Systematic review of open techniques for parastomal hernia repair. Tech Coloproctol. 2014;18(5):427–32.
57. Safadi B. Laparoscopic repair of parastomal hernias: early results. Surg Endosc. 2004;18(4):676–80.
58. DeAsis FJ, et al. Current state of laparoscopic parastomal hernia repair: a meta-analysis. World J Gastroenterol. 2015;21(28):8670–7.
59. Beffa LR, et al. Open retromuscular repair of parastomal hernias with synthetic mesh. Am Surg. 2017;83(8):906–10.
60. Majumder A, et al. Stapled transabdominal ostomy reinforcement with retromuscular mesh (STORRM): technical details and early outcomes of a novel approach for retromuscular repair of parastomal hernias. Am J Surg. 2018;215(1):82–7.
61. Williams NS, et al. A case-controlled pilot study assessing the safety and efficacy of the Stapled Mesh stomA Reinforcement Technique (SMART) in reducing the incidence of parastomal herniation. Hernia. 2015;19(6):949–54.
62. 2018 International hernia congress : March 12–15, 2018 Miami, FL. Hernia. 2018;22(Suppl 1):1–204.
63. Tastaldi L, et al. Single center experience with the modified retromuscular Sugarbaker technique for parastomal hernia repair. Hernia. 2017;21(6):941–9.
64. Petro CC, Rosen MJ. A current review of long-acting resorbable meshes in abdominal wall reconstruction. Plast Reconstr Surg. 2018;142(3 Suppl):84S–91S.
65. Chapman SJ, et al. Systematic review and meta-analysis of prophylactic mesh during primary stoma formation to prevent parastomal hernia. Dis Colon Rectum. 2017;60(1):107–15.
66. Cornille JB, et al. Prophylactic mesh use during primary stoma formation to prevent parastomal hernia. Ann R Coll Surg Engl. 2017;99(1):2–11.
67. Sahoo S, et al. Early wound morbidity after open ventral hernia repair with biosynthetic or polypropylene mesh. J Am Coll Surg. 2017;225(4):472–480 e1.
68. Blatnik JA, et al. In vivo analysis of the morphologic characteristics of synthetic mesh to resist MRSA adherence. J Gastrointest Surg. 2012;16(11):2139–44.
69. Diaz-Godoy A, et al. Searching for the best polypropylene mesh to be used in bowel contamination. Hernia. 2011;15(2):173–9.
70. Schmitt HJ Jr, Grinnan GL. Use of Marlex mesh in infected abdominal war wound. Am J Surg. 1967;113(6):825–8.
71. Stone HH, et al. Management of acute full-thickness losses of the abdominal wall. Ann Surg. 1981;193(5):612–8.
72. Novitsky YW, et al. Transversus abdominis muscle release: a novel approach to posterior component separation during complex abdominal wall reconstruction. Am J Surg. 2012;204(5):709–16.
73. Warren J, et al. Safety and efficacy of synthetic mesh for ventral hernia repair in a contaminated field. J Am Coll Surg. 2020;230:405.
74. Itani KM, et al. Prospective study of single-stage repair of contaminated hernias using a biologic porcine tissue matrix: the RICH Study. Surgery. 2012;152(3):498–505.
75. Rosen MJ, et al. Multicenter, prospective, longitudinal study of the recurrence, surgical site infection, and quality of life after contaminated ventral hernia repair using biosynthetic absorbable mesh: the COBRA study. Ann Surg. 2017;265(1):205–11.

76. Roth JS, et al. Prospective evaluation of poly-4-hydroxybutyrate mesh in CDC class I/high-risk ventral and incisional hernia repair: 18-month follow-up. Surg Endosc. 2018;32(4):1929–36.
77. Byers JM, Steinberg JB, Postier RG. Repair of parastomal hernias using polypropylene mesh. Arch Surg. 1992;127(10):1246–7.
78. Morris-Stiff G, Hughes LE. The continuing challenge of parastomal hernia: failure of a novel polypropylene mesh repair. Ann R Coll Surg Engl. 1998;80(3):184–7.
79. Hofstetter WL, et al. New technique for mesh repair of paracolostomy hernias. Dis Colon Rectum. 1998;41(8):1054–5.
80. van Sprundel TC, Gerritsen van der Hoop A. Modified technique for parastomal hernia repair in patients with intractable stoma-care problems. Color Dis. 2005;7(5):445–9.
81. Rosen M, editor. Atlas of abdominal wall reconstruction. Philadelphia: Elsevier; 2017.

Part V

Pelvic Floor Disorders

Functional Disorders After Colorectal Surgery/IBS

56

Hiroko Kunitake and Kyle Staller

Key Concepts

- Irritable bowel syndrome (IBS) is defined by the Rome IV criteria and divided into three subtypes (diarrhea-predominant (IBS-D); constipation-predominant (IBS-C); mixed bowel habits (IBS-M)) defined by stool form. The diagnosis is one of exclusion.
- Surgery for IBS is not indicated, but patients with IBS frequently have undergone one or more surgical procedures in an attempt to alleviate chronic pain.
- Treatment of IBS depends on the subtype.
- There are three subtypes of chronic anal pain defined by Rome IV criteria: levator ani syndrome, unspecified functional anorectal pain, and proctalgia fugax. These subtypes are distinguished by differences in the duration of pain and the presence or absence of anorectal tenderness.
- Coccygodynia is defined as pain or discomfort at or around the coccyx and may be related to trauma, but also an idiopathic variant exists.
- Pudendal neuralgia produces knifelike pain in the anus, vagina, or perineum. It is felt to be produced from pudendal nerve entrapment in Alcock's canal or in the infrapiriformis canal.

Definitions

Despite being one of the most commonly diagnosed digestive illnesses worldwide, irritable bowel syndrome (IBS) remains a diagnostic and therapeutic dilemma for many clinicians. The high prevalence estimates for IBS are based on formal criteria alone, but IBS is invoked commonly by many medical providers even when a patient does not meet simple, symptom-based criteria. Some of the confusion arises in the absence of reliable biomarkers for what is undoubtedly a heterogeneous disease process, encompassing many pathophysiologic mechanisms [1]. Therefore, we depend on symptom-based criteria which are useful but only modestly differentiates IBS from organic disease. [2] Further confusion arises with the continued updating of the symptom-based criteria as our understanding of the disease improves. The most recent iteration is the Rome IV criteria. IBS is currently defined as recurrent abdominal pain occurring at least weekly in the last 3 months associated with ≥2 of the following: (1) relationship to defecation, (2) change in frequency of stooling, and/or (3) change in stool form. These criteria must be fulfilled for the previous 3 months with onset at least 6 months prior (Fig. 56.1) [3]. Previous definitions have included abdominal pain or discomfort and *improvement* with defecation, but fundamentally IBS remains a disease of abdominal pain and altered bowel habits.

IBS subtypes (diarrhea-predominant (IBS-D); constipation-predominant (IBS-C); mixed bowel habits (IBS-M)) are defined by stool form (Fig. 56.2). More than 25% of bowel movements with loose stools (Bristol types 6 or 7) or hard, lumpy stools (Bristol types 1 and 2) define IBS-D and IBS-C, respectively, while >25% of bowel movements with both stool forms defines IBS-M [3] . Beyond mere classification purposes, the Bristol stool form is a useful surrogate for colonic transit time [4] that can help guide treatment selection to augment or slow down colonic motility.

Diagnosis and Clinical Workup

Even with the limitations of the symptom-based Rome criteria, a diagnosis of IBS is associated with a specificity and positive predictive value as high as 100% in the absence of red flag symptoms [5]. Nevertheless, many feel that the cur-

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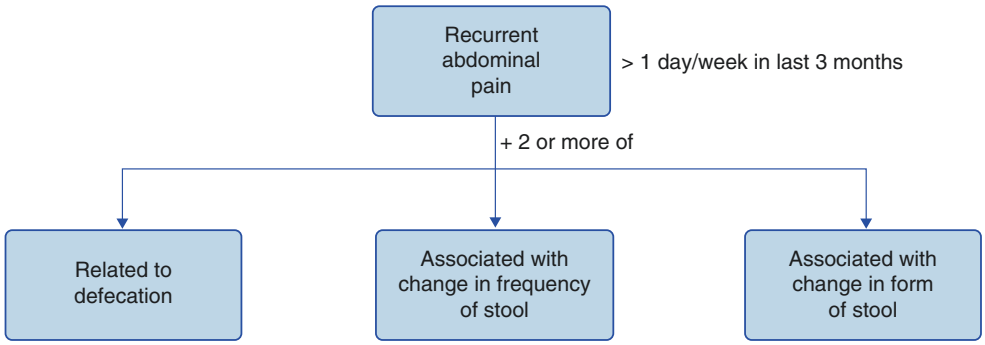
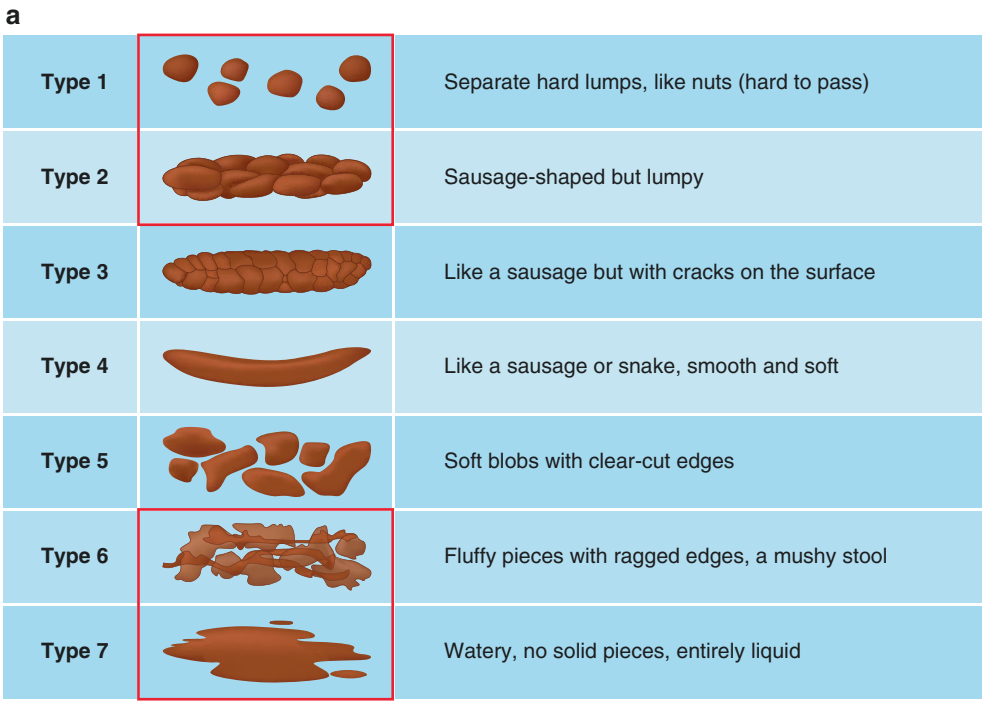


Fig. 56.1 The Rome IV criteria



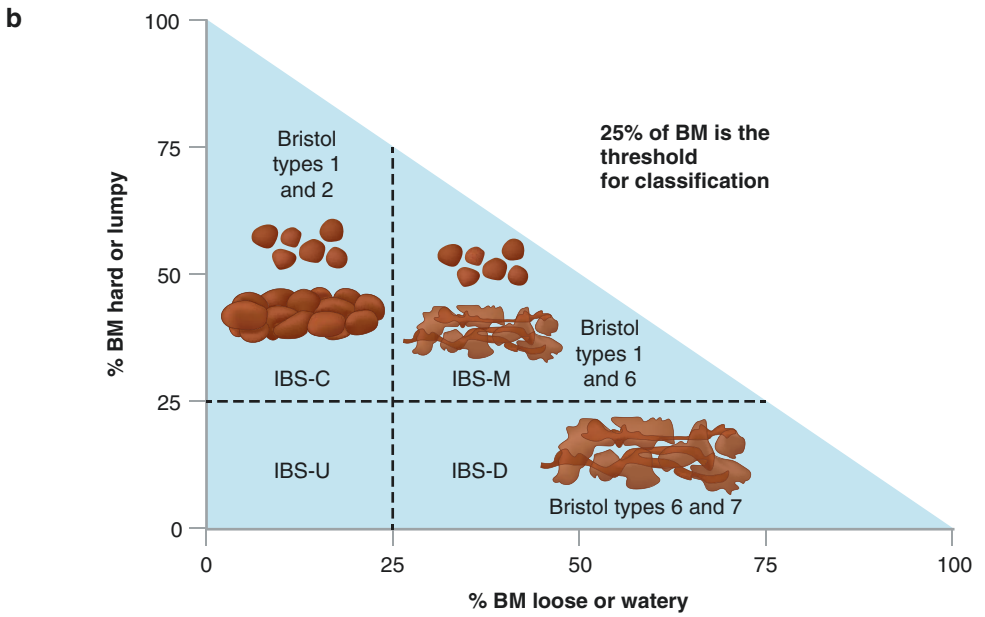


Fig. 56.2 (**a**, **b**) IBS subtype definitions according to stool consistency

rent symptom-based criteria continues to be inadequate for many patients, who ultimately get a positive diagnosis a mean of 6.6 years after the onset of symptoms [6]. Red flags either suggestive of another diagnosis or meriting further diagnostic workup include an abnormal exam, recent antibiotic use, documented weight loss, nocturnal symptoms, bloody stools, or family history of colon cancer. Most analysis suggest that patients with IBS are no more likely than controls to have organic GI disease on symptom criteria alone [7, 8]. All patients will nonetheless benefit from a limited workup guided by the results of a careful history and physical exam in order to avoid unnecessary diagnostic testing and its attendant risks [9].

The diagnostic workup is best understood by IBS subtypes (Fig. 56.3). The differential diagnosis for patients with IBS-D is the broadest, though historical pearls can be helpful. For most alternative diagnoses causing diarrhea, the likelihood of an entity other than IBS is low, with controversy as to whether these diseases have increased prevalence in the IBS population. The most widely accepted workup includes celiac serologies using a tissue transglutaminase (TTG) IgA with an IgA level, C-reactive protein (CRP), and ideally a fecal calprotectin level [10]. Testing for *Giardia* and bile acid diarrhea (where available) should be considered as well [11]. Patients with IBS-M generally undergo the same workup as those with IBS-D.

Two diagnostic entities that deserve special mention include bile acid diarrhea and microscopic colitis. Bile acid diarrhea either due to ileal resection or more commonly malabsorption in an anatomically normal small bowel is increasingly recognized as a cause of diarrhea in patients that would otherwise be labeled as IBS-D (up to 28.1%) [12]. Testing remains difficult with reliance on measurement of fasting serum C4, 48-hour stool collection, or the gold standard—the SeCHAT nuclear medicine test—limited to certain countries and academic centers currently [13]. Empiric use of bile acid sequestrant medications continues to be the most common diagnostic and therapeutic test used in everyday practice. However, tolerance of these drugs is poor due to palatability, and dose titration is often required to reach therapeutic levels [14].

Microscopic colitis is a frequent cause of diarrhea overlooked frequently by nongastroenterologists, presenting as watery diarrhea in older patients with a female predominance. As its name implies, the mucosa of the colon appears endoscopically normal, and biopsies are required for diagnosis [15]. The yield of colonoscopy for diagnosing microscopic colitis in patients with IBS is thought to be slightly higher than controls (2.3%) among patients ≥45 years old [16]. This suggests that diagnostic colonoscopy in the older IBS-D population, especially women, should be a consideration.

The approach to IBS-C is much more straightforward, in that the possible alternative diagnoses are limited. Therefore, testing may be used to better define the physiology of constipation.

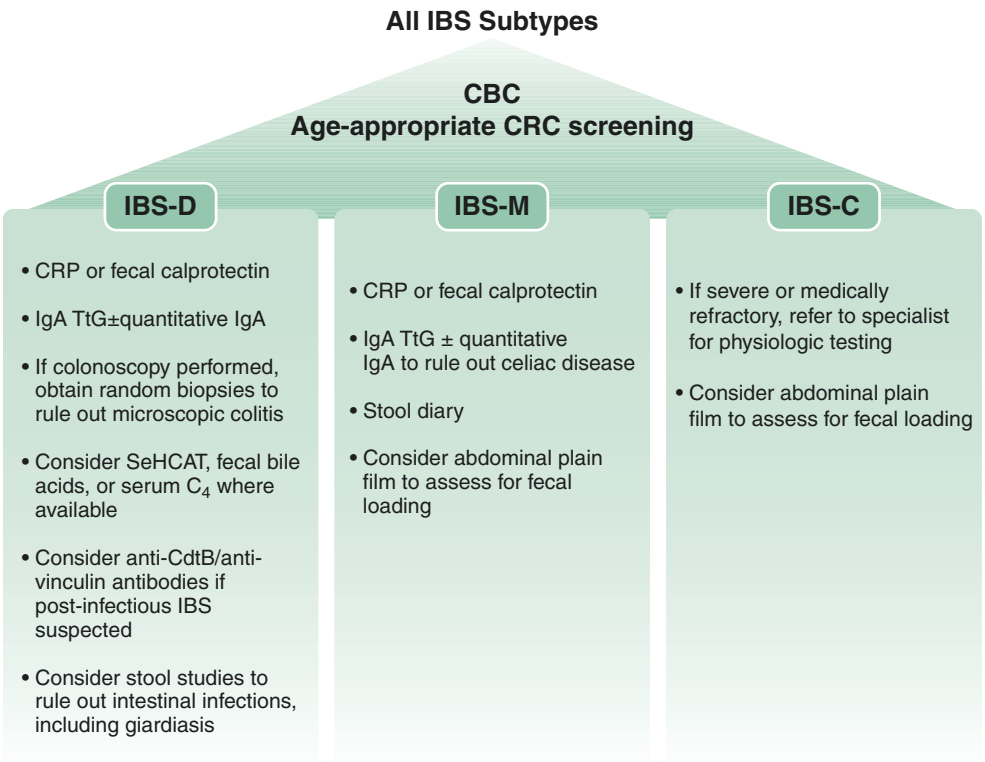


Fig. 56.3 Medical workup for IBS symptoms according to subtype: CRC colorectal cancer, CBC complete blood count, TTG tissue transglutaminase IgA antibody, SeHCAT 23-seleno-25-homotaurocholic acid, selenium homocholic acid taurine, or tauroselcholic acid, C4 serum 7α-hydroxy-4-cholesten-3--one

IBS and the Relationship to Surgery

Although surgery has no role in the treatment of IBS, patients with IBS are much more likely to undergo surgical procedures including cholecystectomy, [17–19] hysterectomy [17, 18], and appendectomy [17]. In many cases, these procedures represent preoperative misdiagnoses in an attempt to search for the etiology of chronic pain symptoms [20]. Extensive workups for an organic disease that an IBS diagnosis may mimic are essential. Because severe IBS can severely impact a patients' quality of life, they frequently call or are seen in their primary care doctor's office, go to the emergency room, or are referred to other specialty caregivers. Their ongoing complaints lead to further testing that can culminate in frequently unnecessary surgical procedures [20].

Colorectal surgical diagnosis is not immune to this phenomenon with diverticular disease, the prototypical example. Diverticulitis leads to acute abdominal pain with associated imaging findings. The associated inflammation can sensitize vulnerable visceral afferent nerves of the affected section of colon through damage followed by regrowth and altered function with resultant hypersensitivity to normal stimuli [21]. Low-grade inflammation can persist in many patients with diverticulosis [22] and is thought to be associated with symptomatic uncomplicated diverticular disease (SUDD). SUDD is a controversial entity that may not be entirely separate from IBS [23]. It is characterized by recurrent abdominal symptoms frequently associated with loose stools in the presence of localized diverticular disease [22, 24]. Like IBS, SUDD is associated with increased somatization [25]. Due to its association with diverticular disease, SUDD skews toward an older population [26].

Patients with functional complaints similar to IBS prior to an elective resection for diverticular disease are less likely to have satisfactory outcomes such as relief of abdominal pain or normalization of altered bowel habits [27]. Persistent symptoms after sigmoid resection for diverticulitis are present in up to 25% of patients, and these symptoms closely mirror those of IBS despite the presence of inflammation in resected specimens [28]. Alternatively, surgery may be a precipitating factor for IBS, with new IBS symptoms found to occur in a significant number of patients after abdominal surgeries [29–31]. A possible mechanism is surgical alteration of gastrointestinal function producing symptomatic IBS in susceptible individuals [18].

IBS Treatment Approach

Assigning a diagnosis of IBS can be unsatisfying for the patient and provider since the disease is mostly a diagnosis of exclusion without a lab or radiology test that is characteristic for this problem. Instead, patients should be reassured about the benign natural history of the disease, and focus should be directed toward symptom-directed treatments [3]. Taking the time to explain the rationale behind the treatment approach can pay long-lasting dividends with a therapeutic patient-provider relationship, an independent predictor of improvement in health status [32]. Many IBS patients come to clinical visits with preexisting negative experiences from previous providers and seek someone to listen, support, and provide hope in addition to comprehensive information about their disease and answers to their questions [33]. Education and reassurance provide the foundation for much of effective IBS treatment with pharmacotherapy, psychological treatments, and multidisciplinary care added in a graded approach for those with more moderate or severe symptoms (Fig. 56.4) [34].

Conservative measures benefit many patients with mild symptoms, and these interventions tend to be agnostic to

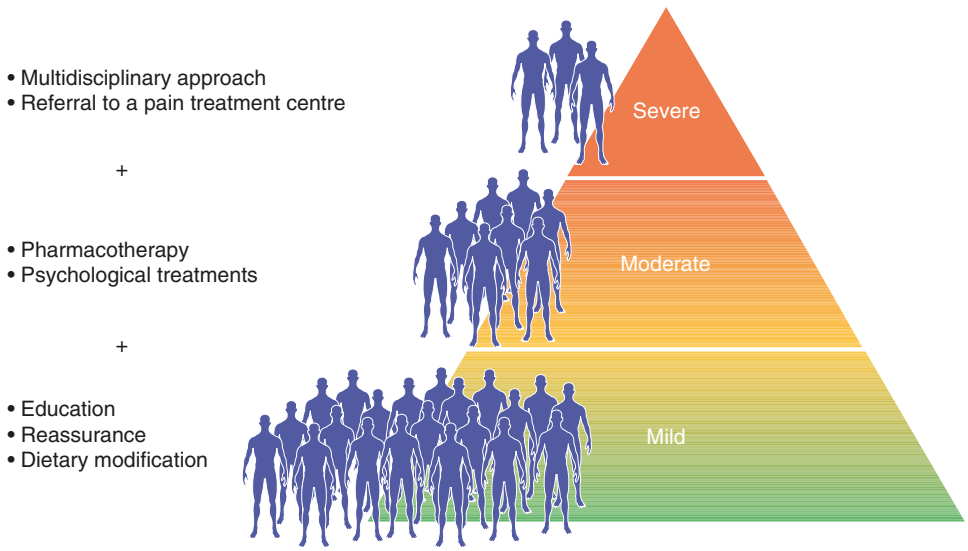


Fig. 56.4 Graduated treatment approach to IBS

IBS subtype, which is particularly useful among patients with mixed bowel habits (IBS-M). Exercise is associated with mild improvements in symptom severity and is associated with overall maintenance of physical and mental health [35]. Probiotics similarly provide a mild benefit for IBS symptoms, though the quality of supporting evidence is quite low. Individual probiotic preparations vary substantially in preparation, strain, and dose—making firm recommendations difficult. Moreover, the more rigorous studies have shown modest treatment effects, [36] with the highest-quality studies demonstrating benefit with *Bifidobacterium infantis* [10]. Peppermint oil also provides a modest benefit in IBS, [37] though a recent well-done randomized trial demonstrated no benefit to either small intestinal- or colonic-release peppermint oil formulations when subjected to rigorous European Medicines Agency (EMA) or US Food and Drug Administration IBS endpoints [38]. Peppermint oil likely acts as an antispasmodic, of which there are several pharmacologic varieties available with limited evidence suggesting a benefit compared to placebo in improving IBS symptoms [35]. The authors prefer to use antispasmodics as either on-demand or as prophylactic agents rather than as a regularly scheduled medication. Such dosing allows for patients to use these agents in response to abdominal pain or cramping or in anticipation of events where abdominal pain and/or cramping would be especially inconvenient (i.e., before meals at a restaurant, for car rides, while using public transportation).

Fiber

Fiber has been a mainstay recommendation for IBS treatment for years and is associated with global improvement in IBS symptoms [39]. Although the reasons for its benefits in IBS are poorly understood, fiber can serve as a bulking agent and a substrate for colonic fermentation and production of beneficial short-chain fatty acids that affect colonic motility and sensation [40]. Fiber should not be thought of as monolithic. Insoluble fibers are generally thought to increase stool bulk and water-holding capacity. Soluble fibers are generally associated with higher fermentability—serving to produce byproducts such as short-chain fatty acids and gas [41]. Soluble fiber (psyllium, ispaghula, calcium polycarbophil) has consistently shown greater benefit in IBS than insoluble fiber (corn, wheat, bran) [39, 41, 42]. Overall, psyllium is the most evidence-supported fiber supplement in IBS, providing both laxation effect and fermentation with some risk of increased gas/flatus [43]. However, patients with IBS-C who suffer from bloating primarily may not tolerate any gas formation and would be better served by insoluble, non-fermentable agents such as cellulose or methylcellulose. Thus, knowing the solubility and fermentability of various fiber supplements can allow personalization based on the predominant IBS symptoms.

Dietary Treatments

Dietary treatments for IBS have emerged as important tool in the arsenal of weapons against the symptoms of IBS. Their growing popularity can be explained by the following: (1) 60–70% of IBS patients' symptoms are worsened by meals, (2) more than 70% of IBS patients believe that food causes their symptoms, [40] and (3) up to 90% of IBS patients exclude or avoid certain foods to prevent or minimize GI symptoms [44]. True food allergies are not more prevalent in IBS patients compared to the overall population, but food intolerances are common and are unrelated to the IBS subtype [40].

Lactase deficiency occurs in approximately 30% of Caucasians and 70% of Asians and deserves special discussion. Most individuals worldwide will develop lactase non-persistence which is a decrease of intestinal lactase expression in the first two decades of life leading to lactose malabsorption and GI symptoms over time. The risk of symptoms in response to lactose ingestion in those with lactase deficiency is thought to be increased in IBS patients [45].

Our understanding of dietary treatment for IBS has evolved over time with earlier literature focusing on a population of patients developing worsening of IBS symptoms in response to ingestion of wheat in the absence of celiac disease or allergy. Among IBS patients without celiac disease, a double-blind, placebo-controlled dietary study demonstrated worsening of symptoms with blinded reintroduction of gluten to the diet [46]. The field has since shifted to embrace the use of a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs). These are carbohydrates that are poorly or partially absorbed in the small intestine resulting in an increased osmotic load (water is drawn into the intestinal lumen) and excess bacterial fermentation in the colon [47]—all leading to symptoms in IBS patients but not normal controls. Wheat is just one of the many FODMAPs, and the relationship between wheat ingestion and a low-FODMAP diet is well demonstrated by another dietary intervention trial from the same research group [48]. Patients with self-reported non-celiac wheat sensitivity and IBS were given a 2-week low-FODMAP diet with improvement in all GI symptoms before being randomly assigned a no-gluten, low-gluten, or high-gluten diet. In all cases, symptoms worsened in patients no longer on the low-FODMAP diet despite exclusion of gluten in some groups.

In principle the low-FODMAP diet has broad appeal, but execution and adherence is difficult. The initial phase of the diet requires elimination of many types of food followed by

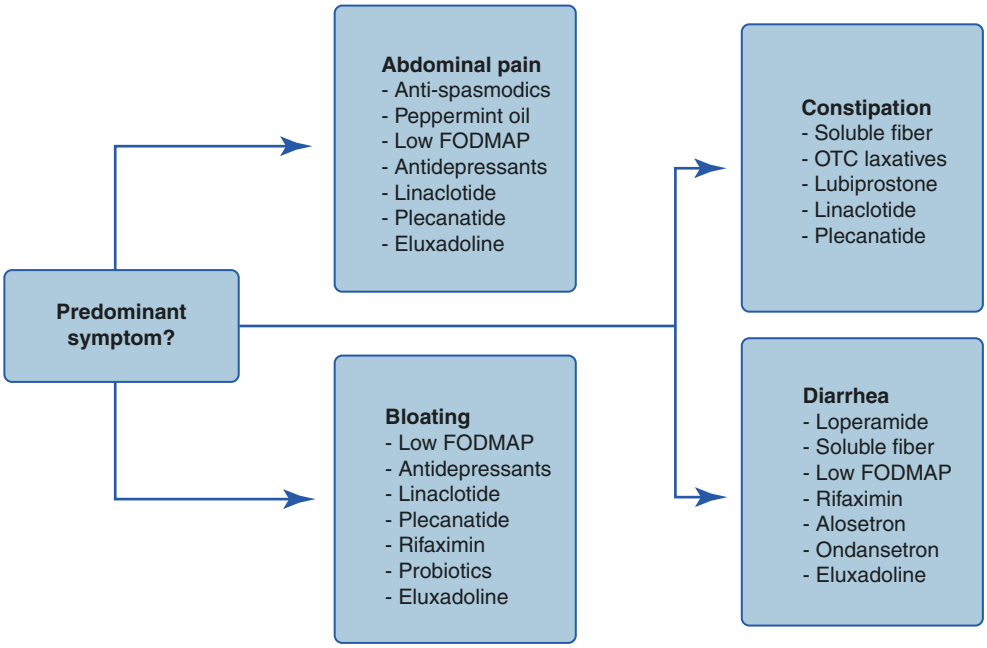


Fig. 56.5 Matching pharmacotherapy choice to predominant symptom complaint

systematic reintroduction of the eliminated foods to test which classes of foods cause symptoms. Because of its complexity, nutritional consultation and management is key but limited by availability of trained practitioners and payment issues. The "FODMAP-gentle" diet is an alternative bottom-up approach that limits the dietary restriction to some of the highest-yielding foods and may be more practical for many patients to follow [49].

Most FDA- or EMA-approved treatments for IBS target symptoms related to the predominant IBS subtype or symptom (Fig. 56.5). Several over-the-counter agents similarly have isolated use in IBS-D or IBS-C. Newer arrivals to the market have been subjected to clinical trials utilizing rigorous IBS-specific endpoints so that the quality of evidence is higher for these agents. Older agents are frequently used successfully but robust data is lacking. A strong placebo effect has been noted in trials examining functional GI disorders like IBS, with response to an active treatment over placebo often around 10%.

IBS-D Treatments

Loperamide is a synthetic mu-opioid receptor agonist with specificity for peripheral receptors to decrease colonic transit allowing increased water absorption in the colon. Many IBS-D patients will use over-the-counter loperamide prior to seeking care for their symptoms. While there it appears that loperamide can improve urgency and stool consistency, [3] its effect on global symptoms and pain is less well established [35]. The authors do find loperamide useful as an adjunctive agent in IBS-D, primarily given as prophylaxis for patients who know they will be in situations with limited bathroom access but rarely as monotherapy for those with consistent, bothersome symptoms.

Because of the increasing recognition of bile acid diarrhea as a driver of IBS-D symptoms, bile acid sequestrants can play an important role in the treatment of these patients when bile acid malabsorption is present. Cholestyramine is the usual first choice treatment given its presumed efficacy and ability to be easily titrated. Its use is heavily limited by poor palatability and GI side effects. More data is available in the form of small pilot studies for the newer agents colesevelam and colestipol, which are better tolerated but also more expensive [50]. In our practice, we often start with cholestyramine to demonstrate proof of principle with aggressive uptitration in dosing should a noticeable but inadequate effect be seen. Once the presence of bile acid diarrhea and response to treatment is established with cholestyramine, we often switch over to the newer agents for long-term treatment.

Rifaximin is a minimally absorbable, gut-specific antibiotic approved for treatment of IBS-D as a 14-day course. Initially, large trials demonstrated an approximate 10% improvement in adequate relief of global IBS symptoms over placebo with minimal adverse effects and no discernable increased risk of *Clostridium difficile* infection or emergence of bacterial resistance [10]. A more recent study evaluating multiple treatment courses of rifaximin demonstrated similar improvement rates over placebo that were sustained with retreatment after reemergence of symptoms. This has led rifaximin to currently be approved in the USA for up to three treatments [51].

Eluxadoline is a combined mu- and kappa-opioid agonist and delta-opioid antagonist approved in the USA for treat-

ment of IBS-D. In two large, phase 3 trials, eluxadoline conferred a clinical benefit over placebo using the FDA and EMA IBS endpoints [52]. Initial clinical experience demonstrated that the medication is overall well tolerated, but severe pancreatitis and Sphincter of Oddi dysfunction has occurred primarily in patients without a gallbladder. Alosetron is a 5-HT_3 antagonist approved in the USA for women with refractory IBS-D, demonstrated to reduce abdominal pain, discomfort, stool frequency, and urgency [10]. Like eluxadoline, its early use was concerning due to reports of severe constipation and ischemic colitis; however, these concerns have been mitigated with a lower initial starting dose and by limiting use to women with severe IBS-D with inadequate response to conventional therapy. Ondansetron and ramosetron are other 5-HT_3 antagonists with efficacy in IBS-D, though traditionally used off-label (ondansetron) or with limited geographic distribution (ramosetron) for this purpose. A recent meta-analysis found ramosetron and alosetron to be more effective than rifaximin and eluxadoline in patients with IBS-D and IBS-M [53].

IBS-C Treatments

IBS-C lies on a spectrum with functional constipation in that both entities are frequently associated with constipation symptoms: hard or lumpy stools, straining during defecation, a sense of incomplete evacuation, fewer than three bowel movements per week, a sense of anorectal blockage, and manual maneuvers to facilitate defecation [3]. For patients with mild to moderate symptoms, the distinction between functional constipation and IBS-C may be academic, as first-line therapy for both includes fiber (20–30 g/day) supplementation. Over-the-counter laxatives are frequently employed as well with polyethylene glycol (PEG), the most common choice. Constipation symptoms typically improve with fiber and/or PEG. However, IBS-C crucially requires abdominal pain in addition to bowel symptoms, and the importance of pain control is likely to be more important in patients with moderate to severe symptoms. In the limited literature for use of PEG in IBS-C, this agent was found to be more effective than placebo for constipation symptoms (i.e., bowel movement frequency, straining, and stool consistency), but there was no improvement in abdominal pain [54].

Since 2006, several new prescription laxative agents have been introduced onto the market with indications for both IBS-C and functional constipation. In most cases, these agents have been rigorously studied in placebo-controlled clinical trials using FDA- and EMA-mandated endpoints incorporating improvements in both stool consistency and abdominal pain. The three "secretagogues" vary in their exact mechanism of action but share an ability to drive net chloride secretion into the GI tract with water following. Lubiprostone dosed at 8 μg bid, linaclotide dosed at 290 μg daily, and plecanatide dosed at 3 mg daily all demonstrated improvement in global IBS symptoms and were all well tolerated. Diarrhea is the most commonly reported adverse event with all of these agents, [35] but lubiprostone is known to be associated with nausea as well [55]. None of these agents have been compared in a head-to-head fashion, and a recent meta-analysis suggests similar efficacy [56]. Our own experience is that there is individual patient variation as to which agent works best, but this does not occur with any discernible pattern. Thus, the decision on which agent to use is frequently dictated by payer coverage and regional availability.

Treating Abdominal Pain with Neuromodulation

IBS likely lies on a pathophysiologic spectrum with chronic abdominal pain, which is now most properly called centrally mediated abdominal pain syndrome (CAPS). CAPS is associated with frequent, almost continuous abdominal pain in the absence of changes in bowel habits—distinguishing this entity from IBS [57]. Chronic pain is a central feature of moderate to severe IBS, generally mediated by visceral hypersensitivity. With chronic stimulation, peripheral gut sensory nerves become increasingly sensitized to normal stimuli. Peripheral sensitization may progress to sensitization of central pathways, which is more common in the setting of comorbid emotional distress or a history of trauma. Thus, these patients are faced with an imbalance of amplified peripheral gut pain sensations and reduced central pain inhibitory mechanisms. Stress amplifies this maladaptive central pain response, a likely explanation for the frequent association between stress and IBS symptom exacerbations [58]. For IBS patients at the more severe end of the spectrum, central nervous system pain dysregulation likely plays a greater role in symptom generation—accompanied by shifting demographics and a greater degree of somatic symptoms (Table 56.1).

Neuromodulators are an underutilized tool in the treatment of IBS and have a well-developed rationale for their use: (1) downregulation of incoming visceral pain signals in the central nervous system, (2) reduction of maladaptive psychological processes (catastrophization, hypervigilance, anxiety), (3) treatment of comorbid psychiatric illness, (4) harnessing of ability to accelerate or slow GI transit, and (5) ability to treat frequent concomitant GI symptoms such as nausea and dyspepsia [60]. We frequently use these agents as monotherapy, in combination with peripheral motility agents (as outlined above for IBS-D and IBS-C) or in combination with behavioral therapies (Fig. 56.6).

Table 56.1 Spectrum of IBS disease severity and associations with predominant pathophysiology and patient characteristics

Clinical feature	Mild (40%)	Moderate (35%)	Severe (25%)
Physiological factors	Primarily bowel dysfunction	Bowel dysfunction and CNS pain dysregulation	Primarily CNS pain dysregulation
Psychosocial	None or mild psychosocial distress	Moderate psychosocial distress	Severe-high psychosocial distress, catastrophizing, abuse history
Sex	Men = women	Women > men	Women >>> men
Age	Older > younger	Older = younger	Younger > older
Abdominal pain	Mild/intermittent	Moderate, frequent	Severe/very frequent or constant
Number of other symptoms	Low (1–3)	Medium (4–6)	High (≥7)
Health-related quality of life	Good	Fair	Poor
Healthcare use	0–1/y	2–4/y	≥5/y
Activity restriction	Occasional (0–15 days)	More often (15–50 days)	Frequent/constant (>50 days)
Work disability	<5%	6%–10%	≥11%

Adapted from Drossman [59]

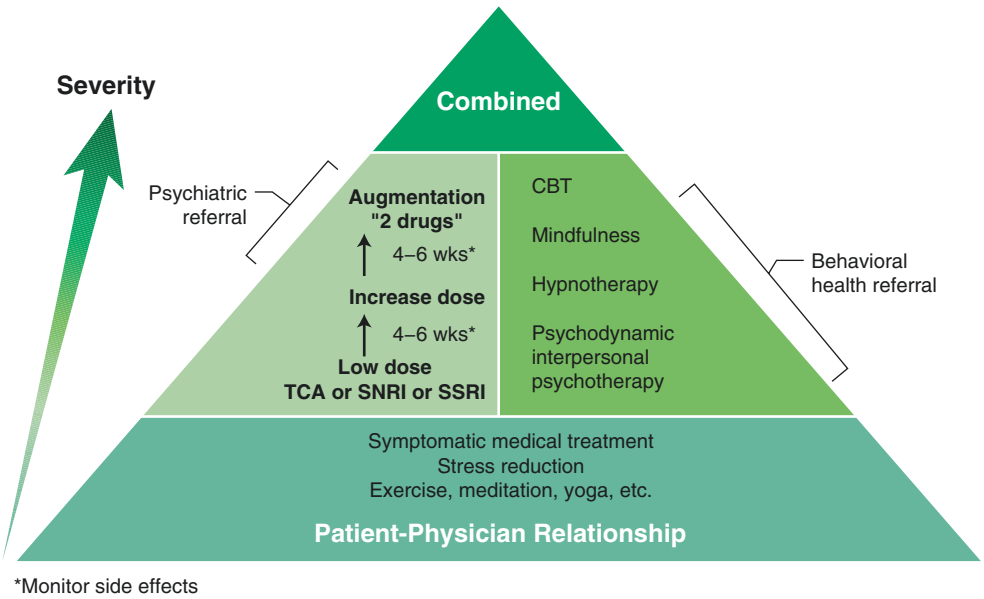


Fig. 56.6 Graduated treatment approach to addressing disordered brain-gut interaction in IBS

We approach neuromodulator agent selection based on the predominant IBS bowel habit (Table 56.2). For those with IBS-D, we favor tricyclic antidepressants (TCAs)—the most effective agents for the treatment of pain [57]. They are used at low doses well below the doses used for treatment of psychiatric disease and thus without the well-known side effects seen at those higher doses. Anticholinergic side effects are responsible for some of the benefit in patients with diarrhea, and we find significant improvements in patients' perception of urgency as well. The mantra of "start low and go slow" is key: using the lowest possible dose of the best tolerated agent. Although the tertiary amine amitriptyline (and to some extent imipramine) is the most well-known TCA for IBS, we prefer the secondary amines, nortriptyline and desipramine, which are much better tolerated with fewer anticholinergic side effects [60]. Patients are encouraged to take the TCAs for at least 2 weeks, as any anticholinergic side effects will wane over time.

Selective serotonin receptor inhibitors (SSRIs) are frequently used in IBS patients, though their ability to treat pain is diminished compared to TCAs [58]. We find these agents are more useful as an adjunct to the TCAs in patients with comorbid anxiety and depression than as a primary treatment agent for IBS. The selective serotonin and norepinephrine reuptake inhibitors (SNRIs), which we employ frequently for patients with IBS-C or IBS-M, are less likely to slow GI transit than the TCAs. Most of the evidence for their use is derived from other chronic pain conditions such as fibromyalgia. Duloxetine and milnacipran are favored over venlafaxine because the latter requires higher doses to achieve noradrenergic effects (useful for pain) and is more commonly associated with nausea and withdrawal side effects [60]. We also use the α2δ ligands gabapentin and pregabalin in both IBS-C and IBS-M, with the latter agent demonstrating some benefit in a recent small randomized, clinical trial [61].

Table 56.2 Neuromodulator/antidepressant treatment options in IBS and centrally mediated abdominal pain syndrome

	Tricyclic antidepressants	Selective serotonin reuptake inhibitors	Serotonin-norepinephrine reuptake inhibitors
Treatment targets	Pain, depression	Pain, depression, panic, anxiety, obsessive compulsive disorder	Pain, depression
Adverse events	Sedation, hypotension, constipation, dry mouth/eyes, arrhythmias, weight gain, sex dysfunction	Insomnia, agitation, diarrhea, night sweats, headache, weight loss, sex dysfunction	Nausea, agitation, dizziness, sleep disturbance, fatigue, liver dysfunction
Risk from overdose	Moderate	Low	Minimal
Dose adjustment	Yes	Not usual	Not usual

Adapted from Keefer et al. [57]

Psychological interventions have a clear role in the treatment of IBS symptoms either as monotherapy or in combination with neuromodulators. There is increasing evidence for cognitive behavioral therapy, relaxation therapy, hypnotherapy, and multicomponent psychological therapy in IBS, though connecting patients with these interventions is limited by the lack of psychological providers experienced in treating IBS and the time intensiveness of these modalities [35].

Chronic Pelvic Pain

Chronic pelvic pain is usually described as lower abdominal pain that has lasted ≥6 months and is unrelated to pregnancy. Chronic pelvic pain syndromes affect up to 11% of the population and are associated with a multitude of factors, both physiologic and psychological, which can make caring for these patients challenging [59]. This section will address the diagnosis, evaluation, and treatment of the following types of pelvic pain disorders: IBS-associated pelvic pain, functional anorectal pain, coccygodynia, and pudendal neuralgia.

IBS and Pelvic Pain

Although IBS is primarily associated with abdominal pain, there is also a strong association between IBS and chronic pelvic pain. IBS symptoms are reported by up to 40% of women with chronic pelvic pain and these two disease entities are similar in terms of symptoms, psychosocial factors, and healthcare utilization [62–64]. A study of 987 women attending a pelvic pain clinic investigated the overlap of IBS and chronic pelvic pain and found that muscular back pain, age > 40, depression, 6 to 8 pain sites, higher symptomatic distress scores (Symptom Checklist-90 Global Score), and a history of adult physical abuse were associated with an IBS diagnosis among chronic pelvic pain patients [63].

For IBS patients, chronic pelvic pain is treated with neuromodulators, similar to the aforementioned treatment of chronic abdominal pain. The selection of neuromodulators is based on minimizing their diarrhea or constipation symptoms. Tricyclic antidepressants are used in IBS-D, and selective serotonin reuptake inhibitors and norepinephrine reuptake inhibitors are favored in IBS-C or IBS-M.

Pelvic floor dyssynergia symptoms including strain and incomplete emptying are also prevalent in IBS patients and likely contribute to chronic pelvic pain. It should be noted, however, that these same symptoms can be seen among many patients with chronic constipation who do not have evidence of pelvic floor dysfunction. We perform anorectal manometry testing on any patient in whom pelvic floor dyssynergia is suspected. In a study of female non-IBS-D patients, over 50% experienced anal pain which was correlated with abnormal anorectal physiology including absent relaxation or paradoxical contraction on strain (91%), inadequate straining rectal pressure (53%), and prolonged balloon expulsion time (47%) [65]. Biofeedback therapy is a suggested treatment approach for these IBS patients with pelvic floor dyssynergia in addition to the use of neuromodulators.

Functional Anorectal Pain

The Rome IV criteria describes three subtypes of functional anorectal pain: (1) levator ani syndrome, (2) unspecified functional anorectal pain, and (3) proctalgia fugax. These three subtypes are primarily distinguished by differences in the duration of pain and the presence or absence of anorectal tenderness [66]. Levator ani syndrome is defined as chronic or recurrent rectal pain or aching lasting at least 30 minutes with tenderness on traction of the puborectalis muscle and the exclusion of other structural or systemic disease that can result in rectal pain. Unspecified functional anorectal pain is also defined as chronic or recurrent rectal pain or aching lasting at least 30 minutes but without tenderness to palpation of the puborectalis muscle. Proctalgia fugax is comprised of recurrent episodes of rectal pain unrelated to defecation which can last from seconds to up to 30 minutes in the absence of anorectal pain between episodes. Each set of criteria must be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Levator Ani Syndrome

Levator ani syndrome is hypothesized to result from spasm of the pelvic floor muscles and elevated anal resting pressures. It has also been attributed to inflammation of the arcus tendon of the levator ani muscle where the muscle inserts into the pubic ramus. The onset of levator ani syndrome may be associated with pelvic injury, childbirth, a history of pelvic and spinal surgery, psychological stress, anxiety, and depression [67]. Diagnosis is based on the Rome IV criteria which includes the clinical finding of tenderness to palpation of the puborectalis muscle on rectal examination, which is usually greater on the left side than the right side. Pain is typically worse when sitting compared to lying down or standing. Imaging or anorectal physiology studies add little to the diagnosis other than to rule out other causes of anorectal pain.

Treatment of levator ani syndrome aims to relax the pelvic floor muscles and includes digital massage of the levator muscles, biofeedback, electrogalvanic stimulation (EGS), and trigger point injections with botulinum toxin or steroids. Treatment with digital massage of the puborectalis sling is the oldest described treatment and in conjunction with hot sitz baths and oral diazepam was able to relieve symptoms in up to 68% of patients with this type of chronic anorectal pain [68]. Digital massage continues to be a staple in the treatment of levator ani syndrome and is usually undertaken prior to other more invasive therapies.

A prospective randomized trial of 157 patients allocated patients to one of the three common treatments for levator ani syndrome: biofeedback to teach relaxation of the pelvic floor muscles, EGS, and digital massage of the levator muscles [69]. Biofeedback was shown to be superior to EGS and digital massage for pain relief in addition to restoration of the appropriate anal canal relaxation with straining (94% successful) and ability to defecate a water-filled balloon (97% successful). The mechanism for improvement in rectal pain was thought to be related to improvement in the overall mechanics of defecation described above. Similarly, biofeedback demonstrated the greatest benefit in another retrospective cohort of patients with levator ani syndrome, outperforming tricyclic antidepressants, Botox injections, and sacral nerve stimulation. The response to biofeedback was greatest in patients reporting difficulty with defecation. In this group 65% described improvement in their pain compared to only 35% of those without defecatory difficulties [67].

A prospective study comparing local steroid injection with a mixture of triamcinolone and lidocaine into the maximal point of tenderness on the arcus tendon in the levator ani muscle versus EGS showed better short-term results in the local injection group than the EGS group. However, there was no difference between pain scores at 12 months [70]. Studies of Botox injection for levator ani syndrome have been less promising. Twelve patients with levator ani syndrome received anal intra-sphincteric injections of 100 units of botulinum toxin A and placebo at 90-day intervals using EMG guidance in a randomized, placebo-controlled, crossover study. The mean frequency, intensity, and duration of pain were unchanged after Botox injection compared with baseline [71]. Botox injection combined with biofeedback was slightly more successful in reducing levator ani pain [72].

Proctalgia Fugax

There are several proposed etiologies of proctalgia fugax, the most widespread is that it is due to abnormal smooth muscle contraction of the anal sphincter complex. It has been shown that proctalgia fugax is associated with a higher mean internal anal sphincter thickness and resting pressure than chronic proctalgia [67]. A familial form of proctalgia fugax has been described which is associated with hypertrophy of the internal anal sphincter and comorbid constipation. In these patients, internal anal sphincter strip myomectomy improves the constipation but is not as effective in resolving pain [73–75]. Pudendal nerve neuralgia is another reported cause of proctalgia fugax which is supported by a study of 68 patients with proctalgia fugax, where 55 had tenderness along the pudendal nerve. In this study, a nerve block relieved symptoms completely in 65 percent of patients and decreased symptoms in 25 percent of patients suggesting that the pathogenesis of proctalgia fugax may be neuralgia of the pudendal nerve [76].

Attacks of proctalgia fugax are often precipitated by stressful life events or anxiety. Changing a patient's position, reassurance, warm baths, sublingual nifedipine or topical nitroglycerin, passing flatus, or a bowel movement with the help of an enema often stops the episode [76]. In a randomized double-blind, placebo-controlled, crossover trial, inhalation of albuterol was reported to shorten the onset of pain relief from 14 minutes to 5 minutes [77]. However, the mechanism of benefit of albuterol is unclear as it has no significant effect on anal resting tone, sphincter relaxation, or rectal compliance when patients are asymptomatic.

In persistent cases, biofeedback therapy, local anesthetic blocks, or Botox injections can be considered. Botulinum toxin was used in a study of five patients versus controls with resolution of symptoms for up to 2 years with 25 units of Botox (and with a further 50 units in 1 patient with persistence of symptoms) [78]. These patients had an increased mean resting pressure on anal manometry compared to controls which returned to normal values after treatment. Internal anal sphincterotomy has also been described when more conservative measures are not successful [79].

Coccygodynia

Coccygodynia is defined as pain or discomfort at or around the coccyx including the sacrum, anorectum, and perineum which is usually aggravated by prolonged sitting on hard surfaces. When the pain lasts longer than 2 months, it is considered chronic. There are two principle subtypes: [1] coccygodynia related to trauma and [2] idiopathic which is commonly attributed to pelvic floor spasm, inflammation of the coccygeal bursa, degenerative joint disease, and hypermobility or hypomobility of the sacrococcygeal joint. Obesity and female gender are considered predisposing factors due to the resulting pelvic rotation and a more posterior location of the coccyx which makes it more vulnerable to injury.

Reproduction of the pain by pressure or manipulation of the coccyx externally or during digital transrectal palpation is key to the diagnosis. Pain is usually worse when leaning back while sitting and may be triggered by moving from sitting to standing. Symptoms improve with relief of pressure when standing or walking. Spasm or tenderness of the pelvic floor muscles may also be seen. Most patients do not require imaging studies. However radiological evaluation using lateral sacral radiographs and dynamic X-rays comparing sitting and standing allows classification of the shape of the coccyx according to its inclination and evaluation of bony pathology. MRI is useful to exclude degenerative spine disease, tumors, or metastatic bone disease as the source of pain [80].

The vast majority of patients (90%) improve with nonoperative treatment including rest, protection of the area with a donut or wedge cushions, nonsteroidal anti-inflammatory drugs, and heat or ice [81]. Coccyx manipulation, ganglion impar blockade, and biofeedback therapy have also been successful in treating coccygodynia.

Coccyx manipulation via the rectum relaxes the muscles attached to the coccyx. Since these muscles may be in spasm, this treatment may make a stiff coccyx more mobile. In a randomized trial of 102 patients with chronic coccygodynia comparing coccygeal manipulation (three 5-minute sessions of intrarectal manipulation over a period of 10 days) and external magnetic field physiotherapy, the group that received coccygeal manipulation was more likely to have decreased pain compared with the placebo group (36% versus 20% at 1 month), but neither group had a large improvement [82].

Ganglion impar blockade using fluoroscopy or CT guidance is another treatment option for coccygodynia. The addition of corticosteroids further enhances the efficacy of the nerve block. In a prospective, randomized, double-blind study of chronic coccygodynia involving over 70 patients, ganglion impar block with local anesthetic plus corticosteroid decreased pain and also depression at 1 and 3 months compared with local anesthetic alone [83].

For those patients who fail nonoperative treatment, surgery may be considered. Coccygectomy has been found to provide good or excellent pain relief in up to 85% of cases [80]. A retrospective cohort study comparing coccygectomy and nonsurgical care in 109 patients with an average 4 year follow-up showed that surgically treated patients had significantly less pain and better health status than nonsurgical patients [84]. The most common reported complication of coccygectomy is wound infection, which can be seen in up to a quarter of patients.

Pudendal Neuralgia

The pudendal nerve derives from sacral roots S2, S3, and S4 and is composed of both motor and sensory fibers which innervate the anogenital area and pelvic muscles. The pudendal nerve passes between the sacrospinous ligament and sacrotuberous ligament close to the ischial spine before entering Alcock's canal. The most common etiology of pudendal neuralgia, also called Alcock's canal syndrome, is pudendal nerve entrapment between the sacrospinous ligament and sacrotuberous ligament, in Alcock's canal or in the infrapiriformis canal (Fig. 56.7).

Pudendal neuralgia may be described as a knifelike pain or a foreign-body sensation in the rectum, vagina, or perineum. The pain usually worsens during the day and may be unilateral. The ischial spine may be tender to palpation, and defecation can trigger pain, generally several minutes to an hour later. Making the diagnosis of pudendal neuralgia is difficult, and patients may suffer for many years before the diagnosis is reached.

In 2006, a multidisciplinary working group in Nantes, France, defined five required criteria for the diagnosis of pudendal neuralgia by pudendal nerve entrapment [85].

1. Pain is in the anatomical territory of the pudendal nerve which extends from the anus to the clitoris or penis.
2. Pain is worsened by sitting due to excessive pressure on the nerve.
3. The patient is not woken at night by the pain.
4. There is no objective sensory loss on clinical examination. A superficial perineal sensory deficit is more suggestive of a sacral nerve root lesion.
5. Pain is relieved by an anesthetic pudendal nerve block. This criterion is not specific as it indicates that the pain is situated in the territory of the pudendal nerve.

The exclusion criteria were purely coccygeal, gluteal, or hypogastric pain which does not correspond to the territory of the pudendal nerve: exclusively paroxysmal pain, exclusively pruritus, and presence of imaging abnormalities able to explain the symptoms.

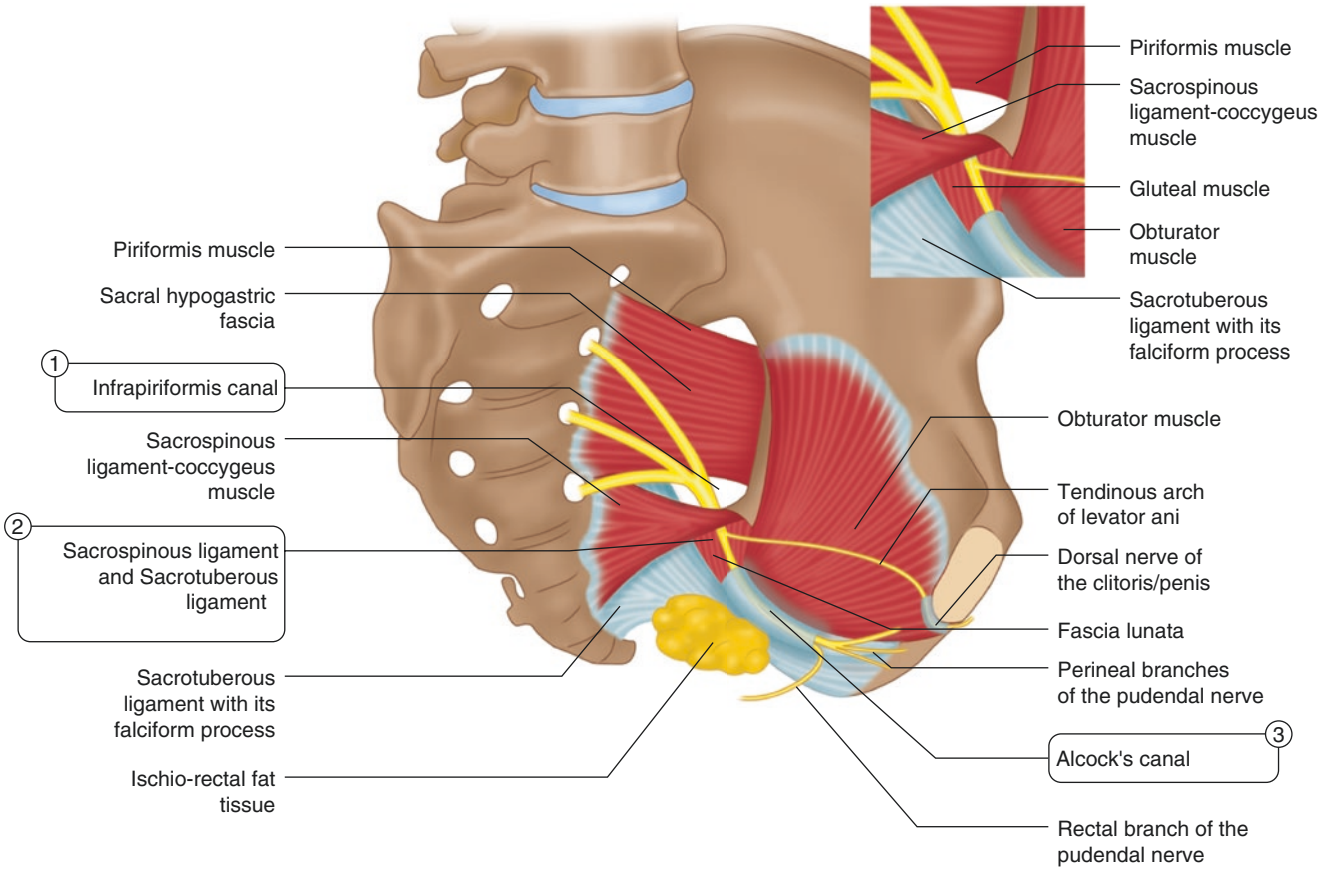


Fig. 56.7 Demonstration of the anatomical course of the pudendal nerve showing different levels of possible pudendal nerve entrapment: (1) in the infrapiriformis canal; (2) between the sacrospinous ligament and sacrotuberous ligament; (3) in Alcock's canal

Only the operative finding of nerve entrapment and postoperative pain relief can formally confirm the diagnosis of pudendal neuralgia due to nerve entrapment. However magnetic resonance neurography is now gaining an increasing role in the diagnosis and management of pudendal neuralgia [86].

Pudendal neuralgia can be treated medically with rehabilitation, psychobehavioral approaches, nerve injection, nerve ablation, or neuromodulation. Patients may undergo multiple treatments, yet achieving sustained improvement is challenging. Surgical decompression of the pudendal nerve may be recommended for patients who fail nonsurgical treatments.

Pudendal Nerve Block

Pudendal nerve block can be performed in the operating room using landmarks to palpate the course of the pudendal nerve either transvaginally or transanally. However, we prefer CT-guided pudendal nerve blocks with injection into the sacrospinous ligament and Alcock's canal. A retrospective review of 95 patients who underwent CT-guided injection of both locations using a combination of lidocaine hydrochloride, ropivacaine chlorhydrate, and cortivazol demonstrated clinical success as defined by at least a 50% reduction in baseline pain scores in 63% of patients at 1-month postprocedure, 50% of patients at 3 months, and 25% of patients at 6 months with no major complications [87]. The efficacy of using steroids in nerve injection was investigated in a randomized, double-blind, controlled study comparing CT-guided pudendal nerve blocks with a local anesthetic versus local anesthetic and corticosteroid. Corticosteroids provided no statistically significant improvement in pain, functional criteria, or quality of life compared with local anesthetic alone [88].

Neuromodulation

In addition to sacral neuromodulation, which has some reported success, pudendal neuromodulation and conus medullaris stimulation have also been used [89–91]. A retrospective review included 19 patients who underwent pudendal neuromodulation with a quadripolar lead (InterStim, Medtronic, Minneapolis, MN, USA) placed at the pudendal

nerve. At the end of a 2-week test period, just prior to implanted pulse generator placement, pain relief was complete in three patients, almost complete in three, significant/remarkably improved in ten patients, and three reported a small/slight amount of relief. Pudendal neuromodulation was felt to be more effective than nerve block. Of the four patients who had previously experienced sacral neuromodulation, three rated pudendal neuromodulation as more effective [90].

Another study included 27 consecutive patients who underwent conus medullaris stimulation for refractory pudendal neuralgia following pudendal nerve decompression surgery. The electrode (Lamitrode TM S8 or TM 44C electrode, St. Jude Medical, Inc., or three column electrode, Medtronic, Inc.) was initially tested for an average of 13 days. Twenty patients had positive tests. The zone of paresthesia was confined to the perineal zone in one quarter of patients, while the other patients also reported paresthesia in the lower limbs (essentially affecting the L4, L5, and S1 dermatomes). One hundred percent of implanted patients remained long-term responders. Mean sitting time tripled and mean estimated percent improvement was 55.5%. Additionally, the effect of conus medullaris stimulation appeared to remain stable over time, as no reduction of the analgesic effect experienced by the patients was observed after a mean follow-up of 15 months after implantation [91].

Nerve Ablation

Nerve ablation can also be used to relieve pudendal neuralgia pain. CT-guided cryoablation was reported to be effective in durably reducing pelvic pain in 9 of the 11 patients (82%) included in a study over a 6-month follow-up period with no procedure-related complications [92]. In a case report, transgluteal pulsed radiofrequency ablation was reported to be successful for at least 6 weeks in a 51-year-old woman who had only transient relief with prior nerve injection [93].

Fat grafting has been considered to alleviate neuropathic pain. The precise mechanism is not clear, but there may be some anti-inflammatory effects of adipose-derived stem cells and mechanical cushioning by fat. In a study of 15 women who underwent pudendal nerve lipofilling with adipose tissue into Alcock's canal, 10 were pain-free at 12 months [94].

Operative Approaches

Pudendal nerve decompression surgery is recommended after failure of medical treatment and ideally should treat all possible entrapment levels including (1) the space between the piriformis muscle and the sacral hypogastric fascia, (2) the interligamentary space, (3) Alcock's canal, and (4) the subpubic dorsal nerve canal [95]. The success of surgery is predicted by a positive response to nerve infiltration. Therefore, surgery is not recommended for patient with a negative response to nerve infiltration. Pudendal nerve decompression and transposition was shown to be superior to nonsurgical treatment at 3 months and 6 months in a randomized controlled trial of 32 patients [96]. The majority of patients (8/10) who had successful surgical decompression at 1 year remained so at 4 years, demonstrating the possibility of a long-term successful outcome with surgical decompression.

Multiple surgical approaches for surgical nerve decompression have been recognized; transgluteal, transperineal, transischiorectal fossa, and laparoscopic. New hybrid techniques including endoscopic assistance are now being investigated to improve visualization and surgical safety.

Laparoscopic pudendal nerve decompression and transposition with omental flap protection of the nerve (Istanbul technique) was performed in 27 patients by Erdogru et al. [97] This technique involved complete division of the sacrospinous ligament and splitting of the inner side of the levator ani muscles to reach the fatty tissue in front of the canal entrance. The aponeurosis of the internal obturator was opened, and an omental flap was used to wrap the decompressed nerve. At 6 months 80% of patients reported a > 80% reduction in pain scores. Quality-of-life scores also improved and were sustained up to 12 months.

A new technique adding an endoscope to a transperineal approach ("operative pudendoscopy") aimed to improve visualization in what was otherwise historically a blind transperineal procedure. With the patient in lithotomy position, a skin incision was made between the ischial tuberosity and the anal margin. Using the endoscope, the surgeon was able to visualize each decompression step, the different levels of entrapment and cut the sacrospinous ligament under visual control. This technique was used in 113 patients with improvement in pain in 73% of patients and a 50% reduction in pain in 42% [95]. A learning curve of 60 interventions was noted and a larger decrease in pain was seen for patients treated by the more experienced surgeon.

In patients who experience failure of surgery, repeat surgery, though technically challenging, can be offered with improvement of symptoms in the majority of patients and minimal postoperative complications as described by Hibner et al. [98]. Using a transgluteal incision, a nerve monitoring system was used to aid in identifying the pudendal nerve. Adhesiolysis was performed from the piriformis muscle to the distal aspect of Alcock's canal with the aid of a surgical microscope. The nerve was enclosed in NeuraWrap Nerve Protector (Integra, Plainsboro, NJ, USA) and coated with active platelet-rich plasma. An On-Q PainBuster (Halyard Health, Alpharetta, GA, USA) catheter was placed along the nerve in Alcock's canal, and the sacrotuberous ligament was

repaired using an Achilles or gracilis cadaver ligament. Mean follow-up was 23 months. Eight of nine patients reported global improvement with two patients reporting complete resolution of symptoms. No patient experienced worsening of symptoms.

Conclusion

Irritable bowel syndrome, chronic abdominal pain and chronic pelvic pain have complex physiologic and psychosocial roots. Patients often experience a delay in diagnosis and may undergo multiple attempts at treatment before achieving resolution of their symptoms. Colorectal surgeons should be well versed in the management of these typically nonoperative chronic conditions, and realistic expectations should be set regarding their management and expected outcomes.

References

1. Barbara G, Stanghellini V. Biomarkers in IBS: when will they replace symptoms for diagnosis and management? Gut. 2009;58(12):1571–5.
2. Sood R, Camilleri M, Gracie DJ, et al. Enhancing diagnostic performance of symptom-based criteria for irritable bowel syndrome by additional history and limited diagnostic evaluation. Am J Gastroenterol. 2016;111(10):1446–54.
3. Mearin F, Lacy BE, Chang L, et al. Bowel disorders. Gastroenterology. 2016;150, 1393
4. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32(9):920–4.
5. Vanner SJ, Depew WT, Paterson WG, et al. Predictive value of the Rome criteria for diagnosing the irritable bowel syndrome. Am J Gastroenterol. 1999;94(10):2912–7.
6. Drossman DA, Morris CB, Schneck S, et al. International survey of patients with IBS: symptom features and their severity, health status, treatments, and risk taking to achieve clinical benefit. J Clin Gastroenterol. 2009;43(6):541–50.
7. Brandt LJ, Bjorkman D, Fennerty MB, et al. Systematic review on the management of irritable bowel syndrome in North America. Am J Gastroenterol. 2002;97(11 Suppl):S7–26.
8. Cash BD, Schoenfeld P, Chey WD. The utility of diagnostic tests in irritable bowel syndrome patients: a systematic review. Am J Gastroenterol. 2002;97(11):2812–9.
9. Lacy BE, Weiser K, Noddin L, et al. Irritable bowel syndrome: patients' attitudes, concerns and level of knowledge. Aliment Pharmacol Ther. 2007;25(11):1329–41.
10. Lacy BE, Chey WD, Lembo AJ. New and emerging treatment options for irritable bowel syndrome. Gastroenterol Hepatol (N Y). 2015;11(4 Suppl 2):1–19.
11. Smalley W, Falck-Ytter C, Carrasco-Labra A, Wani S, Lytvyn L, Falck-Ytter Y. AGA clinical practice guidelines on the laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults (IBS-D). Gastroenterology. 2019;157(3):851–4.
12. Slattery SA, Niaz O, Aziz Q, Ford AC, Farmer AD. Systematic review with meta-analysis: the prevalence of bile acid malabsorption in the irritable bowel syndrome with diarrhoea. Aliment Pharmacol Ther. 2015;42(1):3–11.
13. Carrasco-Labra A, Lytvyn L, Falck-Ytter Y, Surawicz CM, Chey WD. AGA technical review on the evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults (IBS-D). Gastroenterology. 2019;157(3):859–80.
14. Vijayvargiya P, Camilleri M, Shin A, Saenger A. Methods for diagnosis of bile acid malabsorption in clinical practice. Clin Gastroenterol Hepatol. 2013;11(10):1232–9.
15. Pardi DS. Diagnosis and management of microscopic colitis. Am J Gastroenterol. 2017;112(1):78–85.
16. Chey WD, Nojkov B, Rubenstein JH, Dobhan RR, Greenson JK, Cash BD. The yield of colonoscopy in patients with non-constipated irritable bowel syndrome: results from a prospective, controlled US trial. Am J Gastroenterol. 2010;105(4):859–65.
17. Longstreth GF, Yao JF. Irritable bowel syndrome and surgery: a multivariable analysis. Gastroenterology. 2004;126(7):1665–73.
18. Hasler WL, Schoenfeld P. Systematic review: abdominal and pelvic surgery in patients with irritable bowel syndrome. Aliment Pharmacol Ther. 2003;17(8):997–1005.
19. Cole JA, Yeaw JM, Cutone JA, et al. The incidence of abdominal and pelvic surgery among patients with irritable bowel syndrome. Dig Dis Sci. 2005;50(12):2268–75.
20. Longstreth GF. Avoiding unnecessary surgery in irritable bowel syndrome. Gut. 2007;56(5):608–10.
21. Spiller R. How inflammation changes neuromuscular function and its relevance to symptoms in diverticular disease. J Clin Gastroenterol. 2006;40(Suppl 3):S117–20.
22. Tursi A, Elisei W. Role of inflammation in the pathogenesis of diverticular disease. Mediat Inflamm. 2019;2019:8328490.
23. Jung HK, Choung RS, Locke GR 3rd, Schleck CD, Zinsmeister AR, Talley NJ. Diarrhea-predominant irritable bowel syndrome is associated with diverticular disease: a population-based study. Am J Gastroenterol. 2010;105(3):652–61.
24. Peery AF, Keku TO, Addamo C, et al. Colonic diverticula are not associated with mucosal inflammation or chronic gastrointestinal symptoms. Clin Gastroenterol Hepatol. 2018;16(6):884–891 e881.
25. Spiller R. Is it diverticular disease or is it irritable bowel syndrome? Dig Dis. 2012;30(1):64–9.
26. Tursi A. Diverticulosis today: unfashionable and still underresearched. Ther Adv Gastroenterol. 2016;9(2):213–28.
27. Thorn M, Graf W, Stefansson T, Pahlman L. Clinical and functional results after elective colonic resection in 75 consecutive patients with diverticular disease. Am J Surg. 2002;183(1):7–11.
28. Egger B, Peter MK, Candinas D. Persistent symptoms after elective sigmoid resection for diverticulitis. Dis Colon Rectum. 2008;51(7):1044–8.
29. Longstreth GF. Hysterectomy and the irritable bowel. Gut. 1993;34(3):429.
30. Prior A, Stanley KM, Smith AR, Read NW. Relation between hysterectomy and the irritable bowel: a prospective study. Gut. 1992;33(6):814–7.
31. Heaton KW, Parker D, Cripps H. Bowel function and irritable bowel symptoms after hysterectomy and cholecystectomy--a population based study. Gut. 1993;34(8):1108–11.
32. Kaptchuk TJ, Kelley JM, Conboy LA, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. BMJ. 2008;336(7651):999–1003.
33. Halpert A, Dalton CB, Palsson O, et al. Irritable bowel syndrome patients' ideal expectations and recent experiences with healthcare providers: a national survey. Dig Dis Sci. 2010;55(2):375–83.
34. Khan S, Chang L. Diagnosis and management of IBS. Nat Rev Gastroenterol Hepatol. 2010;7(10):565–81.
35. Ford AC, Moayyedi P, Chey WD, et al. American college of gastroenterology monograph on management of irritable bowel syndrome. Am J Gastroenterol. 2018;113(Suppl 2):1–18.

36. Moayyedi P, Ford AC, Talley NJ, et al. The efficacy of probiotics in the treatment of irritable bowel syndrome: a systematic review. Gut. 2010;59(3):325–32.
37. Black CJ, Yuan Y, Selinger CP, et al. Efficacy of soluble fibre, antispasmodic drugs, and gut-brain neuromodulators in irritable bowel syndrome: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2020;5(2):117–31.
38. Weerts Z, Masclee AAM, Witteman BJM, et al. Efficacy and safety of peppermint oil in a randomized, double-blind trial of patients with irritable bowel syndrome. Gastroenterology. 2020;158(1):123–36.
39. Moayyedi P, Quigley EM, Lacy BE, et al. The effect of fiber supplementation on irritable bowel syndrome: a systematic review and meta-analysis. Am J Gastroenterol. 2014;109(9):1367–74.
40. Lacy BE. The science, evidence, and practice of dietary interventions in irritable bowel syndrome. Clin Gastroenterol Hepatol. 2015;13(11):1899–906.
41. Bijkerk CJ, Muris JW, Knottnerus JA, Hoes AW, de Wit NJ. Systematic review: the role of different types of fibre in the treatment of irritable bowel syndrome. Aliment Pharmacol Ther. 2004;19(3):245–51.
42. Bijkerk CJ, de Wit NJ, Muris JW, Whorwell PJ, Knottnerus JA, Hoes AW. Soluble or insoluble fibre in irritable bowel syndrome in primary care? Randomised placebo controlled trial. BMJ. 2009;339:b3154.
43. Eswaran S, Muir J, Chey WD. Fiber and functional gastrointestinal disorders. Am J Gastroenterol. 2013;108(5):718–27.
44. Hayes PA, Fraher MH, Quigley EM. Irritable bowel syndrome: the role of food in pathogenesis and management. Gastroenterol Hepatol (N Y). 2014;10(3):164–74.
45. Misselwitz B, Butter M, Verbeke K, Fox MR. Update on lactose malabsorption and intolerance: pathogenesis, diagnosis and clinical management. Gut. 2019;68(11):2080–91.
46. Biesiekierski JR, Newnham ED, Irving PM, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. Am J Gastroenterol. 2011;106(3):508–14; quiz 515
47. Barrett JS, Gearry RB, Muir JG, et al. Dietary poorly absorbed, short-chain carbohydrates increase delivery of water and fermentable substrates to the proximal colon. Aliment Pharmacol Ther. 2010;31(8):874–82.
48. Biesiekierski JR, Peters SL, Newnham ED, Rosella O, Muir JG, Gibson PR. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. Gastroenterology. 2013;145(2):320–328 e321–323.
49. Halmos EP, Gibson PR. Controversies and reality of the FODMAP diet for patients with irritable bowel syndrome. J Gastroenterol Hepatol. 2019;34(7):1134–42.
50. Mottacki N, Simren M, Bajor A. Review article: bile acid diarrhoea – pathogenesis, diagnosis and management. Aliment Pharmacol Ther. 2016;43(8):884–98.
51. Lembo A, Pimentel M, Rao SS, et al. Repeat treatment with rifaximin is safe and effective in patients with diarrhea-predominant irritable bowel syndrome. Gastroenterology. 2016;151(6):1113–21.
52. Barshop K, Staller K. Eluxadoline in irritable bowel syndrome with diarrhea: rationale, evidence and place in therapy. Ther Adv Chronic Dis. 2017;8(11):153–60.
53. Black CJ, Burr NE, Camilleri M, et al. Efficacy of pharmacological therapies in patients with IBS with diarrhoea or mixed stool pattern: systematic review and network meta-analysis. Gut. 2020;69(1):74–82.
54. Chapman RW, Stanghellini V, Geraint M, Halphen M. Randomized clinical trial: macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. Am J Gastroenterol. 2013;108(9):1508–15.
55. Cryer B, Drossman DA, Chey WD, Webster L, Habibi S, Wang M. Analysis of nausea in clinical studies of lubiprostone for the treatment of constipation disorders. Dig Dis Sci. 2017;62(12):3568–78.
56. Black CJ, Burr NE, Quigley EMM, Moayyedi P, Houghton LA, Ford AC. Efficacy of secretagogues in patients with irritable bowel syndrome with constipation: systematic review and network meta-analysis. Gastroenterology. 2018;155(6):1753–63.
57. Keefer L, Drossman DA, Guthrie E, et al. Centrally mediated disorders of gastrointestinal pain. Gastroenterology. 2016;150:1408.
58. Tornblom H, Drossman DA. Centrally targeted pharmacotherapy for chronic abdominal pain. Neurogastroenterol Motil. 2015;27(4):455–67.
59. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. Gastroenterology. 2016;150:1262–79.
60. Sobin WH, Heinrich TW, Drossman DA. Central neuromodulators for treating functional GI disorders: a primer. Am J Gastroenterol. 2017;112(5):693–702.
61. Saito YA, Almazar AE, Tilkes KE, et al. Randomised clinical trial: pregabalin vs placebo for irritable bowel syndrome. Aliment Pharmacol Ther. 2019;49(4):389–97.
62. Zondervan KT, Yudkin PL, Vessey MP, et al. Chronic pelvic pain in the community--symptoms, investigations, and diagnoses. Am J Obstet Gynecol. 2001;184(6):1149–55.
63. Williams RE, Hartmann KE, Sandler RS, Miller WC, Steege JF. Prevalence and characteristics of irritable bowel syndrome among women with chronic pelvic pain. Obstet Gynecol. 2004;104(3):452–8.
64. Choung RS, Herrick LM, Locke GR 3rd, Zinsmeister AR, Talley NJ. Irritable bowel syndrome and chronic pelvic pain: a population-based study. J Clin Gastroenterol. 2010;44(10):696–701.
65. Prott G, Shim L, Hansen R, Kellow J, Malcolm A. Relationships between pelvic floor symptoms and function in irritable bowel syndrome. Neurogastroenterol Motil. 2010;22(7):764–9.
66. Rao SS, Bharucha AE, Chiarioni G, et al. Functional anorectal disorders. Gastroenterology. 2016;150:1430–42.
67. Atkin GK, Suliman A, Vaizey CJ. Patient characteristics and treatment outcome in functional anorectal pain. Dis Colon Rectum. 2011;54(7):870–5.
68. Grant SR, Salvati EP, Rubin RJ. Levator syndrome: an analysis of 316 cases. Dis Colon Rectum. 1975;18(2):161–3.
69. Chiarioni G, Nardo A, Vantini I, Romito A, Whitehead WE. Biofeedback is superior to electrogalvanic stimulation and massage for treatment of levator ani syndrome. Gastroenterology. 2010;138(4):1321–9.
70. Park DH, Yoon SG, Kim KU, et al. Comparison study between electrogalvanic stimulation and local injection therapy in levator ani syndrome. Int J Color Dis. 2005;20(3):272–6.
71. Rao SS, Paulson J, Mata M, Zimmerman B. Clinical trial: effects of botulinum toxin on Levator ani syndrome--a double-blind, placebo-controlled study. Aliment Pharmacol Ther. 2009;29(9):985–91.
72. Ooijevaar RE, Felt-Bersma RJF, Han-Geurts IJ, van Reijn D, Vollebregt PF, Molenaar CBH. Botox treatment in patients with chronic functional anorectal pain: experiences of a tertiary referral proctology clinic. Tech Coloproctol. 2019;23(3):239–44.
73. König P, Ambrose NS, Scott N. Hereditary internal anal sphincter myopathy causing proctalgia fugax and constipation: further clinical and histological characterization in a patient. Eur J Gastroenterol Hepatol. 2000;12(1):127–8.
74. de la Portilla F, Borrero JJ, Rafel E. Hereditary vacuolar internal anal sphincter myopathy causing proctalgia fugax and constipation: a new case contribution. Eur J Gastroenterol Hepatol. 2005;17(3):359–61.
75. Guy RJ, Kamm MA, Martin JE. Internal anal sphincter myopathy causing proctalgia fugax and constipation: further clinical

and radiological characterization in a patient. Eur J Gastroenterol Hepatol. 1997;9(2):221–4.
76. Takano M. Proctalgia fugax: caused by pudendal neuropathy? Dis Colon Rectum. 2005;48(1):114–20.
77. Eckardt VF, Dodt O, Kanzler G, Bernhard G. Treatment of proctalgia fugax with salbutamol inhalation. Am J Gastroenterol. 1996;91(4):686–9.
78. Sánchez Romero AM, Arroyo Sebastián A, Pérez Vicente FA, Serrano Paz P, Candela Polo F, Calpena RR. Treatment of proctalgia fugax with botulinum toxin: results in 5 patients. Rev Clin Esp. 2006;206(3):137–40.
79. Gracia Solanas JA, Ramírez Rodríguez JM, Elía Guedea M, Aguilella Diago V, Martínez DM. Sequential treatment for proctalgia fugax. Mid-term follow-up. Rev Esp Enferm Dig. 2005;97(7):491–6.
80. Karadimas EJ, Trypsiannis G, Giannoudis PV. Surgical treatment of coccygodynia: an analytic review of the literature. Eur Spine J. 2011;20(5):698–705.
81. Lirette LS, Chaiban G, Tolba R, Eissa H. Coccydynia: an overview of the anatomy, etiology, and treatment of coccyx pain. Ochsner J. 2014;14(1):84–7.
82. Maigne JY, Chatellier G, Faou ML, Archambeau M. The treatment of chronic coccydynia with intrarectal manipulation: a randomized controlled study. Spine (Phila Pa 1976). 2006;31(18):E621–7.
83. Sencan S, Edipoglu IS, Ulku Demir FG, Yolcu G, Gunduz OH. Are steroids required in the treatment of ganglion impar blockade in chronic coccydynia? A prospective double-blinded clinical trial. Korean J Pain. 2019;32(4):301–6.
84. Kleimeyer JP, Wood KB, Lønne G, et al. Surgery for refractory coccygodynia: operative versus nonoperative treatment. Spine (Phila Pa 1976). 2017;42(16):1214–9.
85. Labat JJ, Riant T, Robert R, Amarenco G, Lefaucheur JP, Rigaud J. Diagnostic criteria for pudendal neuralgia by pudendal nerve entrapment (Nantes criteria). Neurourol Urodyn. 2008;27(4):306–10.
86. Ly J, Scott K, Xi Y, Ashikyan O, Chhabra A. Role of 3 tesla MR neurography and CT-guided injections for pudendal neuralgia: analysis of pain response. Pain Physician. 2019;22(4):E333–44.
87. Kastler A, Puget J, Tiberghien F, Pellat JM, Krainik A, Kastler B. Dual site pudendal nerve infiltration: more than just a diagnostic test? Pain Physician. 2018;21(1):83–90.
88. Labat JJ, Riant T, Lassaux A, et al. Adding corticosteroids to the pudendal nerve block for pudendal neuralgia: a randomised, double-blind, controlled trial. BJOG. 2017;124(2):251–60.
89. Siegel S, Paszkiewicz E, Kirkpatrick C, Hinkel B, Oleson K. Sacral nerve stimulation in patients with chronic intractable pelvic pain. J Urol. 2001;166(5):1742–5.
90. Peters KM, Killinger KA, Jaeger C, Chen C. Pilot study exploring chronic pudendal neuromodulation as a treatment option for pain associated with pudendal neuralgia. Low Urin Tract Symp. 2015;7(3):138–42.
91. Buffenoir K, Rioult B, Hamel O, Labat JJ, Riant T, Robert R. Spinal cord stimulation of the conus medullaris for refractory pudendal neuralgia: a prospective study of 27 consecutive cases. Neurourol Urodyn. 2015;34(2):177–82.
92. Prologo JD, Lin RC, Williams R, Corn D. Percutaneous CT-guided cryoablation for the treatment of refractory pudendal neuralgia. Skelet Radiol. 2015;44(5):709–14.
93. Petrov-Kondratov V, Chhabra A, Jones S. Pulsed radiofrequency ablation of pudendal nerve for treatment of a case of refractory pelvic pain. Pain Physician. 2017;20(3):E451–4.
94. Venturi M, Boccasanta P, Lombardi B, Brambilla M, Contessini Avesani E, Vergani C. Pudendal neuralgia: a new option for treatment? Preliminary results on feasibility and efficacy. Pain Med. 2015;16(8):1475–81.
95. Beco J, Seidel L, Albert A. Endoscopic transperineal pudendal nerve decompression: operative pudendoscopy. Surg Endosc. 2018;32(8):3720–31.
96. Robert R, Labat JJ, Bensignor M, et al. Decompression and transposition of the pudendal nerve in pudendal neuralgia: a randomized controlled trial and long-term evaluation. Eur Urol. 2005;47(3):403–8.
97. Erdogru T, Avci E, Akand M. Laparoscopic pudendal nerve decompression and transposition combined with omental flap protection of the nerve (Istanbul technique): technical description and feasibility analysis. Surg Endosc. 2014;28(3):925–32.
98. Hibner M, Castellanos ME, Drachman D, Balducci J. Repeat operation for treatment of persistent pudendal nerve entrapment after pudendal neurolysis. J Minim Invasive Gynecol. 2012;19(3):325–30.

Common Tests for the Pelvic Floor

57

Amy J. Thorsen and Leslie Roth

Key Concepts

- Disorders of anorectal function are common and have a significant impact on individual's quality of life.
- Anal manometry allows assessment of anorectal motor and sensory function to delineate contributing factors leading to symptoms of obstructed defecation, anal pain, and fecal incontinence.
- Ultrasound, fluoroscopic defecography, and MR defecography provide anatomic and dynamic assessment and the impact of anatomy on function in evaluating patients with fecal incontinence, obstructed defecation, and pelvic organ prolapse.

Introduction

Alterations of anal continence and defecation can have a devastating effect on quality of life [1]. Community-based studies suggest fecal incontinence affects 8.4–14.4% of the population [2, 3]. Evacuation disorders are more common, affecting 12–19% of North Americans [4]. Up to one half of all parous women will have some degree of clinical pelvic organ prolapse; 10–20% of these women will have symptoms [5, 6]. Given affected individuals may avoid work and social activities, appropriate evaluation and treatment can have significant impact on patients' lives.

The etiology of these conditions can be quite variable and multifactorial. Serious underlying pathology, such as colonic malignancy or inflammatory bowel disease, should be excluded in patients with new onset of symptoms. Multispecialty evaluation may be indicated to evaluate and treat functional bowel and neurologic issues, as well as concomitant urologic and vaginal symptoms. Pelvic floor testing is indicated in patients who fail first-line conservative management such as optimizing stool consistency and lifestyle modification.

This chapter will focus on the evaluation of patients experiencing fecal incontinence, obstructed defecation, and the spectrum of posterior compartment pelvic organ prolapse. Pelvic floor assessment includes evaluation of motor and sensory function, structural anatomic assessment, and dynamic imaging.

Manometry

Equipment

The first studies of anorectal manometry were done in 1877 by Gowers [7], who measured anal canal resting tone and was reportedly the first to explore the rectoanal inhibitory reflex. The first attempt at measuring colorectal pressures with rectal tubing was described by Joltain et al. in 1919 [8]. Using procedures learned by performing cystometry, White et al. further refined the technique in the evaluation of patients with neurologic injury in 1940 [9]. The various anorectal manometry systems presently used all consist of a pressure sensing probe, an amplifier/recorder which translates the pressure signals, a video monitor to display these signals, and a computer with software to analyze and store data. Present-day probes can be water perfused, air charged, or microballoon [10]. A nonlatex balloon is attached to the end of the catheter where a pressure transducer is located to measure rectal pressure and reflexes.

Water-perfused catheters consist of thin plastic tubing with a central channel connected to a pneumohydraulic pump. Nitrogen gas is used to pump water out of a reservoir through the catheter and out of four to eight side holes spaced 0.5–2.0 cm apart. Water-perfused catheters indirectly measure intraluminal pressures using the resistance pressure of

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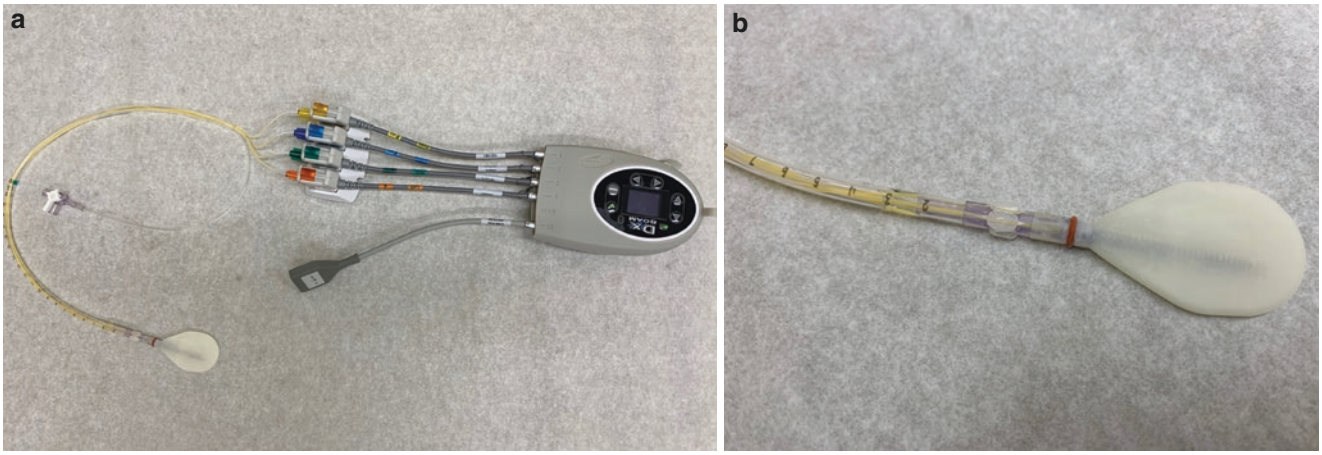

Fig. 57.1 (**a**, **b**) Air-charged manometry catheters

water flow out of the catheter as picked up by transducers [11, 12]. The pressure in each tube is sensed and converted to an electrical signal by a volume displacement transducer. The frequency of the amplifier/recorder should be at least 8 Hz. The recorded pressure rises when the flow of water through the side hole of a tube is impeded by anal contraction.

Prior to beginning a study, the reservoir needs to be filled with water, and the pneumohydraulic pump is started. Water perfusion should be set at a rate of 0.2–0.4 mL/minute at a pressure head of 10 psi. The transducers located on the pump and on the catheter need to be at the same level during calibration and when placed in the patient when performing the study [10]. Conventional manometry probes containing few sensors are incapable of acquiring the pressures of the entire anal canal simultaneously. Therefore, they required pull-through maneuvers or rotation to sample the entire area of interest. This prevents a continuous measurement of pressures throughout the entire anal canal. Radial sensors require a pull-through procedure that may introduce motion artifacts [13]. Water-perfused catheters are low cost and simple but cannot be used in an upright position; tracings can be impacted by anatomic and technique-induced artifact [14].

Solid-state catheters consist of a linear array of miniature, solid-state strain gauge transducers spaced at regular intervals along a flexible tube. Outputs from the strain gauges are passed to an amplifier and then to a computer [15]. Solid-state catheters have much higher frequency- response characteristics, making them able to accurately record the much faster pressure transients produced by striated muscle. Calibration of these catheters is straightforward and does not require the probe and transducers to be at the same level. Solid-state devices require less technical expertise and are less cumbersome to use, but they are fragile and more expensive than water-perfused catheters.

Air-charged catheter technology uses an air column from a balloon to an external transducer which allows circumferential area readings that are gravity independent. Air-charged catheters are low cost and disposable; they avoid the need for high-level disinfection which results in decreased personnel time. Air-charged catheters have been shown to have reproducible results compared with water-perfused and solid-state microtransducers when evaluating intrauterine [16], intraurethral [17], esophageal, and anorectal pressures (Fig. 57.1a, b) [18].

Further advancements in manometry catheters and software have led to the development of high-resolution manometry (HRAM) in 2008, which was soon followed by high-definition 3D manometry and topography (HDAM). The HRAM catheter consists of two sensors in the rectal balloon and ten sensors at 6-mm intervals along the anal canal. Each sensor is able to record pressure changes in excess of 6000 mmHg/s with an accuracy within 1 mmHg of atmospheric pressure. The recording unit and software can accommodate data at 35 Hz frequency. The catheters are susceptible to thermal drift. Thermal compensation is applied during analysis to compensate for temperature changes during prolonged studies [19].

The HDAM probe is a large-diameter (10.75 mm) catheter with 256 pressure sensors that are arranged in 16 rows with each row having 16 circumferentially oriented sensors (Fig. 57.2). Although pressure is sensed at 4-mm intervals, the software linearly interpolates the space between sensors to provide measurements at 1-mm spacing with negligible error. The amplifier and recording system attached to the catheter utilize specialized software to display topographic images. Recording frequency is at >20 Hz with a resolution of 0.1 mmHg. Thermal compensation is also applied similar to HRAM probes [20].

The additional sensors at close intervals on HRAM and HDAM solid-state probes provide a continuum of data acquisition without loss of information. A tool called the eSleeve (Sierra Scientific Instruments, Los Angeles, CA, USA) reduces the data from a number of sensors into a single

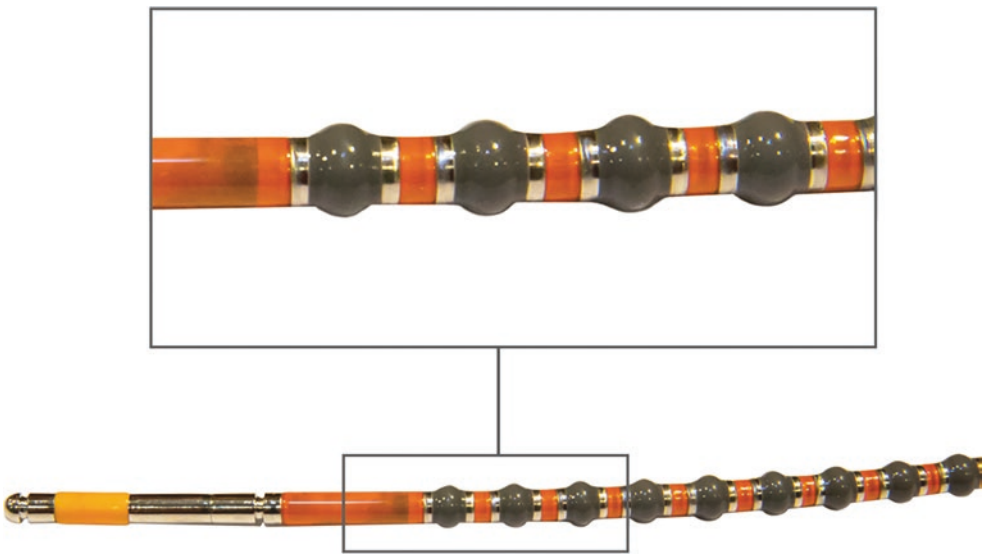

Fig. 57.2 HDAM manometry catheter (Images courtesy of Laborie Medical Technologies, Corp.)

maximum value at each time point. Color topography provides a continuous and dynamic display of the large amount of data gathered by the sensors, allowing simpler and more comprehensive interpretation of the data compared to the linear plots of conventional manometry [21].

Indications

Diagnostic manometry may be indicated in the evaluation of patients with fecal incontinence [22], constipation and obstructed defecation [23, 24], anal pain [25], anal fissure [26], and Hirschsprung's disease [27]. Manometry has been used as a preoperative assessment of anorectal function if intervention is associated with risks to continence (e.g., fistulotomy [28]and lateral sphincterotomy [29]) or ability to evacuate (e.g., rectopexy [30]). Assessment of anorectal function in patients after obstetric injury/traumatic birth may be useful if the clinician and patient wish to quantify anal sphincter function prior to future deliveries [31]. Biofeedback protocols using anal manometry have been developed for the treatment of fecal incontinence [32] and obstructed defecation [33].

Technique

Bowel preparation is optional; however, tap water or Fleets™ phospho-soda enema is indicated if digital rectal exam reveals the rectum is full of stool. Patients are not required to fast but should empty their bowels at least 30 minutes prior to testing for optimal results. The patient should lie in the left lateral position with the knees and hips at 90 degrees flexion. A digital exam is performed noting any local pathology, tenderness, blood, or stool present. The patient's understanding of instructions such as "squeeze" or "push" should be noted. The manometry probe is lubricated with a non-anesthetizing agent and then placed into the rectum and orientated such that the most distal sensor is external to the anal verge. Any rectal balloon attached to the catheter should be 3–5 cm above the upper border of the anal canal to avoid impingement upon inflation. A minimum longitudinal recording length of 6 cm is required.

After probe placement, a rest period of 3–5 minutes should be allowed to give the subject time to relax and the sphincter tone to return to basal levels. Ultraslow wave activity consisting of phasic pressure activity at 1–1.5 cycles/min with amplitude >= 40 mmHg may be noted [11]. Low-amplitude slow waves are more common and occur at a frequency of 10–20/minute. They are frequently seen in the lower anal canal and may promote anal continence by causing an upward movement of rectal contents [34].

There are several techniques to perform manometry with water-perfused and air-charged catheters. The stationary technique involves leaving the catheter in one position during recording. With the stationary pull-through method, the catheter is replaced within the anal canal. The resting pressure and the squeeze increase at 6, 5, 4, 3, 2, and 1 cm from the anal verge are measured by extracting the probe in increments of 1 cm from the rectum to the anal verge. With the continuous pull-through technique, the catheter is moved through the lower rectum and the anal canal at a constant speed (often 1 cm/second) with a specialized puller, and the pressures are simultaneously recorded [35]. The stationary pull-through technique is today the recommended method of choice since the continuous pull-through technique creates a reflex sphincter contraction due to the stimulation generated by the probe resulting in higher anal pressures [36].

The multiple sensors of HRAM and HDAM probes allow for a stationary exam to be performed after probe placement.

This allows for a shorter exam time, which in theory may lead to more patient comfort. Although studies have not suggested a greater comfort with HRAM than with a water-perfused manometer of a similar diameter and stiffness, HDAM was felt to be somewhat more comfortable compared to HRAM [37].

Resting Pressure

The resting tone created by the internal and external anal sphincter, and to a lesser extent the hemorrhoidal plexus, contributes to resting anal pressure. Up to 80% of resting tone may depend on internal sphincter tone. Resting anal pressures should be recorded approximately 3 minutes after probe insertion to allow reflex contractions from probe placement to abate. Resting pressure is generally recorded for 20–30 seconds. Mean resting pressure represents the averaged pressure recorded over this time, whereas the maximum resting pressure is the highest pressure measured at any instant. The high-pressure zone (HPZ) represents the length of anal canal over which the pressures are greater than half the maximum resting pressure. Resting anal pressures are lower in women than in men [38, 39] and decrease in women as they age [39–41]. Hypotonic resting pressures may be associated with passive fecal incontinence [42–44]. Hypertonic pressures at rest may be seen with anal fissure [45–47] or constipation [48].

Squeeze Pressure

The squeeze anal pressure measures voluntary contraction of the external anal sphincter muscle. Anal squeeze pressure is usually measured for 30 seconds after the patient is asked to maximally squeeze as hard as possible as long as he/she can. Squeeze endurance can also be assessed. A short 5-second squeeze can be measured by asking the patient to squeeze as hard as possible as if avoiding to pass flatus or stool. Similar to resting pressures, squeeze pressures or the squeeze increment (mean squeeze pressure minus mean resting pressure) are lower in women than in men and lower in older compared to younger women [38–41]. HDM can distinguish the contribution of the squeeze pressure from the puborectalis muscle [39, 49], but has not yet been shown to be better in identifying injury to the puborectalis or external sphincter than simpler forms of manometry [50].

Cough Reflex

The cough reflex assesses the response of the anal canal to a sudden increase in intraabdominal pressure. The patient is requested to perform a single cough, and this is repeated 30 seconds later. The rapid rise in intraabdominal pressure with a cough should cause a reflex contraction of the external anal sphincter. This reflex assesses the integrity of the sacral reflex arc. The reflex is preserved in patients with spinal lesions above the sacral level but is absent in patients with cauda equina lesions or pudendal neuropathy [51, 52].

Push/Simulated Evacuation

Evacuation requires an adequate propulsive force, measured as an increase in rectal pressure, with simultaneous anal canal relaxation noted as a decrease in anal pressure. The patient is requested to push down as if she is trying to pass a bowel movement. Three pushes are performed for 15 seconds at 30-second intervals with the catheter in place. The rectal balloon does not need to be inflated. The best attempt is used for analysis.

Dyssynergic defecation was initially thought to be caused by paradoxic anal canal contraction or involuntary anal spasm during defecation [53]. A prospective study by Rao et al. [54] revealed that most patients with dyssynergic defecation demonstrate the inability to coordinate the abdominal, rectoanal, and pelvic floor muscles to facilitate defecation. This may be due to inadequate pushing force, paradoxical anal sphincter contraction, impaired anal sphincter relaxation, or a combination of these mechanisms (Fig. 57.3a, b). Based on these features, at least four types of reproducible dyssynergic defecation [55, 56] have been recognized:

- *Type I:* The patient can generate an adequate push (rise in intraabdominal pressure) along with a paradoxical anal sphincter contraction.
- *Type II:* The patient is unable to generate an adequate push but displays a paradoxical increase in anal sphincter pressures.
- *Type III:* The patient can generate an adequate push, but either has absent or incomplete (<20%) reduction in anal sphincter pressure.
- *Type IV:* The patient is unable to produce an adequate push and demonstrates an absent or deficient anal sphincter relaxation.

Manometry alone cannot diagnose dyssynergic defecation, given some studies have suggested up to 90% of asymptomatic controls and patients with proctalgia without constipation can exhibit dyssynergic patterns [57, 58]. This may be due to the nonphysiologic positioning of the patient in the left lateral position, as well as the lack of rectal con-

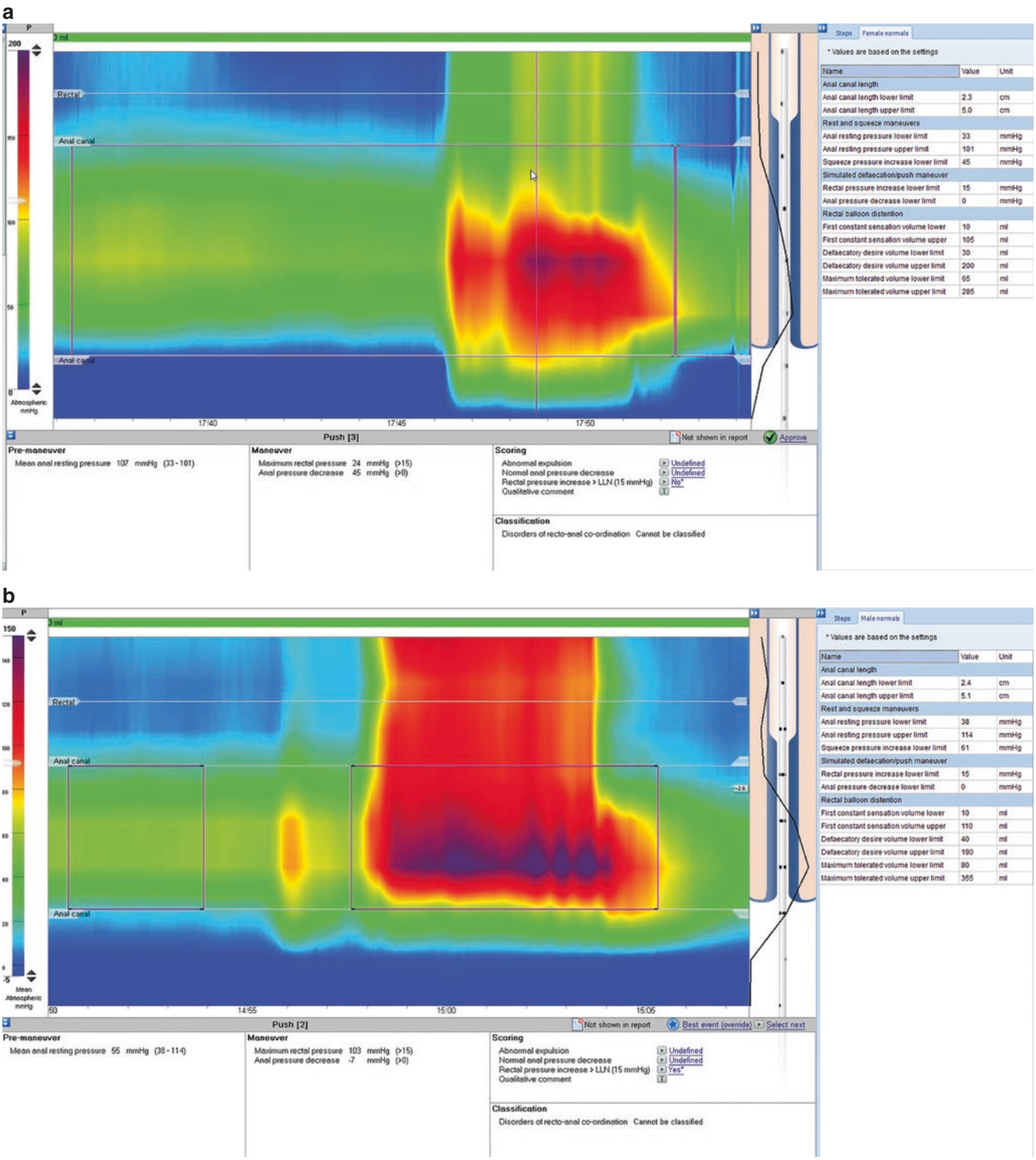

Fig. 57.3 (**a**) Normal response with push on HDAM. (**b**) Paradoxic contraction of the anal canal with push on HDAM (Images courtesy of Laborie Medical Technologies, Corp.)

tents when the patient is asked to simulate defecation [59]. The rectoanal gradient, which is the difference between rectal pressure and anal pressure during simulated evacuation, is negative in a majority of asymptomatic women, undermining the utility of a negative gradient for diagnosing defecatory disorders by HRM [40]. The defecation index (normal >= 1.2), which is the ratio of maximal intrarectal pressure and anal sphincter residual pressure, is a simple and useful quantitative measure of rectoanal coordination during defecation [54, 60].

Rectoanal Inhibitory Reflex (RAIR)

Gowers [7] first noted that distension of the rectal wall leads to first a reflexive contraction of the external sphincter followed by relaxation of the internal sphincter (Fig. 57.4). This rectoanal inhibitory reflex (RAIR) is mediated by the myenteric plexus. The RAIR is performed by inflating the rectal balloon with at least 30 mL air. Failure to elicit the RAIR may be seen with low distending volumes in a large capacity rectum; therefore the test should be repeated with increasing balloon volumes if megarectum is suspected. A RAIR may also be very difficult to detect in the setting of very low resting pressures. The RAIR reflex may be absent in Hirschsprung's disease [61], in the presence of acquired myenteric neuropathies [62, 63], and after rectal reconstruction [52].

Rectal Sensation

Rectal sensitivity to distension is measured by utilizing a rectal balloon placed at least 3–5 cm proximal to the upper border of the anal canal. Either ramp (continuous 1–2 cc/s) or phasic air insufflation can be performed with a hand-held syringe or pump [12]. The volume of the balloon is recorded for three sensory thresholds: (1) first sensation, the first time the patient constantly feels sensation from the balloon pressure; (2) first urge/desire to defecate, the volume the patient feels the persistent urge to defecate; and (3) maximum tolerated volume, when the volume in the balloon causes the patient to feel too uncomfortable to continually tolerate. Intra-balloon volumes and intrarectal pressures are recorded concurrently, allowing rectal compliance to be calculated from the derived pressure–volume curve. Rectal capacity can also be measured.

Rectal sensation volumes can be normal, reduced (hypersensitive), or elevated (hyposensitive) in both chronic constipation and fecal incontinence [64–66]. Rectal hypersensitivity can be seen with urge fecal incontinence [67], radiation proctitis, ulcerative colitis, IBS-D [68], and low anterior syndrome [69]. Improvement of symptoms after behavioral therapy [70], pharmacological therapy [71], or surgical therapy [72] may occur with improvement in sensory thresholds.

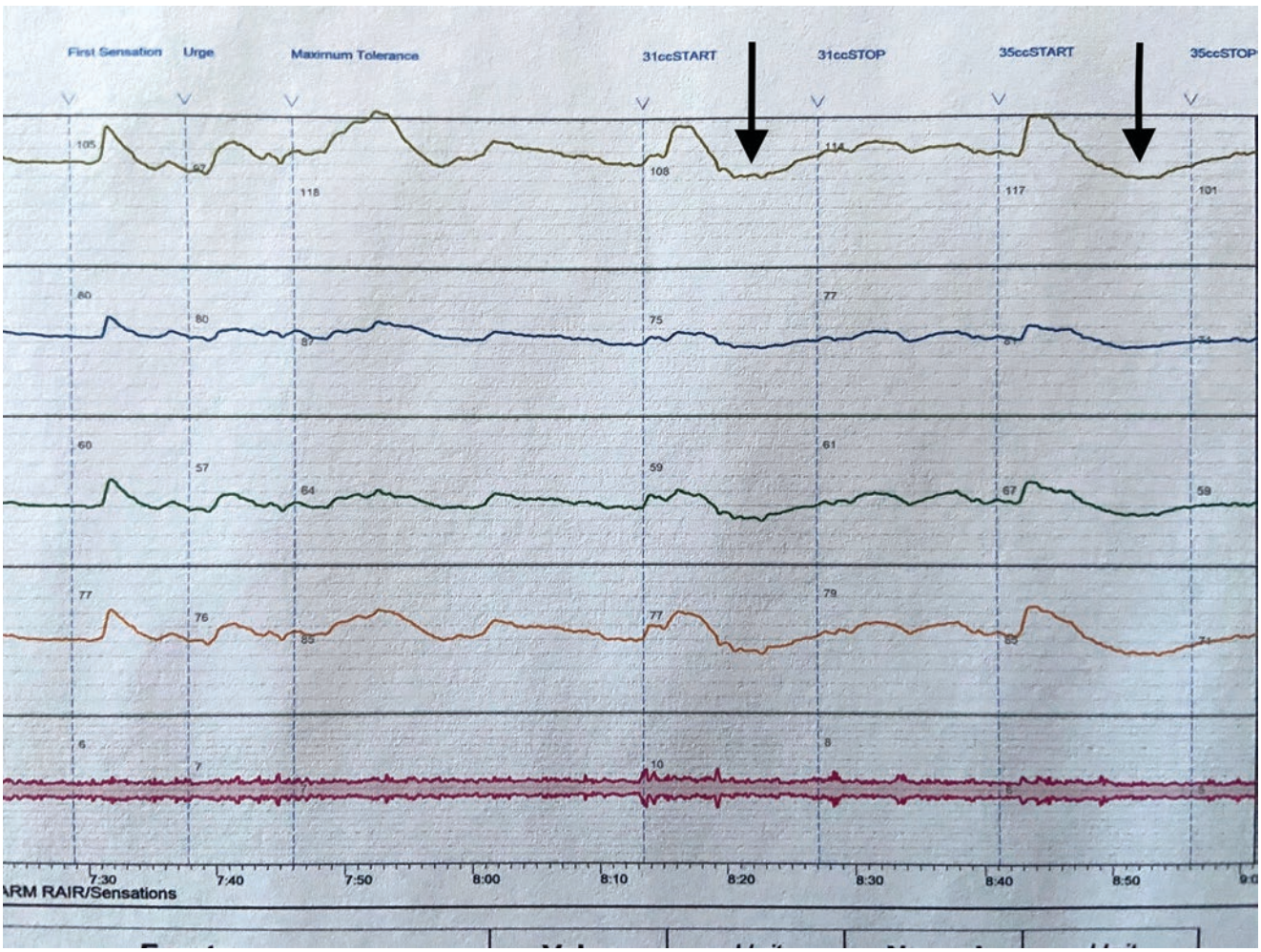

Fig. 57.4 Arrows show RAIR response: internal sphincter relaxation after rectal distension

Rectal hyposensitivity can be seen in 18–66% of patients with chronic constipation [66] and can identify a subset of patients who respond poorly to biofeedback [73] and colectomy [74]. Patients successfully treated for obstructed defecation with neuromodulation therapy have been shown to exhibit improved rectal sensation [75].

Balloon Expulsion Test (BET)

The balloon expulsion test is a screening test for obstructed defecation. A 4-cm balloon filled with 50 mL of warm water is placed into the rectum. The patient is then allowed to sit on a commode and pass the balloon privately. A functional defecation disorder is suggested if the patient cannot pass the balloon or if it takes more than 1 minute to pass [76]. A positive delayed BET is highly specific for obstructed defecation but with a low sensitivity of 50% [77, 78]. It does not define the mechanism of disordered evacuation.

London Protocol and Criteria

Between 2014 and 2018, the international anorectal physiology working group (IAPWG), consisting of 29 gastroenterologists, gastrointestinal physiologists, and colorectal surgeons, met to develop a consensus document on the performance of anorectal manometry and BET as well as a classification of anorectal disorders, similar to the Chicago classification of esophageal motility disorders [79]. The four-part London classification delineates (a) disorder of the rectoanal inhibitory reflex, (b) disorders of anal tone and contractility, (c) disorders of rectoanal coordination, and (d) disorders of rectal sensation. Major findings not found in healthy controls by this classification are rectoanal areflexia (absent RAIR), anal hypotension and hypocontractility, rectal hyposensitivity, and hypersensitivity. Minor and inconclusive findings, such as anal hypertension and dyssynergia, can be found in health as well as with symptoms. The development of the London protocol and classification aims to standardize a common language and testing protocol in the evaluation of patients with anorectal dysfunction [80].

Authors Note Conventional Versus High-Definition 3D Manometry

Presently both authors (AJT, LR) use conventional manometry with air-charged disposable catheters at our anorectal physiology labs. This is a more economical choice given the systems and disposable catheters are at lower costs compared to HRAM/HDAM and their fragile, reusable catheters. Present CPT codes do not differentiate reimbursement between conventional and HRAM/HDAM manometry exams. Although we are intrigued by the topography plots and analysis that higher resolution provides, we have not yet found this information to aid in our decision-making in treating patients with pelvic floor disorders.

A recent study by Benezech et al. [81] noted that an anterior additional high-pressure area on HDAM associated with an excessive perineal descent allowed the diagnosis of rectal intussusception with a positive predictive value and a specificity of 100% compared with fluoroscopic defecography. While this could be a possible clinical advantage of HDAM in diagnosing the etiology of obstructed defecation or fecal incontinence, it would not obviate the need to perform dynamic imaging in surgical candidates in our opinion.

Neurophysiologic Testing

EMG

Pelvic floor electromyography permits mapping of external anal sphincter defects, determination of striated muscle function, and assessment of denervation–reinnervation potentials [82]. Advances in anal sphincter imaging by endoanal ultrasound and MRI have diminished the clinical utility of needle EMG [83]. Needle electrodes are placed into the external sphincter or puborectalis to assess the muscle and innervation as a function of their electrical activity in the resting and squeeze phases. The test is painful and poorly tolerated by patients, leading to poor diagnostic yield.

Surface EMG allows a more global assessment of sphincter function and is easy to perform. Although surface pads may be better tolerated, the anal plug intraluminal electrode is believed to be more accurate given its close position to the external sphincter muscle which prevents artifact from gluteal and other accessory muscles [84]. EMG recruitment is seen simultaneously with an increase in anal pressures during squeeze and correlates well with sphincter pressures [85]. Surface EMG can be very useful in detecting paradoxical contraction or a lack of relaxation in patients with defecatory dysfunction [86]. A normal response would be a decrease in activity with push compared to rest; elevated activity is seen with push with paradoxical relaxation (Fig. 57.5). EMG is frequently used to retrain external anal function in patients with fecal incontinence and obstructed defecation [86, 87].

Pudendal Nerve Terminal Motor Latency (PNTML)

The pudendal nerve and its branches are vulnerable to stretch injury during the third trimester of pregnancy, sec-

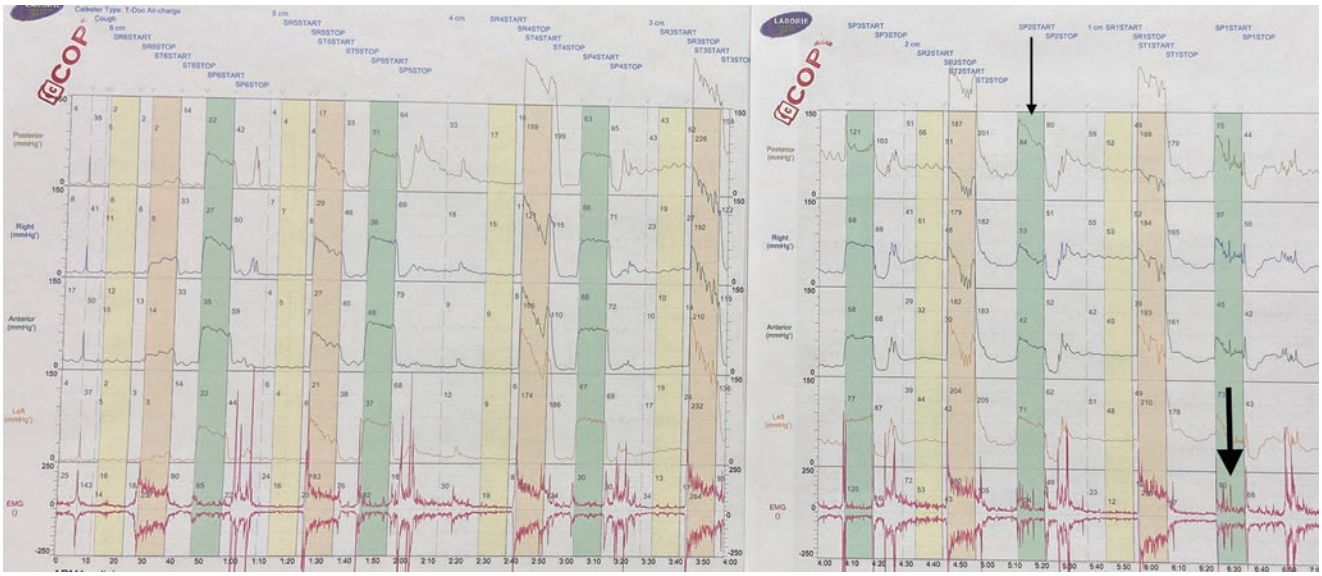

Fig. 57.5 Dyssynergic defecation with 2D manometry and simultaneous surface EMG. Yellow bars represent rest; orange bar is squeeze; green bars are push. Small arrow shows elevation of anal pressures with push. Large arrow reveals increased EMG activity with push, indicating paradoxical contraction

ond stage of labor, and forceps-assisted vaginal delivery. Injury can lead to denervation of the external sphincter muscle and fecal incontinence [88, 89]. PNTML measures the neuromuscular integrity between the pudendal nerve and external anal sphincter [82, 90]. The PNTML is performed by stimulating each pudendal nerve with a bipolar disposable electrode. This generates a compound muscle action response of the external anal sphincter (EAS); the time from stimulation to the beginning of the response is the PNTML [90]. A prolonged PNTML may suggest pudendal neuropathy or injury to some of its fast firing fibers [91]. There are many criticisms of the test and its utility: the test is very operator dependent [92]; it has poor sensitivity and specificity [90, 93]; it can have normal results if only some nerve fibers are damaged [94]; the latency has variable limits in health [12]; and its prediction on outcomes of clinical intervention, such as sphincteroplasty, is inconsistent [95, 96].

Spinal Motor Latency

Neurologic injury contributing to fecal incontinence can occur proximal to the origin of the pudendal nerves at the ischial spines. Transcutaneous stimulation of the cauda equina over the lumbar spine measures conduction along the cauda equina, the sacral plexus, and the branches from the plexus. Evoked responses can be recorded using standard EMG needles placed at the puborectalis, the external anal sphincter, and the urethral sphincter. Comparing latencies between multiple spinal levels allows the assessment of the level of neurologic injury [97]. Up to 23% of patients with idiopathic fecal incontinence will have cauda equina delay [98, 99].

Magnetic stimulation at multiple neurologic levels has been shown to induce motor-evoked potentials (MEPs) in the rectum and anus [100]. Using a probe with steel electrodes spaced to be in the rectum and low anal canal, rectal and anal MEPs can be measured after translumbar and transsacral magnetic stimulation. Rao et al. [101] found that TL and TS MEPs were significantly prolonged in patients with fecal incontinence compared to normal controls and that the MEP test was better tolerated than PNTML. MEPs were found to be prolonged in 87% of subjects with fecal incontinence, compared to prolonged PNTML in 63%. The clinical significance of prolonged spinal latencies in determining therapy for fecal incontinence remains to be seen.

Ultrasound and Dynamic Imaging

Anal ultrasound is the gold standard for evaluating anal sphincter pathology in the investigation of fecal incontinence [102]. Ultrasound works by measuring the reflection of sound waves off the structure being examined. Tissues that reflect ultrasound waves are hyperechoic and appear white on the image, whereas tissues that let more waves through are hypoechoic and appear black on the image. The external anal sphincter and puborectalis have higher reflection of sound waves, so they appear more hyperechoic, whereas the smooth muscle of the internal sphincter with its high water content appears more hypoechoic.

Indication

Anal ultrasound can help identify anatomic abnormalities of the anal sphincter complex. This has replaced electromyographic mapping as the modality of choice to assess sphincter defects for surgical repair [103]. Ultrasound is useful in patients with incontinence and fistulas (rectovaginal, cryptoglandular, or Crohn's). It can help determine defects in the sphincter complex that may be amenable to surgical repair and can measure the amount of muscle involvement in fistulas. It can also be useful in assessing the success of surgical repair of the sphincter complex and fistulas.

Equipment and Technique

The three-dimensional endoanal ultrasound has an endocavitary probe with a rotating transducer which acquires a 360-degree image. Most investigators use a BK Medical Anorectal 3D 20R3 high-resolution probe which has a frequency range of 3–20 MHz. This allows automatic collection of images over a 6-cm axis without moving the probe. In preparation, patients receive two enemas prior to the exam to clean the rectum of stool. The ultrasound is performed with the patient awake in the left lateral decubitus position. The probe is then inserted, and the tip of the probe is placed at the puborectalis, and the three-dimensional image is collected. Afterward, the images can be manipulated to visualize the sphincter complex in any plane making angles and distances measured more accurately [104].

Interpretation

The normal anal canal is divided into three sections: upper, mid-, and distal anal canal. The upper anal canal is identified by the hyperechoic horseshoe appearance of the puborectalis muscle (Fig. 57.6). In the mid-anal canal, you have the intact circles of the internal (hypoechoic) and external (hyperechoic) anal sphincters (Fig. 57.7a, b). In the distal anal canal, you have loss of the internal anal sphincter and visualize only the external anal sphincter. Ultrasound can visualize anterior sphincter defects from childbirth (Fig. 57.8).

To measure the perineal body length, digital pressure is placed to the posterior vaginal wall, which shows hyperechoic on image allowing distance measurement. Mean perineal body length in nulliparous healthy volunteers was 17.4+/−2.7 [105, 106]. A perineal body measurement <10 mm has been associated with an anterior sphincter defect [107]. The average anal canal length in females is 3 cm.

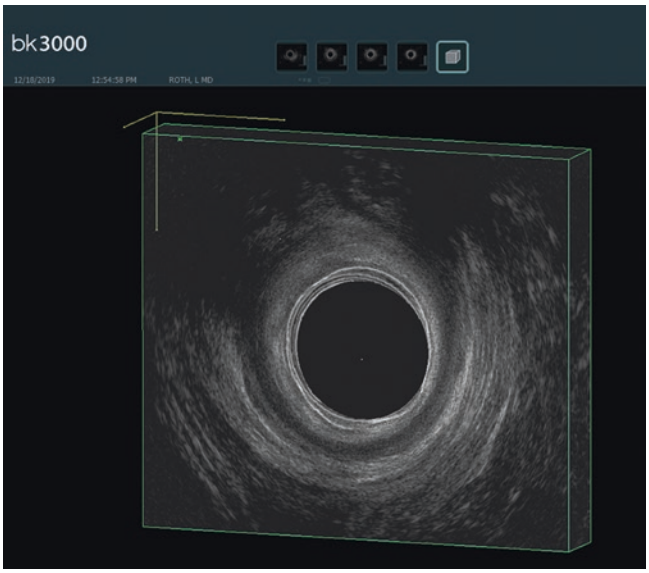

Fig. 57.6 Ultrasound image of upper anal canal

Looking at the sphincter complex, the average thickness of the internal anal sphincter in nulliparous women less than 30 years was 4.5 +/−0.7 mm vs. women over 50 5.9+/−1 mm. Older women have a 33% thicker internal anal sphincter [108]. The external anal sphincter in Nulliparous women is thicker posteriorly 24.7+/− 4.6 mm than anteriorly 6.6+/−1.7 mm [109].

MRI

Static MRI of the anal sphincter complex with or without an endoanal coil has fallen out of favor. It is expensive when compared to anal ultrasound and anal ultrasound. In a prospective study looking at patients with fecal incontinence for selection of surgical intervention, both endoanal MRI and anal ultrasound are sensitive tools and can be used to depict surgically repairable anterior external anal sphincter defects [110]. With the advancement of MR defecography, there is a limited role for static MRI.

Dynamic Imaging of the Pelvic Floor

Functional imaging of the pelvic floor has been an important step in the management of many pelvic floor disorders as multiple abnormalities can exist. For a long time, defecography was the only option. With the advancement of technology, MR defecography and dynamic ultrasound have come into play. We will look at the value of each of these as it pertains to colorectal surgery.

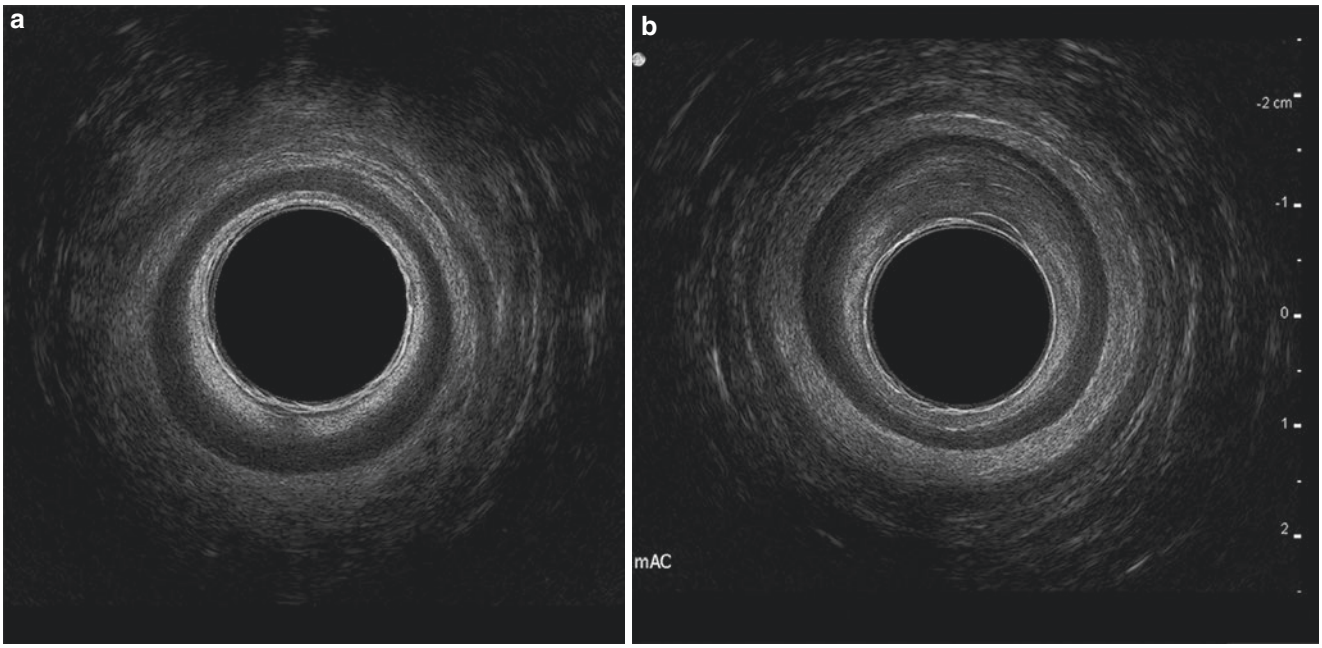

Fig. 57.7 (**a**-**b**) Ultrasound images of mid-anal canal

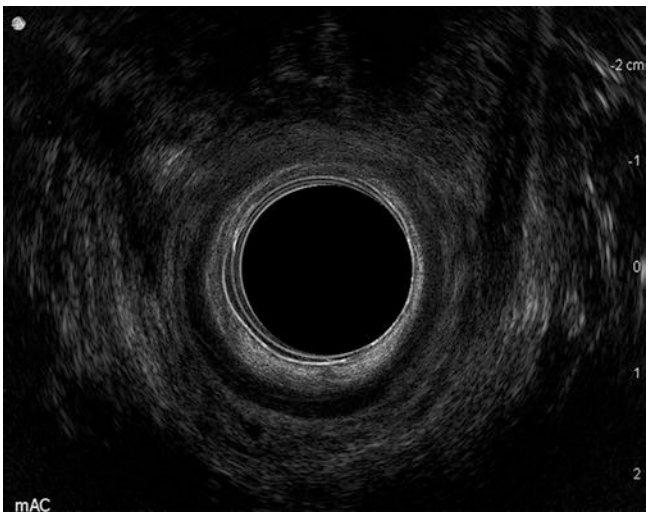

Fig. 57.8 Large anterior sphincter defect in the internal and external anal sphincters

Defecography

Evacuation proctography is the fluoroscopic imaging of defecation. It is a cost-effective procedure with an easy protocol, using standard radiology equipment, and allows the evaluation of the defecation process in the physiological sitting position. Defecography is used mainly to evaluate patients with difficulty in defecation (obstructed defecation) and pelvic organ prolapse (rectal prolapse, enterocele, cystocele). Thickened barium paste to simulate stool is placed in the rectum. Contrast can also be ingested orally to look for an enterocele and placed into the vagina and bladder to evaluate additional pelvic organs [111]. Images are captured on still and cine loop images. Defecography exposes patients to a mean radiation dose of 0.5–5.0 mSv [112, 113].

Normal Evaluation

The initial study in 1984 found five criteria for normal evacuation exist which include (1) increase in anorectal angulation, (2) obliteration of the impression of the puborectalis muscle, (3) wide opening of the anal canal, (4) total evacuation of rectal contents, and (5) normal pelvic floor resistance.

The anorectal angle is measured between the anal canal axis and the posterior rectal wall. There is variability in measuring this angle, as the structures are not fixed, making it somewhat unreliable. The mean value of the anorectal angle at rest was 91.96 degrees and during straining 136.76 degrees, for an increase of 44.8 degrees [114]. Subsequent studies of normal patients have shown a wide range of normal values, and the accepted range of normal for rest is 90–110 degrees and evacuation 110–180 degrees [115, 116]. The pubococcygeal line (line between the pubis and the tip of the coccyx) is the standard definition of the pelvic floor. Definitions of pelvic organ prolapse are based on how far below this line organs descend. Patients are asked during the exam to strain without evacuating contrast to assess pelvic floor descent (Fig. 57.9).

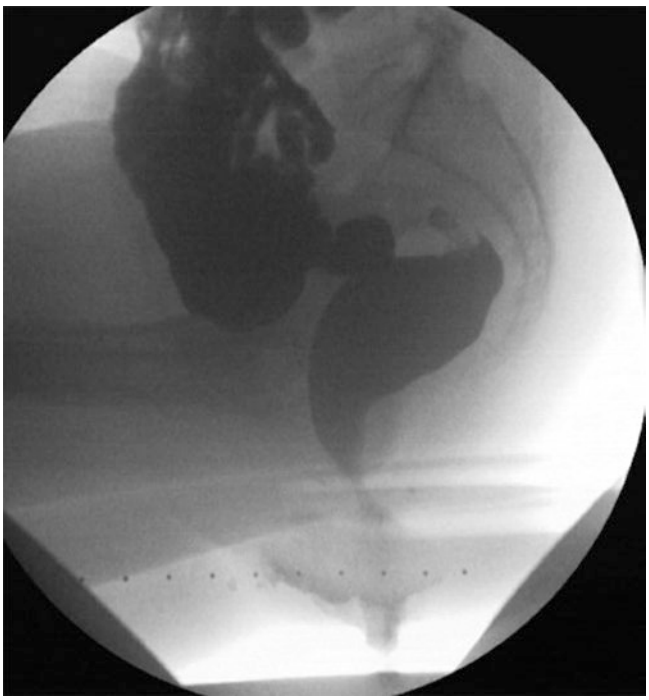

Fig. 57.9 Defecogram image at rest

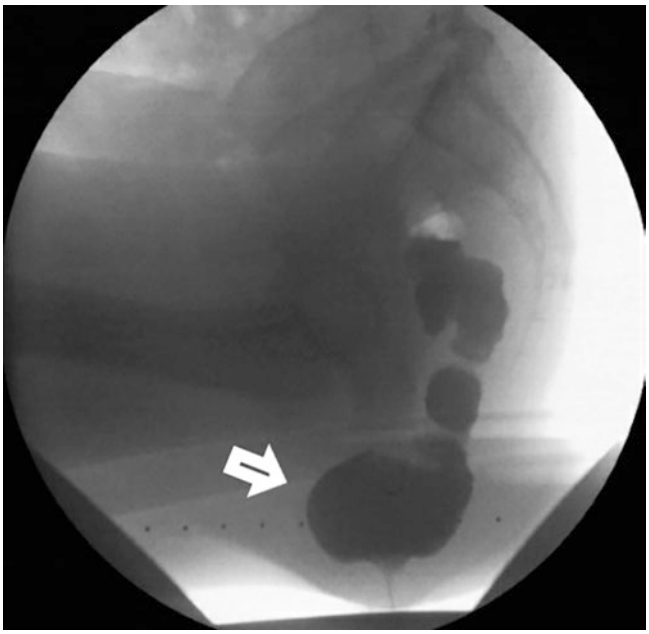

Fig. 57.10 Defecogram with rectocele during evacuation. Arrow points to rectocele

Rectocele

A rectocele is the weakening of the tissues of the rectovaginal septum causing the anterior rectal wall to bulge into the vagina. Rectoceles less than 2–3 cm are normal in female patients and considered insignificant. Rectoceles can be seen in up to 93% of asymptomatic females [115]. The depth of the rectocele can be measured from the anterior border of the anal canal to the most anterior part of the rectocele (Fig. 57.10).

A rectocele is much better defined by defecography than by physical exam. A rectocele does not always interfere with evacuation and should be assessed post-evacuation to determine barium trapping. Large rectoceles must be associated with outlet dysfunction symptoms to be considered pathologic. Digitalization with pressure applied to the posterior vaginal wall or perineum is a common maneuver to help with evacuation of the rectocele [117, 118].

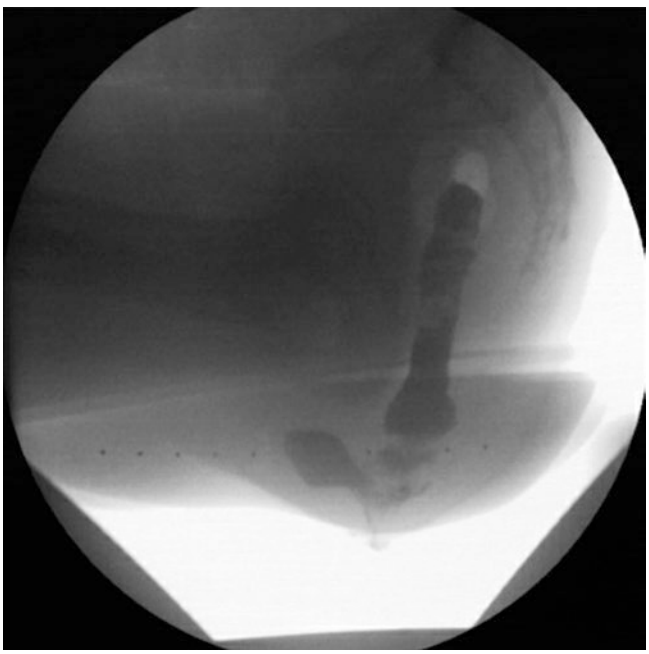

Fig. 57.11 Defecogram with internal prolapse

Intussusception/Prolapse

Occasionally on defecography the rectum can be seen to invaginate on straining. Intussusception is the unilateral or circumferential infolding of the rectum during straining (Fig. 57.11) [119]. Intussusception can be intrarectal, intra-anal, or external (complete rectal prolapse). The Oxford grading for rectal prolapse has five grades: Grades I and II do not descend into the anal canal, Grades III and IV descend into the anal canal but not protruding from the anus, and Grade V protrudes from the anus [113, 119, 120]. In a recent study, it was found that increasing grades of rectal intussusception are associated with increasing fecal incontinence but not constipation [120].

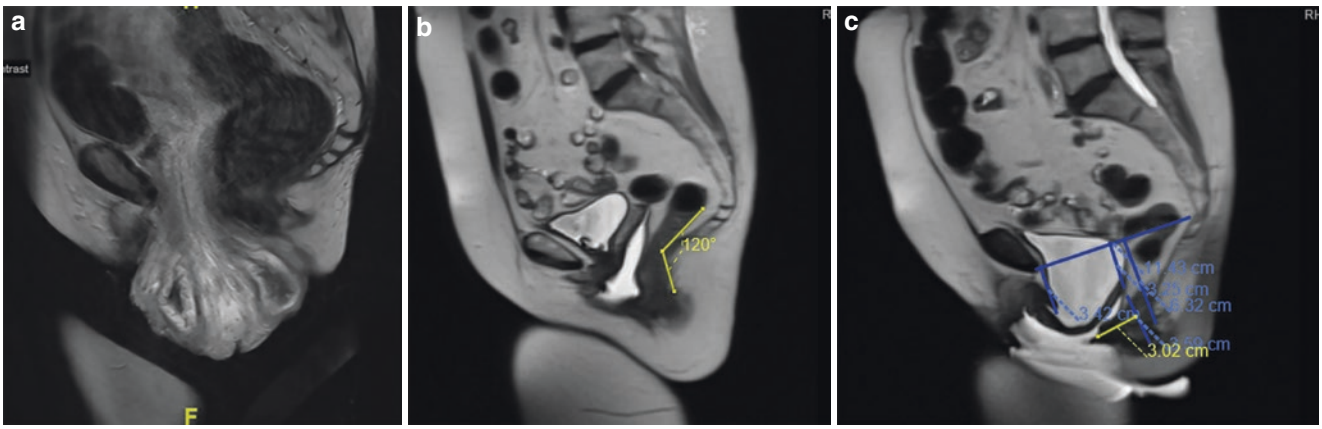

Fig. 57.12 (**a**) Sigmoidocele through vagina on MRI. (**b**) MR defecography at rest (and measurements). (**c**) MR defecography with rectocele (and measurements)

Enterocele/Sigmoidocele

An enterocele is a hernia of the small bowel between the rectum and vagina (pouch of Douglas). It is most common after a hysterectomy [121]. A sigmoidocele is a hernia of the sigmoid colon into the pouch of Douglas. These both are best seen during straining phase of defecography with oral contrast and cause symptoms of obstructed defecation. On normal defecography, bowel should not descend below the upper rectum.

Anismus

Anismus is the failure of normal relaxation of pelvic floor muscles during normal defecation. In a study evaluating the predictive value of impaired evacuation during defecography, it was found that 90% of patients who were unable to evacuate two thirds of a 120-cc contrast enema in 30 seconds had animus confirmed on further physiologic testing [122].

Pelvic Floor Descent

The pelvic floor descends normally during evacuation. This descent is usually less than 3 cm. This is measured by the descent of the anorectal junction during evacuation. Chronic straining and constipation can lead to abnormal descent of more than 3.5 cm. This can lead to hypermobility and stretching of muscles and nerves resulting in functional loss [123].

MR Defecography

MR defecography is similar to traditional defecography in that it takes images during the act of defecation. Before the exam, the vagina and rectum are filled with ultrasound gel. The patient is placed supine with knees slightly bent, and images are obtained during different maneuvers including defecation.

MR defecography allows for comprehensive structural and functional evaluation of the pelvic floor without radiation. The issue arises with the supine position of the patient, as patients do not normally defecate supine (they may find it very difficult) and some symptoms may not occur without the sitting position and gravity. This may limit validity of the findings of MR defecography (Fig. 57.12a–c) [124, 125].

A study from 2016, comparing MR defecography a traditional defecography, looked at 50 females who underwent both tests and compared the results of posterior compartment dysfunction (peritoneocele, rectocele, rectal prolapse, and anismus). In the study, they found no statistical significance in the tests and recommend that both tests can be used based on local availability and expertise. In difficult cases, both imaging modalities can be used to increase accuracy [125].

Dynamic Ultrasound

Defecography and MR defecography both have issues with radiation, cost, and accessibility in rural areas. They also require defecation of contrast material which can be embarrassing for the patient. Dynamic ultrasound removes these issues and has been shown to be a cheap, safe, well-tolerated dynamic assessment of the pelvic floor and allows visualization of anatomical and functional abnormalities and can visualize placement of tape and mesh [126, 127].

Dynamic ultrasound uses three separate probes (transperineal, transvaginal, and endoanal). The patient is given an enema prior to the exam for the endoanal ultrasound. They are positioned on the stretcher in dorsal lithotomy with hips flexed and abducted.

The transperineal portion is completed with a convex transducer positioned on the perineum from the mons pubis

to the anal margin with minimal pressure but maintaining good contact. Imaging is performed with the patient at rest, during maximal Valsalva maneuver and during pelvic floor muscle contraction, and the data is recorded as a cine loop which can be reviewed. This allows visualization of the entire puborectalis muscle and its attachment to the pubic rami. The transvaginal portion is performed in the same position with a biplane probe with a 360-degree rotational mechanical probe with minimal pressure as to not distort anatomy. This allows for imaging of the anterior and posterior compartments at rest, during maximal Valsalva and during pelvic floor muscle contraction. These images are recorded and saved for later review. The endoanal ultrasound uses the same probe as previously discussed in this chapter. The patient's position can be the same as the other tests or can be performed in left lateral decubitus. The images are recorded from the upper aspect of the puborectalis to the anal verge as previously described [127].

Dynamic transperineal ultrasound has been compared to standard defecography and MR defecography for evaluation of obstructed defecation. It has been shown that in experienced hands, dynamic transperineal ultrasound can more effectively diagnose peritoneocele, enterocele, and perineal muscle alterations and provides more information about the anterior and central compartments [128]. Some studies do show a lower detection rate of prolapse in transperineal ultrasound than defecography [129]. The three-dimensional transperineal ultrasound was also compared to two-dimensional endoanal ultrasound to look at anal sphincter defects and was found to have good agreement between the two modalities in detecting injuries [130].

A study looked at the accuracy of dynamic ultrasound (with three probes) compared to MR defecography in detecting rectocele, enterocele, intussusception, and cystocele. They blindly reviewed 68 females who underwent both tests. They found that dynamic ultrasound had a high negative predictive value and may serve as a screening tool for defecatory dysfunction, when normal, MR defecography can be avoided as abnormalities are unlikely [131].

Echodefecography

Echodefecography is a 3D dynamic ultrasound using ultrasound gel in the rectum to assess obstructive defecation. Patients receive an enema and then are examined in the left lateral decubitus position. Scan 1 is at rest without gel and visualized the anatomic integrity of the anal sphincters. Scan 2 is at rest/straining/rest without gel and evaluates muscle relaxation during defecation effort to demonstrate anismus. Scan 3 is at rest/straining/rest with rectal gel. This is repeated up to three times [132].

A prospective multicenter trial compared echodefecography to defecography in patients with obstructive defecation. They evaluated 86 women and found that it clearly demonstrates all the anatomic structures involved in defecation. Echodefecography is able to detect the same anorectal dysfunctions that defecography can detect, is minimally invasive and well tolerated, and avoids radiation [133].

Conclusion

Testing may be indicated for planning treatment in many patients with pelvic floor problems. Understanding how each study is done aids in determining which test(s) to order.

References

1. Perry S, et al. Prevalence of faecal incontinence in adults aged 40 years or more living in the community. Gut. 2002;50:480–4.
2. Ditah I, Devaki P, Luma HN, et al. Prevalence, trends, and risk factors for fecal incontinence in United States adults, 2005–2010. Clin Gastroenterol Hepatol. 2014;12:636–43e1–2.
3. Menees SB, et al. Prevalence of and factors associated with fecal incontinence: results from a population-based survey. Gastroenterology. 2018;154(6):1672–1681 e1673.
4. Higgins PD, Johanson JF. Epidemiology of constipation in North America: a systematic review. Am J Gastroenterol. 2004;99(4):750–9.
5. Milsom I, Altman D, Herbison P, Lapitan MC, Nelson R, Sillén U, et al. Epidemiology of urinary (UI) and faecal (FI) Incontinence and pelvicorgan prolapse (POP). In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence. Paris: Health Publications Ltd; 2009. p. 35–111.
6. Bidmead J, Cardozo LD. Pelvic floor changes in the older woman. Br J Urol. 1998;82(Suppl. 1):18–25.
7. Gowers WR. The autonomic action of the sphincter ani. Proc R Soc Med (Lond). 1877;26:77–84.
8. Joltrain E, Baufle P, Coope R. Essai de measure de la pression du gros intestin. Bull et Mem Soc Med Hop de Paris. 1919;43:211–9.
9. White JC, Verlot MG, Ehrentheil O. Neurogenic disturbances of the colon and their investigation by the colonmetrogram: a preliminary report. Ann Surg. 1940;112(6):1042–57.
10. Rao S, Azpiroz F, Diamant N, Enck P, Tougas G, Wald A. Minimum standards of anorectal manometry. Neurogastroenterol Motil. 2002;14:553–9.
11. Sun WM, Rao SS. Manometric assessment of anorectal function. Gastroenterol Clin N Am. 2001;30(1):15–32.
12. Scott SM, Gladman MA. Manometric, sensorimotor, and neurophysiologic evaluation of anorectal function. Gastroenterol Clin N Am. 2008;37(3):511–38. vii.
13. Wickramasinghe D, Warusavitarne J. The evolution of anal anometry. Int J Med Med Res. 2018;4:5–7.
14. Hancock BD. Measurement of anal pressure and motility. Gut. 1976;17(8):645–51.
15. Humphries TJ, Castell DO. Pressure profile of esophageal peristalsis in normal humans as measured by direct intraesophageal transducers. Am J Digestive Dis. 1977;222:641–5.
16. Dowdle M. Evaluating a new intrauterine pressure catheter. J Reprod Med. 1997;42:505–13.

17. Pollak JT, Davila GW. A comparison between air-charged versus microtransducer catheter urodynamic evaluation of urethral function. Abstract, AUGS, Oral Poster 48, 2002.
18. Fang JC, Hilden K, Tuteja AK, et al. Comparison of air-coupled balloon esophageal and anorectal manometry catheters with solid-state esophageal manometry and water-perfused anorectal manometry catheters. Dig Dis Sci. 2004;49:1657–63.
19. Robertson EV, Lee YY, Derakshan MH, Wirz AA, Whiting JR, Seenan JP, et al. High-resolution esophageal manometry: addressing thermal drift of the manoscan system. Neurogastroenterol Motil. 2012;24:61–4. e11.
20. Lee YY, Erdogan A, Rao SSC. High resolution and high definition anorectal manometry and pressure topography: diagnostic advance or a new kid on the block? Curr Gastroenterol Rep. 2013;15:360.
21. Clouse RE, Staiano A, Alrakawi A, Haroian L. Application of topographical methods to clinical esophageal manometry. Am J Gastroenterol. 2000;95:2720–30.
22. Olson C. Diagnostic testing for fecal incontinence. Clin Colon Rectal Surg. 2014;27(03):85–90.
23. Liu TT, Chen CL, Yi CH. Anorectal manometry in patients with chronic constipation. Hepato-Gastroenterology. 2008;55(82–3):426–9.
24. Xu C, Zhao R, Conklin JL, et al. Three-dimensional high resolution anorectal manometry in the diagnosis of paradoxical puborectalis contraction syndrome compared to healthy adults: a retrospective study of 79 cases. Eur J Gastroenterol Hepatol. 2014;26(6):621–9.
25. Eckardt VF, Dodt O, Kanzler G, et al. Anorectal function and morphology in patients with sporadic proctalgia fugax. Dis Colon Rectum. 1996;39(7):755–62.
26. Opazo A, Aguirre E, Saldana E, et al. Patterns of impaired anal sphincter activity in patients with anal fissure. Color Dis. 2013;15(4):492–9.
27. Tang YF, Chen JG, An HL, et al. High resolution anorectal manometry in newborns: normative values and diagnostic utility in Hirschsprung's disease. Neurogastroenterol Motil. 2014;26(11):1565–72.
28. Pescatori M, Ayabaca S, Caputo D. Can anal manometry predict anal incontinence after fistulectomy in males? Color Dis. 2004;6(2):97–102.
29. Prohm P, Bönner C. Is manometry essential for surgery of chronic fissure-in-ano? Dis Colon Rectum. 1995;38(7):735–8.
30. Dimitriou N, Shah V, Stark D, Mathew R, Miller AS, Yeung JM. Defecating disorders: a common cause of constipation in women. Womens Health. 2015:485–500.
31. Karmarkar R, Bhide A, Digesu A, Khullar V, Fernando R. Mode of delivery after obstetric anal sphincter injury. Eur J Obstet Gynecol Reprod Biol. 2015;194:7–10.
32. Jelovsek JE, Markland AD, Whitehead WE, et al. Pelvic Floor Disorders Network. Controlling anal incontinence in women by performing anal exercises with biofeedback or loperamide (CAPABLe) trial: design and methods. Contemp Clin Trials. 2015;44:164–74.
33. Ba-Bai-Ke-Re MM, Wen NR, Hu YL, Zhao L, Tuxun T, Husaiyin A, Sailai Y, Abulimiti A, Wang YH, Yang P. Biofeedback-guided pelvic floor exercise therapy for obstructive defecation: an effective alternative. World J Gastroenterol. 2014 Jul 21;20(27):9162–9.
34. Eckardt VF, Schmitt T, Bernhard G. Anal ultra slow waves: a smooth muscle phenomenon associated with dyschesia. Dig Dis Sci. 1997;42(12):2439–45.
35. Pfeifer J, Oliveira L. Anorectal manometry and the rectoanal inhibitory reflex'. In: Wexner SD, Duthie GS, editors. Constipation: etiology, evaluation and management. London: Springer; 2007. p. 71–83.
36. Mellgren AF. Physiologic testing. In: Beck DE, Roberts PL, Saclarides TJ, Senagore AJ, Stamos MJ, Wexner SD, editors. The ASCRS textbook of colon and rectal surgery. New York, NY: Springer; 2011.
37. Coss-Adame E, Nguyen M, Valestin J, Meduri K, Rao SS. Tu2028 evaluation of anorectal function in healthy adults with 3-D high definition manometry (Hdar-3D). Gastroenterology. 2012;142 Suppl 1:S905–6.
38. Lee HJ, Jung KW, Han S, Kim JW, Park SK, Yoon IJ, et al. Normal values for high-resolution anorectal manometry/topography in a healthy Korean population and the effects of gender and body mass index. Neurogastroenterol Motil. 2014;26(4):529–37.
39. Coss-Adame E, Rao SS, Valestin J, Ali-Azamar A, Remes-Troche JM. Accuracy and reproducibility of high-definition anorectal manometry and pressure topography analyses in healthy subjects. Clin Gastroenterol Hepatol. 2015;13(6):1143–50.
40. Noelting J, Ratuapli SK, Bharucha AE, Harvey DM, Ravi K, Zinsmeister AR. Normal values for high-resolution anorectal manometry in healthy women: effects of age and significance of rectoanal gradient. Am J Gastroenterol. 2012;107(10):1530–6.
41. Li Y, Yang X, Xu C, Zhang Y, Zhang X. Normal values and pressure morphology for three-dimensional high-resolution anorectal manometry of asymptomatic adults: a study in 110 subjects. Int J Color Dis. 2013;28(8):1161–8.
42. Lestar B, Penninckx F, Kerremans R. The composition of anal basal pressure. An in vivo and in vitro study in man. Int JColor Dis. 1989;4:118–22.
43. Engel AF, et al. Relationship of symptoms in faecal incontinence to specific sphincter abnormalities. Int J Color Dis. 1995;10:152–5.
44. Vaizey CJ, Kamm MA, Bartram CI. Primary degeneration of the internal anal sphincter as a cause of passive faecal incontinence. Lancet. 1997;349:612–5.
45. Farouk R, et al. Sustained internal sphincter hypertonia in patients with chronic anal fissure. Dis Colon Rectum. 1994;37:424–9.
46. Xynos E, et al. Anal manometry in patients with fissure-in-ano before and after internal sphincterotomy. Int J Color Dis. 1993;8:125–8.
47. Jones OM, et al. Digital rectal examination of sphincter pressures in chronic anal fissure is unreliable. Dis Colon Rectum. 2005;48:349–52.
48. Staller K, et al. Resting anal pressure, not outlet obstruction or transit, predicts healthcare utilization in chronic constipation: a retrospective cohort analysis. Neurogastroenterol Motil. 2015;27:1378–88.
49. Raizada V, Bhargava V, Karsten A, Mittal RK. Functional morphology of anal sphincter complex unveiled by high definition anal manometery and three dimensional ultrasound imaging. Neurogastroenterol Motil. 2011;23(11):1013–9.
50. Carrington E, Scott S, Bharucha A, et al. Advances in the evaluation of anorectal function. Nat Rev Gastroenterol Hepatol. 2018;15:309–23.
51. Chan CLH, Ponsford S, Swash M. The anal reflex elicited by cough and sniff: validation of a neglected clinical sign. J Neurol Neurosurg Psychiatry. 2004;75:1449–51.
52. Azpiroz F, Enck P, Whitehead WE. Anorectal functional testing: review of collective experience. Am J Gastroenterol. 2002;97(2):232–40.
53. Preston DM, Lennard-Jones JE. Anismus in chronic constipation. Dig Dis Sci. 1985;30:413–8.
54. Rao SS, Welcher KD, Leistikow JS. Obstructive defecation: a failure of rectoanal coordination. Am J Gastroenterol. 1998;93:1042–50.
55. Rao SS, Mudipalli RS, Stessman M, et al. Investigation of the utility of colorectal function tests and Rome II criteria in dyssynergic defecation (Anismus). Neurogastroenterol Motil. 2004;16:589–96.

56. Ratuapli S, Bharucha AE, Noelting J, Harvey D, Zinsmeister AR. Phenotypic identification and classification of functional defecatory disorders using high-resolution anorectal manometry. Gastroenterology. 2013;144:314–22. e2.
57. Chiarioni G, Nardo A, Vantini I, Romito A, Whitehead W. Biofeedback is superior to electrogalvanic stimulation and massage for treatment of levator ani syndrome. Gastroenterology. 2010;138:1321–9.
58. Grossi U, Carrington EV, Bharucha AE, Horrocks EJ, Scott SM, Knowles CH. Diagnostic accuracy study of anorectal manometry for diagnosis of dyssynergic defecation. Gut. 2016;65:447–55.
59. Rao SS, Kavlock R, Rao S. Influence of body position and stool characteristics on defecation in humans. Am J Gastroenterol. 2006;101:2790–6.
60. Rao SS, Hatfield R, Soffer E, Rao S, Beaty J, Conklin JL. Manometric tests of anorectal function in healthy adults. Am J Gastroenterol. 1999;94:773–83.
61. de Lorijn F, Kremer LC, Reitsma JB, Benninga MA. Diagnostic tests in Hirschsprung disease: a systematic review. J Pediatr Gastroenterol Nutr. 2006;42(5):496–505.
62. Faussone-Pellegrini MS, Fociani P, Buffa R, Basilisco G. Loss of interstitial cells and a fibromuscular layer on the luminal side of the colonic circular muscle presenting as megacolon in an adult patient. Gut. 1999;45(5):775–9.
63. Basilisco G, Gebbia C, Peracchi M, Velio P, Conte D, Bresolin N, et al. Cerebellar degeneration and hearing loss in a patient with idiopathic myenteric ganglionitis. Eur J Gastroenterol Hepatol. 2005;17(4):449–52.
64. Bharucha AE, et al. Relationship between symptoms and disordered continence mechanisms in women with idiopathic faecal incontinence. Gut. 2005;54:546–55.
65. Sun WM, Donnelly TC, Read NW. Utility of a combined test of anorectal manometry, electromyography, and sensation in determining the mechanism of 'idiopathic' faecal incontinence. Gut. 1992;33:807–13.
66. Gladman MA, et al. Rectal hyposensitivity. Am J Gastroenterol. 2006;101:1140–51.
67. Chan CL, et al. Rectal hypersensitivity worsens stool frequency, urgency, and lifestyle in patients with urge fecal incontinence. Dis Colon Rectum. 2005;48:134–40.
68. Simren M, et al. Visceral hypersensitivity is associated with GI symptom severity in functional GI disorders: consistent findings from five different patient cohorts. Gut. 2018;67:255–62.
69. Rao GN, et al. Anterior resection syndrome is secondary to sympathetic denervation. Int J Color Dis. 1996;11:250–8.
70. Houghton LA, et al. Visceral sensation and emotion:a study using hypnosis. Gut. 2002;51:701–4.
71. Houghton LA, et al. Effect of a second-generation α2 δ ligand (pregabalin) on visceral sensation in hypersensitive patients with irritable bowel syndrome. Gut. 2007;56:1218–25.
72. Algladi T, et al. Modulation of human visceral sensitivity by non-invasive magnetoelectrical neural stimulation in health and irritable bowel syndrome. Pain. 2015;156:1348–56.
73. Rhee PL, et al. An increased rectal maximum tolerable volume and long anal canal are associated with poor short-term response to biofeedback therapy for patients with anismus with decreased bowel frequency and normal colonic transit time. Dis Colon Rectum. 2000;43:1405–11.
74. Knowles CH, Scott M, Lunniss PJ. Outcome of colectomy for slow transit constipation. Ann Surg. 1999;230:627–38.
75. Knowles CH, et al. Prospective randomized double-blind study of temporary sacral nerve stimulation in patients with rectal evacuatory dysfunction and rectal hyposensitivity. Ann Surg. 2012;255:643–9.
76. Remes-Troche JM, Rao SS. Diagnostic testing in patients with chronic constipation. Curr Gastroenterol Rep. 2006;8:416–24.
77. Rao SS, Ozturk R, Laine L. Clinical utility of diagnostic tests for constipation in adults: a systematic review. Am J Gastroenterol. 2005;100:1605–15.
78. Chiarioni G, Kim SM, Vantini I, Whitehead WE. Validation of the balloon evacuation test: reproducibility and agreement with findings from anorectal manometry and electromyography. Clin Gastroenterol Hepatol. 2014;12:2049–54.
79. Kahrilas PJ, Bredenoord AJ, Fox M, et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil. 2015;27(2):160–74. https://doi.org/10.1111/nmo.12477.
80. Carrington EV, Heinrich H, Knowles CH, et al. The international anorectal physiology working group (IAPWG) recommendations: standardized testing protocol and the London classification for disorders of anorectal function. Neurogastroenterol Motil. 2020;32(1):e13679.
81. Benezech A, Cappiello M, Baumstarck K, Grimaud JC, Bouvier M, Vitton V. Rectal intussusception: can high resolution three-dimensional ano-rectal manometry compete with conventional defecography? Neurogastroenterol Motil. 2017;29(4):e12978.
82. Lefaucheur JP. Neurophysiological testing in anorectal disorders. Muscle Nerve. 2006;33:324–33.
83. Law PJ, Kamm MA, Bartram CI. A comparison between electromyography and anal endosonography in mapping external anal sphincter defects. Dis Colon Rectum. 1990;33:370–3.
84. Merletti R, Bottin A, Cescon C, et al. Multichannel surface EMG for the non-invasive assessment of the anal sphincter muscle. Digestion. 2004;69(2):112–22.
85. Sørensen M, Tetzschner T, Rasmussen OO, Christiansen J. Relation between electromyography and anal manometry of the external anal sphincter. Gut. 1991;32(9):1031–4.
86. Enck P, Van der Voort IR, Klosterhalfen S. Biofeedback therapy in fecal incontinence and constipation. Neurogastroenterol Motil. 2009;21(11):1133–41.
87. Wexner SD, Cheape JD, Jorge JM, Heymen S, Jagelman DG. Prospective assessment of biofeedback for the treatment of paradoxical puborectalis contraction. Dis Colon Rectum. 1992;35(2):145–50.
88. Snooks S, et al. Effect of vaginal delivery on the pelvic floor: a 5-year follow-up. Br J Surg. 1990;77:1358–60.
89. Parks A, Swash M, Urich H. Sphincter denervation in anorectal incontinence and rectal prolapse. Gut. 1977;18:656–65.
90. Rogers J, Henry M, Misiewicz J. Disposable pudendal nerve stimulator: evaluation of the standard instrument and new device. Gut. 1988;29:1131–3.
91. Olsen AL, Rao SS. Clinical neurophysiology and electrodiagnostic testing of the pelvic floor. Gastroenterol Clin North Amer. 2001;30:33–54.
92. Diamant NE, et al. AGA technical review on anorectal testing techniques. Gastroenterology. 1999;116:735–60.
93. Thomas C, et al. Respective value of pudendal nerve terminal motor latency and anal sphincter electromyography in neurogenic fecal incontinence. Neurophysiol Clin. 2002;32:85–90.
94. Cheong DM, et al. Electrodiagnostic evaluation of fecal incontinence. Muscle Nerve. 1995;18:612–9.
95. Lacima G, et al. Is electromyography a predictive test of patient response to biofeedback in the treatment of fecal incontinence? Neurourol Urodynam. 2016;35:390–4.
96. Goetz LH, Lowry AC. Overlapping sphincteroplasty: is it the standard of care? Clin Colon Rectal Surg. 2005;18(1):22–31.
97. Weledji EP. Electrophysiological basis of fecal incontinence and its implications for treatment. Ann Coloproctol. 2017;33(5):161–8.
98. Snooks SJ, Swash M, Henry MM. Abnormalities in central and peripheral nerve conduction in patients with anorectal incontinence. J R Soc Med. 1985;78:294–300.

99. Setti Carraro P, Kamm MA, Nicholls RJ. Long-term results of postanal repair for neurogenic faecal incontinence. Br J Surg. 1994;81:140–4.
100. Tantiphlachiva K, Attaluri A, Valestin J, Yamada T, Rao SS. Translumbar and transsacral motor-evoked potentials: a novel test for spino-anorectal neuropathy in spinal cord injury. Am J Gastroenterol. 2011;106:907–14.
101. Rao SS, et al. Translumbar and transsacral magnetic neurostimulation for the assessment of neuropathy in fecal incontinence. Dis Colon Rectum. 2014;57:645–52.
102. Abdool Z, Sultan AH, Thakar R. Ultrasound imaging of the anal sphincter complex: a review. Br J Radiol. 2012;85(1015):865–75.
103. Burenett SJ, Speakman CT, Kamm MA, Bartram CI. Confirmation of endosonographic detection of external anal sphincter defects by simultaneous electromyographic mapping. Br J Surg. 1991;78(4):448–50.
104. Christensen AF, Nyhuus B, Nielsen MB, Christensen H. Three-dimensional anal endosonography may improve diagnostic confidence of detecting damage to the anal sphincter complex. Br J Radiol. 2005;78(928):308–11.
105. Thakar R, Sultan AH. Anal endosonography and its role in assessing the incontinent patient. Best Pract Res Clin Obstet Gynaecol. 2004;18(1):157–73.
106. Asfour V, Digesu GA, Fernando R, Khullar V. Ultrasound imaging of the perineal body: a useful clinical tool. Int Urogynecol J. 2020;31:1197–202.
107. Zetterstrom JP, Mellgren A, Madoff RD, Kim DG, et al. Perineal body measurement improves evaluation of anterior sphincter lesions during endoanal ultrasonography. Dis Colon Rectum. 1998;41(6):705–13.
108. Huebner M, Margulies RU, Fenner DE, Ashton-Miller JA, et al. Age effects on internal anal sphincter thickness and diameter in nulliparous females. Dis Colon Rectum. 2007;50(9):1405–11.
109. Fenner DE, Kriegshauser JS, Lee HH, Beart RW, et al. Anatomic and physiologic measurements of the internal and external anal sphincters in normal females. Obstet Gynecol. 1998;91(3):369–74.
110. Dobben AC, Terra MP, Slors JF, Deutekom M, et al. External anal sphincter defects in patients with fecal incontinence: comparison of endoanal MR imaging and endoanal US. Radiology. 2007;242(2):463–71.
111. Iacobellis F, Reginelli A, Berritto D, Gagliardi G, et al. Pelvic floor dysfunctions: how to image patients? Jpn J Radiol. 2020;38(1):47–63.
112. Goei R, Kemerink G. Radiation dose in defecography. Radiology. 1990;176(1):137–9.
113. Grossi U, Di Tanna GL, Heinrich H, Taylor SA, et al. Systematic review with meta-analysis: defecography should be a first-line diagnostic modality in patients with refractory constipation. Aliment Pharmacol Ther. 2018;48(11–12):1186–201.
114. Mahieu P, Pringot J, Bodart P. Defecography: I. Description of a new procedure and results in normal patients. Gastrointest Radiol. 1984;9(3):247–51.
115. Palit S, Bhan C, Lunniss PJ, Boyle DJ, et al. Evacuation proctography: a reappraisal of normal variability. Color Dis. 2014;16(7):538–46.
116. Bartram CI, Turnbull GK, Lennard-Jones JE. Evacuation proctography: an investigation of rectal expulsion in 20 subjects without defecatory disturbance. Gastrointest Radiol. 1988;13(1):72–80.
117. Greenberg T, Kelvin FM, Maglinte DD. Barium trapping in rectoceles: are we trapped by the wrong definition? Abdom Imaging. 2001;26(6):587–90.
118. Halligan S, Bartram CI. Is barium trapping in rectoceles significant? Dis Colon Rectum. 1995;38(7):764–8.
119. Mahieu P, Pringot J, Bodart P. Defecography: II. Contribution to the diagnosis of defecation disorders. Gastrointest Radiol. 1984;9(3):253–61.
120. Hawkins AT, Olariu AG, Savitt LR, Gingipally S, et al. Impact of rising grades of internal rectal intussusception on fecal continence and symptoms of constipation. Dis Colon Rectum. 2016;59(1):54–61.
121. Holley RL. Enterocele: a review. Obstet Gynecol Surv. 1994;49(4):284–93.
122. Halligan S, Malouf A, Bartram CI, Marshall M, et al. Predictive value of impaired evacuation at proctography in diagnosing anismus. AJR Am J Roentgenol. 2001;177(3):633–6.
123. Chaudry Z, Tarnay C. Descending perineum syndrome: a review of the presentation, diagnosis, and management. Int Urogynecol J. 2016;27(8):1149–56.
124. Ribas Y, Hotouras A, Chan CL, Clave P. Imaging of pelvic floor disorders: are we underestimating gravity? Dis Colon Rectum. 2014;57(10):1242–4.
125. Poncelet E, Rock A, Quinton JF, Cosson M, et al. Dynamic MR defecography of the posterior compartment: comparison with conventional X-ray defecography. Diagn Interv Imaging. 2017;98(4):327–32.
126. Hainsworth AJ, Solanki D, Hamad A, Morris SJ, et al. Integrated total pelvic floor ultrasound in pelvic floor defaecatory dysfunction. Color Dis. 2017;19(1):O54–o65.
127. Santoro GA, Wieczorek AP, Dietz HP, Mellgren A, et al. State of the art: an integrated approach to pelvic floor ultrasonography. Ultrasound Obstet Gynecol. 2011;37(4):381–96.
128. Martelluci J, Brusciano L. The dynamic transperineal ultrasound era of the evaluation of obstructed defecation syndrome. Dis Colon Rectum. 2016;59(8):800–3.
129. Perniola G, Shek C, Chong CC, Chew S, et al. Defecation proctography and translabial ultrasound in the investigation of defecatory disorders. Ultrasound Obstet Gynecol. 2008;31(5):567–71.
130. Oom DM, West RL, Schouten WR, Steensma AB. Detection of anal sphincter defects in female patients with fecal incontinence: a comparison of 3-dimensional transperineal ultrasound and 2-dimensional endoanal ultrasound. Dis Colon Rectum. 2012;55(6):646–52.
131. Hainsworth AJ, Pilkington SA, Grierson C, Rutherford E, et al. Accuracy of integrated total pelvic floor ultrasound compared to defaecatory MRI in females with pelvic floor defaecatory dysfunction. Br J Radiol. 2016;89(1068):20160522.
132. Murad-Regadas SM, Regadas FS, Rodrigues LV, Silva FR, et al. A novel three-dimensional dynamic anorectal ultrasonography technique (echodefecography) to assess obstructed defecation, a comparison with defecography. Surg Endosc. 2008;22(4):974–9.
133. Regadas FS, Haas EM, Abbas MA, Marcio Jorge J, et al. Prospective multicenter trial comparing echodefecography with defecography in the assessment of anorectal dysfunction in patients with obstructed defecation. Dis Colon Rectum. 2011;54(6):686–92.

Evaluation of Constipation and Treatment of Abdominal Component

58

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Key Concepts

- There are different subtypes of constipation requiring a careful history and selective diagnostic testing to elucidate.
- Most treatment algorithms of constipation begin with medical management.
- Abdominal constipation severely affecting quality of life may require surgical intervention.

Introduction

Constipation is a complex disorder. It is difficult to estimate its actual prevalence due to the different ways it has been defined or reported and the fact that many symptomatic people may not seek diagnostic testing or treatment. Chronic constipation has been estimated to affect approximately 15–20% of people in North America [1–3]. It is one of the most frequent gastrointestinal diagnoses made in outpatient clinics and is a common cause for referrals to gastroenterologists and colorectal surgeons. It accounted for approximately eight million annual visits to physicians in the United States between 2001 and 2004 [4]. A recent community healthy survey estimated the total direct health-care costs for patients with constipation were about $19 million per year [5].

Definition

In general, constipation has been defined as infrequent bowel movements; however, other symptoms such as excessive straining, hard or lumpy stools, a sense of incomplete evacuation or anorectal blockage, and the use of manual maneuvers to facilitate evacuation may be equally significant and maybe even more common [1, 6]. Symptoms that last less than a week are considered acute, whereas chronic constipation is defined by symptoms that persist for at least 3 months [7]. It is important to differentiate chronic constipation from other forms of functional bowel disorders. The Rome IV criteria categorizes disorders of chronic constipation into four subtypes: (a) functional constipation, (b) irritable bowel syndrome with constipation (IBS-c), (c) opioid-induced constipation, and (d) functional defecation disorders including inadequate defecatory propulsion and dyssynergic defecation (Table 58.1). If individuals have symptoms of chronic constipation for the last 3 months (with onset at least 6 months prior) and no organic gastrointestinal pathology, they can be categorized according to the Rome IV criteria [7, 8].

Etiology and Pathophysiology

Defecation relies on the formation of stool, motor function of the colon, and the muscles of the pelvic floor. Chronic constipation can be a primary disorder resulting from interruption at any portion of this pathway and can be categorized as normal transit constipation, slow transit constipation, and defecatory disorders. Slow transit constipation reflects colonic motor dysfunction, although it can also result from inadequate caloric intake [9]. Constipation can also be a secondary disorder due to diet, medications, endocrine disorders, or anatomic, neurologic, or psychosocial disease (Table 58.2). Patients can have a combination of both slow transit and defecatory dysfunction that may both need to be addressed.

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Table 58.1 Rome IV criteria: constipation

Rome IV constipation subtype	Characteristics
Irritable bowel syndrome with constipation (IBS-C)	Predominant stool abnormality on days when they have abnormal stools is constipation (at least 25% of all stools Bristol types 1 and 2 and less than 25% types 6 and 7) Abdominal pain at least 1 day per week, where the pain is associated with at least two of the following: 1. Change in stool frequency – toward infrequent bowel movements 2. Change in stool form – toward harder stools 3. Related to defecation
Functional constipation (FC)	These patients do not fulfill the criteria for IBS Abdominal pain is absent or not predominant or occurs less than 1 day per week Must include two or more of the following: 1. Straining more than 25% of defecations 2. Lumpy or hard stools (Bristol stool type 1 or 2) more than 25% of defecation 3. Sensation of incomplete evacuation more than 25% of defecations 4. Sensation of anorectal obstruction/ blockage more than 25% of defecations 5. Manual maneuvers (digital assistance, support of pelvic floor) to facilitate more than 25% of defecations 6. Fewer than three spontaneous bowel movements per week
Opioid-induced constipation (OIC)	Diagnostic criteria similar to FC, but with the requirement that new or worsening symptoms of constipation occurred when initiating, changing, or increasing opioid therapy
Function defecation disorders (inadequate propulsion and dyssynergic defecation)	These patients must satisfy the criteria for IBS-C or FC but also demonstrate features of impaired rectal evacuation as demonstrated by two of the following three tests: 1. Abnormal balloon expulsion test 2. Abnormal anorectal evacuation pattern with anorectal manometry (or surface electromyography (EMG)) 3. Impaired rectal evacuation on defecography, but without structural lesions

Adapted from Lacy et al. [7]

Table 58.2 Factors associated with constipation

Medications (examples)	Opioids Anticholinergic agents Tricyclic antidepressants Calcium channel blockers Diuretics Bile acid sequestrants Calcium Iron
Mechanical	Colon cancer External compression Ischemic or diverticular strictures Endometriosis Inflammatory bowel disease Hirschsprung's disease Pseudo-obstruction
Metabolic	Diabetes mellitus Hypothyroidism Hypercalcemia Hypokalemia Hypomagnesemia Uremia Heavy metal poisoning
Myopathies	Amyloidosis Scleroderma
Neuropathies	Parkinson's disease Spinal cord injury or tumor Multiple sclerosis
Psychiatric	Depression Psychiatric illness Sexual abuse Eating disorder
Pelvic floor	Anal fissure Non-relaxing puborectalis Anal stenosis Pelvic organ prolapse
Other conditions	Degenerative joint disease Scleroderma Autonomic neuropathy Cognitive impairment Immobility Cardiac disease

Adapted from Bharucha et al. [10]

History and Physical

As with any patient, evaluation should begin with a thorough history and physical examination. When taking a history, it is important to understand what the patient means when reporting constipation. The history should include the duration of symptoms, frequency, and consistency of stools which can be aided by using the Bristol Stool Chart (refer to Fig. 56.2), the presence of excessive straining, feelings of incomplete evacuation, or need to use manual maneuvers in order to defecate. It is important also to obtain information on prior bowel habits, when bowel habits change, if a trigger can be identified, and what patients consider as normal. One should also be wary of identifying "alarm symptoms" such as sudden changes in bowel habits, unexpected weight loss, a family history of colon cancer, and rectal bleeding in the absence of bleeding hemorrhoids or fissure [10]. It should be noted if the patient has had a previous colonoscopy. A detailed medical and surgical history should be taken to exclude other organic causes as well as a complete medication list including over-the-counter medications, herbal supplements, and vitamins.

Physical examination should focus on the abdomen and the pelvic floor. Abdominal exam may be unremarkable but may also be significant for bloating and distention and should exclude any palpable masses. Anorectal and pelvic floor exam can be conducted in the prone position, left lateral position, and/or over the commode to exclude pelvic organ prolapse. On external anal exam, one can look for fissures, prolapsing internal hemorrhoids or engorged or inflamed external hemorrhoids, or evidence of full-thickness rectal prolapse. Digital rectal exam should focus on the presence of tenderness or palpable abnormalities such as a mass, stricture, impaction or rectocele, length of the anal canal, anal resting and squeeze tone, and ability to relax the pelvic floor muscles with straining. Anoscopy or rigid or flexible proctosigmoidoscopy can be performed in the office to look for any inflammation or other mucosal abnormalities such as solitary rectal ulcer.

Diagnostic Testing

A complete blood count (CBC) to look for anemia should be obtained if not recently performed. Thyroid-stimulating hormone and serum calcium should be performed when clinically indicated. Colonoscopy should be performed in patients with alarm symptoms or as required for age-appropriate screening [7, 11].

Testing for slow transit constipation or dyssynergic defecation is not justified in all patients presenting with constipation. Testing should be performed on a case-by-case basis and in general on patients who have not responded to trials of empiric therapy. In addition, providers may consider tailoring their workup based on patient's symptoms. If there is a suspicion for motility issues due to predominance of abdominal symptoms such as bloating and need to use large volumes of laxatives to have a bowel movement, one may choose to start with transit studies. In contrast, for patients with symptoms of outlet obstruction—the need to strain or use digital maneuvers—one may consider starting with manometry and defecography studies.

There are three techniques for assessing colonic transit: radiopaque markers, scintigraphy, and a colonic pH-pressure capsule. The simplest and most inexpensive method is using radiopaque markers. Patients ingest a gelatin capsule that contains radiopaque markers. Abdominal X-rays are then used to count the number of ingested markers in the abdomen. There is no standard way to perform this test, and there are different methods involving ingesting more than one capsule or getting one or more X-rays. In general, if a patient swallows one capsule and more than five (20%) of the markers are retained by day 5, slow transit constipation is diagnosed (Fig. 58.1) [12]. This is a reliable method; however, the number of retained markers has not been shown to correlate with symptom severity or quality of life (QOL) [13]. In addition, it is suggested that if markers are clustered at the rectosigmoid, this is suspicious for dyssynergic defecation. However, this has been challenged by several studies [14, 15]. Less widely used approaches are radionuclide gamma scintigraphy and wireless pH-pressure capsule. Scintigraphy tracks radioisotope movement from cecal instillation to defecation [12]. The wireless pH-pressure capsule determines when the capsule empties into the small intestine and thereafter into the colon by measuring pH. The SmartPill™ capsule also measures colonic motor activity which may be useful for discriminating among subtypes of chronic constipation. Motor activity may be greater in IBS or "painful" constipation than slow transit or "painless" constipation [16]. The benefit of these studies is that they can both also measure gastric emptying and small intestinal transit. Colonic scintigraphy is measured over 24–48 hours as opposed to 5–7 days for the radiopaque marker test which is beneficial for patients who cannot be off laxatives for a long time [17]. A large study comparing scintigraphy with the pH-pressure capsule and a smaller study comparing scintigraphy with radiopaque markers observed greater than 80% agreement between these techniques for discriminating between normal and slow colonic transit [18, 19]. Colonic manometry is another method that has been considered a standard diagnostic examination in pediatric patients. This study evaluates the intraluminal pressure activity of the colon and rectum by inserting a manometry catheter into the ileocecal junction through the anus. This test is invasive and not widely avail-

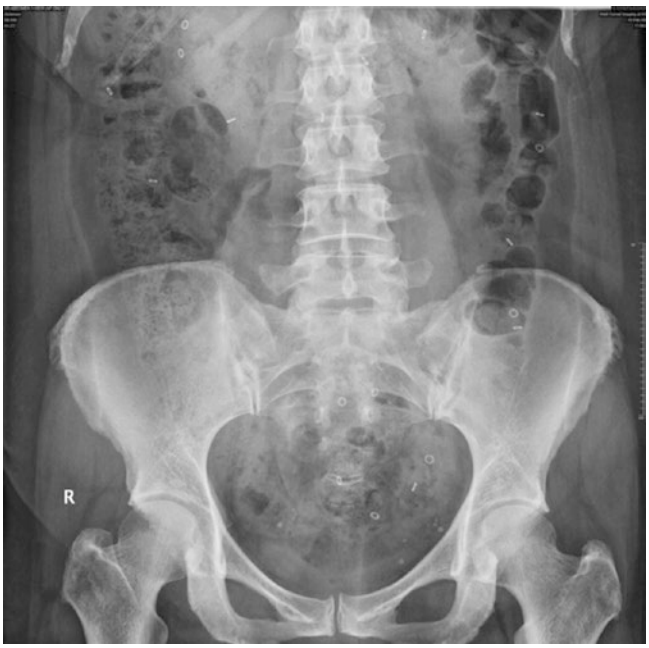

Fig. 58.1 Sitz marker study showing markers scattered throughout colon, consistent with abdominal constipation (slow transit constipation)

able, but it has been shown to help choose patients that would benefit from surgery by helping to distinguish between colonic neuropathy and myopathy [20]. This test may serve as an adjunct to current methods of assessing colonic function.

Pelvic floor function can be assessed by a variety of methods including anorectal manometry, balloon expulsion test, and barium and magnetic resonance imaging (MRI) defecography. Anorectal manometry provides a comprehensive assessment of the pressure activity in the rectum and anal sphincter region together with an assessment of rectal sensation, rectoanal reflexes, and rectal compliance. This can be used in combination with the balloon expulsion test to detect abnormalities during attempted defecation. Defecography provides information about anatomical and functional changes of the anus and rectum during defecation. This can be done seated on a commode with barium paste instilled in the rectum (also may be instilled in the vagina or orally) or in the supine position with MRI. Barium defecography or cine defecography has the advantage of simulating defecation in the normal posture; however, the techniques are incompletely standardized. There is limited reproducibility of the anorectal angle measurement; however, the significance of the anorectal angle is not always straightforward [21, 22]. In contrast, MRI defecography is performed in the supine position which is not the traditional position for evacuation; however, it is better for visualizing pelvic organ prolapse and bony landmarks which are necessary to measure pelvic floor motion [23]. These tests can be used alone or in conjunction to facilitate diagnosis of defecatory disorders.

Medical Management

Treatment should start by educating the patient and eliminating secondary causes of constipation. Once this is done, behavioral modification is one of the first steps in treatment. This includes increasing dietary fiber or considering the addition of a fiber supplement, increasing fluid intake, advising regular exercise, and allowing adequate time for bowel movements. A high-fiber diet increases stool weight and accelerates colonic transit time. Fiber supplements are divided into insoluble and soluble. Insoluble, non-fermentable fiber accelerates transit by increasing stool mass leading to direct stimulation of secretion and motility. Soluble, more fermentable fiber accelerates transit by hydrophilic properties and the osmotic effects of fermentation byproducts. A total of 20–30 grams per day of fiber is recommended, although bloating, distention, and flatulence can affect compliance. Patients with slow transit constipation and pelvic floor dysfunction are less likely to improve with fiber; therefore, fiber may not be a solution for all patients [10, 24, 25]. Although common sense supports increasing fluid intake, in a small study of healthy volunteers, consumption of extra fluid produced no difference in stool output [26]. Similarly, there is little evidence to support the role of exercise in improving constipation, but epidemiologic studies suggest that sedentary people are three times more likely to report constipation [27]. In addition, a recent meta-analysis of nine randomized controlled trials concluded that the real effect of exercise on constipation could not be definitely determined [28].

Laxatives are still commonly used as first-line therapy for constipation as they are cheap and readily available over the counter. Docusate sodium decreases the surface tension at the stool oil-water interface, allowing water to penetrate the stool. Although it is often recommended, there is limited data to support its use. In a double-blind, randomized, controlled trial of 170 patients with constipation, 100 mg of docusate sodium twice a day was less effective than psyllium [29]. Osmotic laxatives include polyethylene glycol (PEG)-based solutions, magnesium citrate-based products, sodium phosphate-based products, and non-absorbable carbohydrates (lactulose). These products work based on their hypertonicity by extracting fluid into the intestinal lumen to soften stools and accelerate colon transit. Side effects include dose-dependent abdominal cramping and bloating. A Cochrane review of ten randomized controlled trials concluded that PEG was superior to lactulose for improving stool frequency, stool consistency, and abdominal pain [30]. Among non-absorbable carbohydrates, lactulose and sorbitol have similar laxative effects, but lactulose was associated with more nausea in a randomized crossover study [31].

Stimulant laxatives include diphenylmethane derivatives such as bisacodyl and sodium picosulfate and conjugated anthraquinone derivatives such as cascara sagrada, aloe, and senna. This group of medications works by decreasing water absorption and stimulating intestinal motility and prostaglandin release [32–34]. The use of these laxatives is often limited by abdominal pain and diarrhea. In addition, these laxatives may be underused by physicians because of concerns that they can damage the colon when used long term. There has been concern about the possibility that stimulant laxatives, specifically anthraquinone laxatives, can induce permanent enteric nerve or muscle damage in the colon. This may be due in part to the development of melanosis coli, a brown pigment of the colonic mucosa that can occur within several months of regular use. This pigmentation is related to a substance called lipofuscin which is released during cellular apoptosis and contained in mucosal macrophages. Its functional significance is unknown, and it is completely reversible when laxative use is stopped [35]. There is no evidence to support the belief that stimulant laxatives are permanently harmful to the colon.

Secretagogues or prosecretory agents stimulate the net efflux of ions and water into the intestinal lumen, likely

accelerating transit and facilitating ease of defecation. Prosecretory agents available include lubiprostone which is a chloride-channel activator and linaclotide and plecanatide which are minimally absorbed guanylate cyclase-C agonists. In a 4-week randomized trial, lubiprostone was more effective than placebo in improving bowel symptoms in patients with chronic constipation. Nausea was the most commonly reported side effect [36]. Linaclotide and plecanatide are of similar efficacy and tolerability for treatment of chronic constipation [37]. Diarrhea is the most common adverse side effect which can require discontinuation of treatment in <5% of patients [38, 39]. Tenapanor, which was approved by the Food and Drug Administration in 2019, is a first-in-class, small-molecule inhibitor of the gastrointestinal sodium-hydrogen exchanger-3. This increases intestinal fluid volume and transit. This was shown to be superior to placebo in improving constipation symptoms in phase 2 and 3 studies [40, 41].

Serotonin (5-hydroxytryptamine, 5-HT4) agonists stimulate peristalsis and accelerate gastrointestinal transit. Tegaserod is a highly selective, partial 5-HT4 receptor agonist which was found to be superior to placebo in improving stool frequency and other constipation-associated symptoms in two randomized, double-blind, controlled trials [42, 43]. This medication was then taken off the market in 2007 due to concerns about a high rate of ischemic cardiovascular events inpatients on this medication. In April 2019, after re-examining the data that led to its withdrawal, the FDA approved the use of tegaserod in women younger than 65 years of age who do not have a history of ischemic cardiovascular disease and who have no more than one risk factor for cardiovascular disease [11, 44]. Prucalopride is a dihydrobenzofurancarboxamide derivative with greater selectivity for the 5-HT4 receptor compared with other 5-HT4 agonists [7]. In an integrated analysis of 6 randomized controlled trials, comprising 2484 patients with functional constipation, prucalopride was superior to placebo toward achieving at least 3 spontaneous bowel movements per week [45]. Prucalopride has also been shown to be superior to placebo in patients with opioid-induced constipation [46]. Common side effects include diarrhea and headache which normally disappear within the first week of treatment [6].

Opioid-induced constipation (OIC) is a consequence of the action of opioids on their receptors in the gastrointestinal tract. OIC occurs in 51–87% of patients receiving opioids for cancer and between 41% and 57% of patients receiving opioids for chronic non-cancer pain [47]. The key aspect of managing this subset of patients is early recognition. Initial management can begin with standard laxatives as well as addressing exacerbating factors. For patients who do not respond to a standard laxative regimen, second-line medications which consist of peripherally acting mu-opioid receptor antagonists (PAMORAs) should be considered. PAMORAs (i.e., nalexago, naldemedine, alvimopan, and subcutaneous methylnaltrexone) alleviate the symptoms of OIC by blocking the mu-opioid receptors within the gastrointestinal tract. These medications do not cross the blood-brain barrier, so they maintain central analgesia and minimize withdrawal symptoms. A systematic review and meta-analysis of 27 randomized controlled trials found PAMORAs more effective than placebo for the treatment of OIC. Naloxone and naldemedine were found to be the most efficacious treatments for OIC with naloxone being the safest [48].

Elobixibat is an inhibitor of the ileal bile acid transporter. This medication induces a state of bile acid malabsorption, increasing bile acid in the colon, thereby leading to increased stool frequency and looser stool consistency. In a randomized, double-blind, placebo-controlled, phase 3 trial conducted in Japan, researchers found that elobixibat resolved constipation in the short term and was well tolerated with both short-term and long-term treatments [49]. This drug is currently only approved in Japan for the treatment of chronic constipation.

Surgical Options for Slow Transit Constipation

When a patient presents for surgical consideration of abdominal or slow transit constipation, the ultimate question to consider is whether or not constipation is truly refractory to medical management. Unfortunately, as opposed to other chronic medical conditions, there are no existing standard definitions or algorithms to assist in decision-making whether a patient has reached a medically refractory state. Likewise, there is currently no consensus on which drugs, their dosages, or duration of use that would assist clinicians trying to decide if surgical management should be recommended [50]. It is therefore not surprising that as a result of the functionality of the disease process and the nature of surgical retrospective studies, some have advocated for a very cautious surgical approach or even none at all [51, 52]. Nevertheless, the number of colectomies for constipation has marginally increased in the United States during the early 2000s according to a Nationwide Inpatient Sample study [53]. Therefore, it is important for the gastroenterologist and surgeon to work together planning an individualized treatment approach, particularly if surgery is contemplated.

Abdominal Colectomy

The simple rationale behind abdominal colectomy with ileorectal anastomosis is to decrease the colonic transit time of stool resulting in more liquid contents delivered to the rec-

tum. This leads to easier evacuation and a noticeable increase in stool frequency. Since the first reports of colectomy for constipation over 100 years ago, retrospective surgical series have attempted to identify which subset of patients may benefit from surgery. The first step in proper selection is identification of constipation. As previously mentioned earlier in this chapter, typically this is done via a colonic transit study. As mentioned above, it cannot be surmised that a more abnormal transit study equates to worsening constipation or in turn improved outcomes following colectomy. Indeed, a study of 159 patients after colonic transit study found no correlation between location or number of retained markers and symptom severity [54]. Symptomatology does not show direct correlation with transit times, nor does success after surgery [55, 56]. Transit studies may also be limited by their reproducibility. In a study of 51 patients with chronic constipation in which two separate transit studies were performed, 31% had disparate findings on their second study [15]. When translated into surgical results, those with two abnormal tests that confirmed slow transit constipation were significantly more likely to have a successful outcome following surgery. Colonic transit studies should therefore be utilized mostly to identify those with normal transit and not as a marker of those who would most likely succeed after surgery.

Selecting patients for abdominal colectomy should also include an evaluation for any concomitant pelvic floor dysfunction. Some authors have suggested that of those with chronic constipation, the majority will have some degree of outlet obstruction [57]. While an adequate pelvic floor physical examination will often identify most patients with pelvic floor dysfunction, additional testing such as anorectal manometry or defecography may be used to identify other contributors to constipation [58]. This becomes critical because smaller subsets of patients with co-existing outlet obstruction demonstrated by either surface electromyography or defecography prior to surgery were much less likely to have satisfactory results after surgery [59, 60]. Abnormal manometric findings of rectal hyposensitivity have also been associated with decreased satisfaction after surgery [56, 61]. It should also be noted however that the mere presence of an abnormal defecography or manometry finding does not preclude surgery, as many findings are either asymptomatic in nature or a byproduct of the constipation itself. As Reshef et al. demonstrated in a study of 41 patients with abnormal test finding that suggested obstructed defecation, some patients may still have satisfactory results after colectomy and ileorectal anastomosis, and therefore all findings must be taken in context as part of careful patient selection [62].

An additional consideration in patient selection is the presence of simultaneous gastric or small bowel dysmotility. In smaller retrospective series, those with delayed gastric emptying consistently had less successful outcomes following total colectomy [63–65]. When evaluating outcomes based on the results of small bowel studies, Zmora et al. identified a cohort of 17 patients and found no difference in success rates of total colectomy based on small bowel transit findings [66]. Nevertheless, it is generally recommended that prior to considering surgery, a full enteric motility workup be considered.

Another area that may enter into patient selection for surgical consideration but difficult to tease out is the role of the underlying mental health issues, psychiatric disease, and/or history of sexual trauma that may accompany abdominal constipation. Psychologic disturbances and psychiatric disease have been associated with chronic constipation for decades. Psychiatric assessment has revealed higher levels of anxiety and depression compared to matched controls [67]. While these factors, including a history of sexual abuse, do not guarantee an unsuccessful outcome, they may help predict the likelihood of additional abdominal complaints after surgery [68]. A formal psychiatric evaluation may not be indicated in every situation; however, cognitive behavioral therapy with trained psychologists can play an important role in helping patients improve their behavior and coping mechanisms associated with functional disorders or chronic conditions such as constipation, especially prior to surgery.

Appropriate patient selection for abdominal colectomy, as for any surgery, but especially for constipation, centers on appropriate preoperative counseling and managing expectations. It should be emphasized that all functional bowel disorders represent a spectrum of disease. For example, while both slow transit constipation and irritable bowel syndrome with predominant constipation (IBS-C) have a decrease in the frequency of bowel motions, the symptoms of pain and bloating have often been attributed mainly to IBS-C (Fig. 58.2). Nevertheless, the latest Rome criteria highlight that even pain and bloating will be present to a degree in cases of functional constipation, albeit not the predominant symptoms [7]. If they are, surgery should be cautiously entertained but not abandoned [13]. Recent retrospective surgical series have consistently identified preoperative abdominal pain and bloating, via SF-36 questionnaires, Wexner Constipation Scores, or Gastrointestinal Quality of Life scores to be present in preoperative patients [69–71]. In each of these series, symptoms were significantly improved post-surgery. The degree of improvement in abdominal pain that can be expected after surgery is not clear. In one study utilizing postoperative telephone interviews, 41% had ongoing abdominal pain, yet 81% were "at least somewhat pleased" with the frequency of bowel motions [72].

With these caveats in mind, a reasonable multidisciplinary approach to patient selection was published by Dr. Staller and colleagues (Fig. 58.3) [13]. If surgery is to be considered, the 2016 ASCRS Clinical Practice Guidelines gave strong recommendations (based on low-quality evidence) that a total abdominal colectomy with ileorectal anastomosis

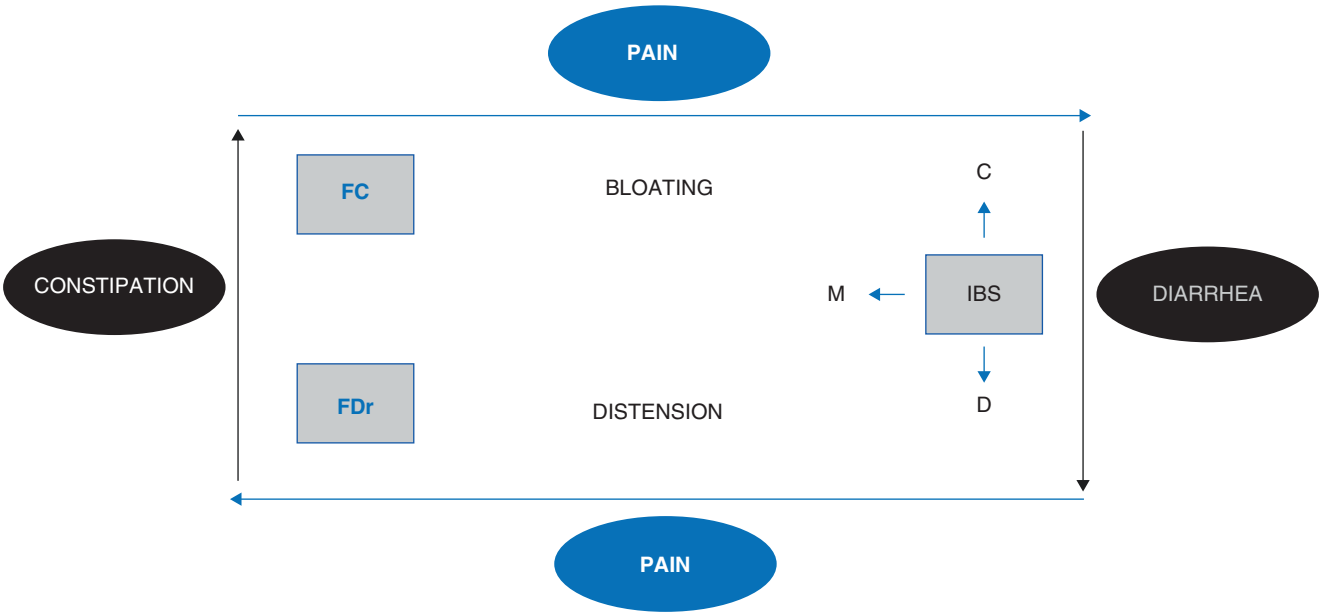

Fig. 58.2 Spectrum of functional bowel disorders. FC functional constipation, FDr functional diarrhea, IBS-C irritable bowel syndrome with predominant constipation, IBS-D irritable bowel syndrome with predominant diarrhea, IBS-M irritable bowel syndrome with predominant irregular bowel habits (mixed D/C). (Modified from Lacy et al. [7])

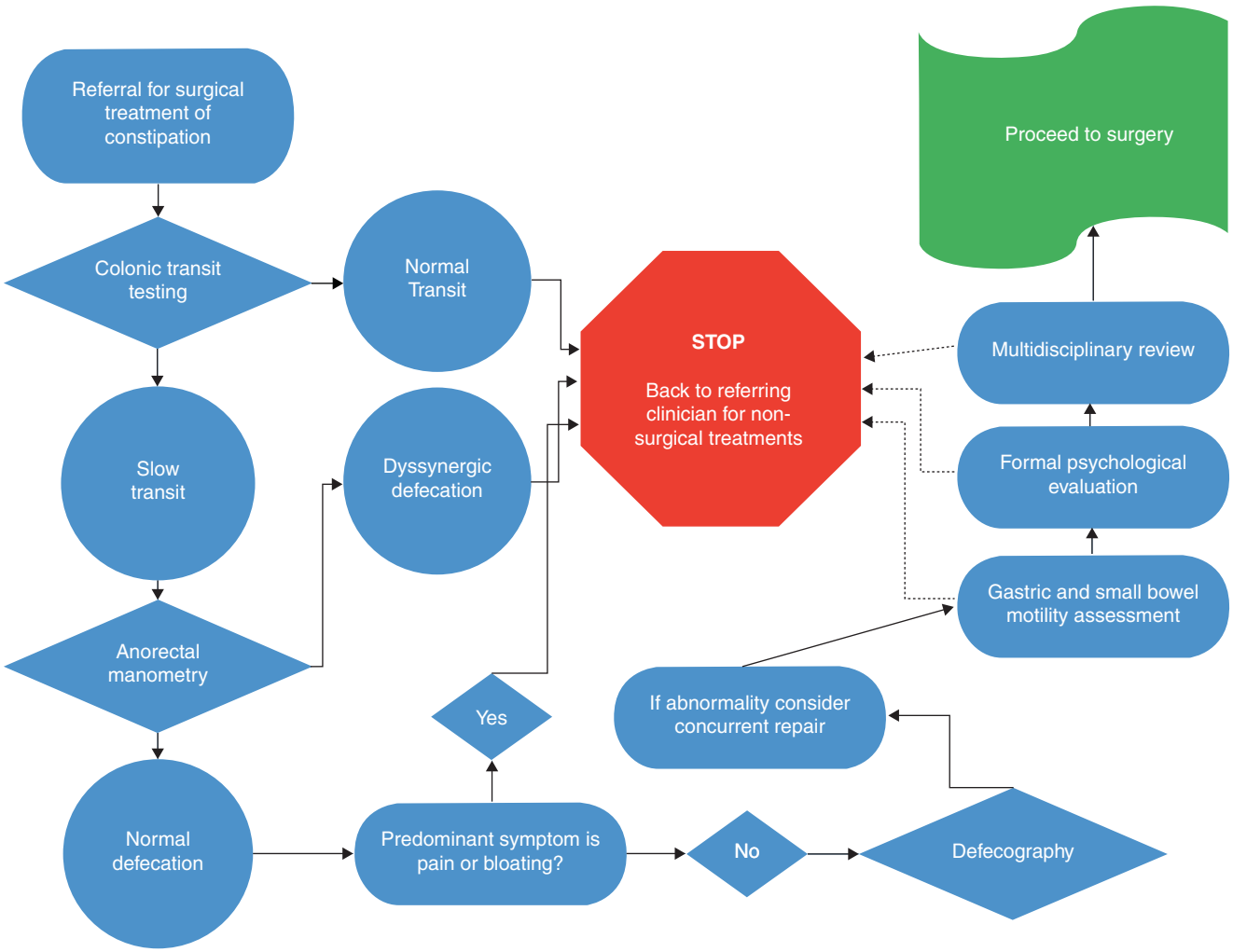

Fig. 58.3 Algorithm for the surgical evaluation of slow transit constipation. (Adapted from Ref. [13]. Reused with permission. Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved)

is the procedure of choice [73]. Likewise, a 2017 dedicated review by the Association of Coloproctology of Great Britain and Ireland concluded that colectomy may benefit some but again cautioned that insufficient evidence exists to guide adequate patient selection [74]. Although the abdominal colectomy has been best studied and recommended by these associations, it should be noted that multiple centers have reported small series involving segmental colon resections based on preoperative transit studies that have identified certain locations to be more abnormal than others [56, 75]. Although the tailored approach of a lesser degree of colectomy may sound appealing, it is hampered by the accurate isolation of the certain "diseased" segment, the lack of larger data sets, and the number of reported treatment failures post-segmental colectomy [51].

In appropriated selected patients, long-term results following total abdominal colectomy are satisfactory. After a median of almost 11 years, Zutshi et al. found that 77% of respondents remained pleased with the results after surgery [76]. The most frequent morbidity was small bowel obstruction (20%, 8 of 14 who required repeat surgery), although 90% of cases were done in an open fashion. After a median of 16 years, Patton et al. also reported high satisfaction, although again noting a 21% rate of small bowel obstruction requiring admission. Detailed investigations into bowel frequency have revealed the majority (41%) of patients had between 1 and 3 bowel motions a day, albeit 8 of 17 remained on laxatives. Small numbers (18%) had 7–10 bowel motions/day and fewer (7%) with >10 per day [77]. Therefore, it is not surprising that 29% reported moderate incontinence and 21% had severe incontinence as graded by the St. Mark's incontinence score.

Worries over incontinence and diarrhea after total colectomy have prompted some investigators to modify the classic ileorectal anastomosis by sparing the ileocecal valve via an anti-peristaltic cecorectal anastomosis (double-stapled anastomosis from rectal stump to cecum). Others have endorsed a cecorectal anastomosis with colonic bypass (without colectomy) or a side-to-side anastomosis between the ascending colon and rectum (Jinling procedure) [78–81]. Despite reporting satisfactory results, there are few comparative studies looking at these technical variations. Xie et al. compared 20 patients who had abdominal colectomy with anti-peristaltic cecorectal anastomosis to 35 who had standard ileorectal anastomosis and found no difference in postoperative outcomes including Wexner Constipation scores, Cleveland Clinic Incontinence and Constipation scores, as well as Gastrointestinal Quality of Life scores [71].

Less Standard Approaches

While the diagnosis of slow transit constipation implies some degree of a functioning rectum, a small number of patients may present with dysfunctional bowel that continues down through the rectum. In these rare situations where constipation is combined with some degree of megarectum or rectal inertia, colectomy with ileorectal anastomosis may prove inferior. If a formal diagnosis of megarectum (dilation of >6.5 cm at level of pelvic brim as seen on contrast enema) is made, then an abdominal colectomy has been associated with poorer outcomes, especially in terms of recurrent constipation [82]. In such cases, there are small series suggesting restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) may improve quality of life, but even in one small series of 15 patients, 13% underwent eventual pouch excision [83, 84]. It is imperative to ensure that the anus and/or pelvic floor relax appropriately before considering a pelvic pouch. The ASCRS Clinical Practice Guidelines Committee warns that even in cases of refractory constipation, available studies do not justify IPAA, and this should only be offered after all other options have been exhausted [73].

Less Invasive Surgical Alternatives

In lieu of bowel resection for refractory constipation, the principle of regular colonic irrigation has been employed either retrograde via a transanal delivery system or antegrade via an appendicostomy or other conduit (antegrade colonic enemas, ACE). Transanal irrigation (TAI) has been successful for patients with neurogenic constipation or obstructed defecation and has been expanded to chronic refractory constipation [85, 86]. In one study of 102 patients with idiopathic constipation, using 500–1000 mL of water delivered ~3×/week, 63% were moderately or much improved after 12 months, and 53% continued to perform irrigations [87]. Other studies have found lower success rates (34–45%) within the subgroup of chronic constipation [85, 88]. Regardless, successful acceptance of this form of treatment requires appropriate training and follow-up as discontinuation rates can be high [89].

Given the relative success of ACE in the pediatric population, it has been used at various centers in the adult population as well. A 2016 systematic review identified 209 patients who had an ACE for constipation. After a median of 39 months, 68% were deemed to have a successful outcome, despite the lack of validated outcome measures in the majority of studies [90]. Few studies define success—other than ongoing usage of the ACE. A Dutch cohort found only 37% were successful using the ACE and measuring long-term quality of life, the results were no different than controls [91]. Moreover the need for surgical revision for stenosis and leakage remains high, even at specialized centers where reoperation rates approach 90% [92]. As a result, the ASCRS practice guidelines warn that this is not a common alternative and should be reserved for only highly selected, motivated patients [73].

A more recent, intriguing minimally invasive option for slow transit constipation is the expanding use of sacral neu-

romodulation (SNM). Physiologic data have shown that stimulation of the S3 or S4 nerve root will increase the transit and contractility of the distal colon [93]. Despite the current lack of approval by the US Food and Drug Administration, multiple centers outside the United States have reported their retrospective experience with this modality. Unfortunately, recent clinical data with longer follow-up have not been as promising as initial results with success ranging from 5% to 30% [94–96]. One drawback looking at studies of SNM for constipation is that all constipated patients are grouped together. A more rigorous prospective study grouping patients with similar constipation (i.e. abdominal in one group and pelvic in another) may provide a better idea of who would benefit. The indiscriminate grouping of constipated patients may help explain why SNM studies have failed to find predictors that may identify the small percentage of potential responders [93].

Ileostomy creation for slow transit constipation may be reasonable in the setting of significant fecal incontinence, increased operative risk, or those adverse to a colectomy. All retrospective series suggest ileostomy is a reasonable alternative either as a salvage maneuver after complications (diarrhea, incontinence) related to abdominal colectomy or as a final resort when other non-surgical modalities have failed [97]. A 2018 retrospective review from St. Mark's in the United Kingdom reported on 24 patients who underwent an ostomy for refractory constipation [98]. Only 59% responded to post-surgical questionnaires to measure quality of life, but they found 64% were satisfied with the ostomy despite a lower than average health-related quality of life and 20% reoperation rate. Similar reoperations rates (29%) for stomal retraction and hernia have also been reported from other institutions [99]. While surgeon familiarity with ostomy creation may allow better navigation of the associated complications, there still remains a paucity of studies to guide clinicians on appropriately patient selection.

Conclusion

Constipation can present with a myriad of symptoms. A thorough history and physical examination is important. Diagnostic treatment is not always necessary but can help differentiate between subtypes of constipation. Initial treatment should begin with fiber supplementation, dietary manipulation, behavioral modification, and over-the-counter or prescription laxatives. If patients with constipation fail medical management, surgical treatment may be considered.

References

1. Pare P, Ferrazzi S, Thompson WG, Irvine EJ, Rance L. An epidemiological survey of constipation in Canada: definitions, rates, demographics, and predictors of health care seeking. Am J Gastroenterol. 2001;96(11):3130–7. https://doi.org/10.1111/j.1572-0241.2001.05259.x.
2. Stewart WF, Liberman JN, Sandler RS, et al. Epidemiology of constipation (EPOC) study in the United States: relation of clinical subtypes to sociodemographic features. Am J Gastroenterol. 1999;94(12):3530–40. https://doi.org/10.1111/j.1572-0241.1999.01642.x.
3. Everhart JE, Go VL, Johannes RS, Fitzsimmons SC, Roth HP, White LR. A longitudinal survey of self-reported bowel habits in the United States. Dig Dis Sci. 1989;34(8):1153–62. https://doi.org/10.1007/bf01537261.
4. Shah ND, Chitkara DK, Locke GR, Meek PD, Talley NJ. Ambulatory care for constipation in the United States, 1993-2004. Am J Gastroenterol. 2008;103(7):1746–53. https://doi.org/10.1111/j.1572-0241.2008.01910.x.
5. Singh G, Lingala V, Wang H, et al. Use of health care resources and cost of care for adults with constipation. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2007;5(9):1053–8. https://doi.org/10.1016/j.cgh.2007.04.019.
6. Aziz I, Whitehead WE, Palsson OS, Törnblom H, Simrén M. An approach to the diagnosis and management of Rome IV functional disorders of chronic constipation. Expert Rev Gastroenterol Hepatol. 2020;14(1):39–46. https://doi.org/10.1080/17474124.2020.1708718.
7. Mearin F, Lacy BE, Chang L, et al. Bowel disorders. Gastroenterology. 2016;150:1393–407. https://doi.org/10.1053/j.gastro.2016.02.031.
8. Rao SS, Bharucha AE, Chiarioni G, et al. Functional anorectal disorders. Gastroenterology. 2016;150:1430. https://doi.org/10.1053/j.gastro.2016.02.009.
9. Hadley SJ, Walsh BT. Gastrointestinal disturbances in anorexia nervosa and bulimia nervosa. Curr Drug Targets CNS Neurol Disord. 2003;2(1):1–9. https://doi.org/10.2174/1568007033338715.
10. Bharucha AE, Pemberton JH, Locke GR. American Gastroenterological Association technical review on constipation. Gastroenterology. 2013;144(1):218–38. https://doi.org/10.1053/j.gastro.2012.10.028.
11. Bharucha AE, Lacy BE. Mechanisms, evaluation, and management of chronic constipation. Gastroenterology. 2020;158:1232. https://doi.org/10.1053/j.gastro.2019.12.034.
12. Bharucha AE, Anderson B, Bouchoucha M. More movement with evaluating colonic transit in humans. Neurogastroenterol Motil. 2019;31(2):e13541. https://doi.org/10.1111/nmo.13541.
13. Staller K. Refractory constipation: what is the clinician to do? J Clin Gastroenterol. 2018;52(6):490–501. https://doi.org/10.1097/MCG.0000000000001049.
14. Cowlam S, Khan U, Mackie A, Varma JS, Yiannankou Y. Validity of segmental transit studies used in routine clinical practice, to characterize defaecatory disorder in patients with functional constipation. Colorectal Dis. 2008;10(8):818–22. https://doi.org/10.1111/j.1463-1318.2008.01566.x.
15. Nam YS, Pikarsky AJ, Wexner SD, et al. Reproducibility of colonic transit study in patients with chronic constipation. Dis Colon Rectum. 2001;44(1):86–92. https://doi.org/10.1007/bf02234827.
16. Lanfranchi GA, Bazzocchi G, Brignola C, Campieri M, Labò G. Different patterns of intestinal transit time and anorectal motility in painful and painless chronic constipation. Gut. 1984;25(12):1352–7. https://doi.org/10.1136/gut.25.12.1352.
17. Camilleri M. Scintigraphic biomarkers for colonic dysmotility. Clin Pharmacol Ther. 2010;87(6):748–53. https://doi.org/10.1038/clpt.2010.23.
18. Stivland T, Camilleri M, Vassallo M, et al. Scintigraphic measurement of regional gut transit in idiopathic constipation. Gastroenterology. 1991;101(1):107–15. https://doi.org/10.1016/0016-5085(91)90466-x.
19. Camilleri M, Thorne NK, Ringel Y, et al. Wireless pH-motility capsule for colonic transit: prospective com-

parison with radiopaque markers in chronic constipation. Neurogastroenterol Motil. 2010;22(8):874–82, e233. https://doi.org/10.1111/j.1365-2982.2010.01517.x.
20. Rao SSC, Sadeghi P, Beaty J, Kavlock R. Ambulatory 24-hour colonic manometry in slow-transit constipation. Am J Gastroenterol. 2004;99(12):2405–16. https://doi.org/10.1111/j.1572-0241.2004.40453.x.
21. Palit S, Thin N, Knowles CH, Lunniss PJ, Bharucha AE, Scott SM. Diagnostic disagreement between tests of evacuatory function: a prospective study of 100 constipated patients. Neurogastroenterol Motil. 2016;28(10):1589–98. https://doi.org/10.1111/nmo.12859.
22. Noelting J, Bharucha AE, Lake DS, et al. Semi-automated vectorial analysis of anorectal motion by magnetic resonance defecography in healthy subjects and fecal incontinence. Neurogastroenterol Motil. 2012;24(10):e467–75. https://doi.org/10.1111/j.1365-2982.2012.01962.x.
23. Reiner CS, Tutuian R, Solopova AE, Pohl D, Marincek B, Weishaupt D. MR defecography in patients with dyssynergic defecation: spectrum of imaging findings and diagnostic value. Br J Radiol. 2011;84(998):136–44. https://doi.org/10.1259/bjr/28989463.
24. Burkitt DP, Walker AR, Painter NS. Effect of dietary fibre on stools and the transit-times, and its role in the causation of disease. Lancet Lond Engl. 1972;2(7792):1408–12. https://doi.org/10.1016/s0140-6736(72)92974-1.
25. Ford AC, Moayyedi P, Lacy BE, et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. Am J Gastroenterol. 2014;109 Suppl 1:S2–26; quiz S27. https://doi.org/10.1038/ajg.2014.187.
26. Chung BD, Parekh U, Sellin JH. Effect of increased fluid intake on stool output in normal healthy volunteers. J Clin Gastroenterol. 1999;28(1):29–32. https://doi.org/10.1097/00004836-199901000-00006.
27. Whitehead WE, Drinkwater D, Cheskin LJ, Heller BR, Schuster MM. Constipation in the elderly living at home. Definition, prevalence, and relationship to lifestyle and health status. J Am Geriatr Soc. 1989;37(5):423–9. https://doi.org/10.1111/j.1532-5415.1989.tb02638.x.
28. Gao R, Tao Y, Zhou C, et al. Exercise therapy in patients with constipation: a systematic review and meta-analysis of randomized controlled trials. Scand J Gastroenterol. 2019;54(2):169–77. https://doi.org/10.1080/00365521.2019.1568544.
29. McRorie JW, Daggy BP, Morel JG, Diersing PS, Miner PB, Robinson M. Psyllium is superior to docusate sodium for treatment of chronic constipation. Aliment Pharmacol Ther. 1998;12(5):491–7. https://doi.org/10.1046/j.1365-2036.1998.00336.x.
30. Lee-Robichaud H, Thomas K, Morgan J, Nelson RL. Lactulose versus polyethylene glycol for chronic constipation. Cochrane Database Syst Rev. 2010;7:CD007570. https://doi.org/10.1002/14651858.CD007570.pub2.
31. Lederle FA, Busch DL, Mattox KM, West MJ, Aske DM. Cost-effective treatment of constipation in the elderly: a randomized double-blind comparison of sorbitol and lactulose. Am J Med. 1990;89(5):597–601. https://doi.org/10.1016/0002-9343(90)90177-f.
32. Frexinos J, Staumont G, Fioramonti J, Bueno L. Effects of sennosides on colonic myoelectrical activity in man. Dig Dis Sci. 1989;34(2):214–9. https://doi.org/10.1007/bf01536053.
33. Schang JC, Hémond M, Hébert M, Pilote M. Changes in colonic myoelectric spiking activity during stimulation by bisacodyl. Can J Physiol Pharmacol. 1986;64(1):39–43. https://doi.org/10.1139/y86-005.
34. Ikarashi N, Baba K, Ushiki T, et al. The laxative effect of bisacodyl is attributable to decreased aquaporin-3 expression in the colon induced by increased PGE2 secretion from macrophages. Am J Physiol Gastrointest Liver Physiol. 2011;301(5):G887–95. https://doi.org/10.1152/ajpgi.00286.2011.
35. Wald A. Is chronic use of stimulant laxatives harmful to the colon? J Clin Gastroenterol. 2003;36(5):386–9. https://doi.org/10.1097/00004836-200305000-00004.
36. Johanson JF, Morton D, Geenen J, Ueno R. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. Am J Gastroenterol. 2008;103(1):170–7. https://doi.org/10.1111/j.1572-0241.2007.01524.x.
37. Shah ED, Kim HM, Schoenfeld P. Efficacy and tolerability of guanylate cyclase-C agonists for irritable bowel syndrome with constipation and chronic idiopathic constipation: a systematic review and meta-analysis. Am J Gastroenterol. 2018;113(3):329–38. https://doi.org/10.1038/ajg.2017.495.
38. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. N Engl J Med. 2011;365(6):527–36. https://doi.org/10.1056/NEJMoa1010863.
39. Miner PB, Koltun WD, Wiener GJ, et al. A randomized phase III clinical trial of plecanatide, a uroguanylin analog, in patients with chronic idiopathic constipation. Am J Gastroenterol. 2017;112(4):613–21. https://doi.org/10.1038/ajg.2016.611.
40. Chey WD, Lembo AJ, Rosenbaum DP. Tenapanor treatment of patients with constipation-predominant irritable bowel syndrome: a phase 2, randomized, placebo-controlled efficacy and safety trial. Am J Gastroenterol. 2017;112(5):763–74. https://doi.org/10.1038/ajg.2017.41.
41. Chey WD, Lembo AJ, Rosenbaum DP. Efficacy of tenapanor in treating patients with irritable bowel syndrome with constipation: a 12-week, placebo-controlled phase 3 trial (T3MPO-1). Am J Gastroenterol. 2020;115(2):281–93. https://doi.org/10.14309/ajg.0000000000000516.
42. Johanson JF, Wald A, Tougas G, et al. Effect of tegaserod in chronic constipation: a randomized, double-blind, controlled trial. Clin Gastroenterol Hepatol. 2004;2(9):796–805. https://doi.org/10.1016/s1542-3565(04)00356-8.
43. Kamm MA, Müller-Lissner S, Talley NJ, et al. Tegaserod for the treatment of chronic constipation: a randomized, double-blind, placebo-controlled multinational study. Am J Gastroenterol. 2005;100(2):362–72. https://doi.org/10.1111/j.1572-0241.2005.40749.x.
44. In brief. Tegaserod (Zelnorm) returns. Med Lett Drugs Ther. 2019;61(1571):72.
45. Camilleri M, Piessevaux H, Yiannakou Y, et al. Efficacy and safety of prucalopride in chronic constipation: an integrated analysis of six randomized, controlled clinical trials. Dig Dis Sci. 2016;61(8):2357–72. https://doi.org/10.1007/s10620-016-4147-9.
46. Sloots CEJ, Rykx A, Cools M, Kerstens R, De Pauw M. Efficacy and safety of prucalopride in patients with chronic noncancer pain suffering from opioid-induced constipation. Dig Dis Sci. 2010;55(10):2912–21. https://doi.org/10.1007/s10620-010-1229-y.
47. Farmer AD, Drewes AM, Chiarioni G, et al. Pathophysiology and management of opioid-induced constipation: European expert consensus statement. United Eur Gastroenterol J. 2019;7(1):7–20. https://doi.org/10.1177/2050640618818305.
48. Luthra P, Burr NE, Brenner DM, Ford AC. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and network meta-analysis. Gut. 2018;68:434. https://doi.org/10.1136/gutjnl-2018-316001.
49. Nakajima A, Seki M, Taniguchi S, et al. Safety and efficacy of elobixibat for chronic constipation: results from a randomised, double-blind, placebo-controlled, phase 3 trial and an open-label, single-arm, phase 3 trial. Lancet Gastroenterol Hepatol. 2018;3(8):537–47. https://doi.org/10.1016/S2468-1253(18)30123-7.
50. Soh AYS, Kang J-Y, Siah KTH, Scarpignato C, Gwee K-A. Searching for a definition for pharmacologically refractory constipation: a systematic review. J Gastroenterol Hepatol. 2018;33(3):564–75. https://doi.org/10.1111/jgh.13998.

51. Gladman MA, Knowles CH. Surgical treatment of patients with constipation and fecal incontinence. Gastroenterol Clin N Am. 2008;37(3):605–25, viii. https://doi.org/10.1016/j.gtc.2008.06.009.
52. Riss S, Herbst F, Birsan T, Stift A. Postoperative course and long term follow up after colectomy for slow transit constipation–is surgery an appropriate approach? Colorectal Dis. 2009;11(3):302–7. https://doi.org/10.1111/j.1463-1318.2008.01592.x.
53. Dudekula A, Huftless S, Bielefeldt K. Colectomy for constipation: time trends and impact based on the US Nationwide Inpatient Sample, 1998–2011. Aliment Pharmacol Ther. 2015;42(11–12):1281–93. https://doi.org/10.1111/apt.13415.
54. Staller K, Barshop K, Ananthakrishnan AN, Kuo B. Number of retained radiopaque markers on a colonic transit study does not correlate with symptom severity or quality of life in chronic constipation. Neurogastroenterol Motil. 2018;30(5):e13269. https://doi.org/10.1111/nmo.13269.
55. Bouchoucha M, Devroede G, Dorval E, Faye A, Arhan P, Arsac M. Different segmental transit times in patients with irritable bowel syndrome and "normal" colonic transit time: is there a correlation with symptoms? Tech Coloproctol. 2006;10(4):287–96. https://doi.org/10.1007/s10151-006-0295-9.
56. Lundin E, Karlbom U, Påhlman L, Graf W. Outcome of segmental colonic resection for slow-transit constipation. Br J Surg. 2002;89(10):1270–4. https://doi.org/10.1046/j.1365-2168.2002.02213.x.
57. Ragg J, McDonald R, Hompes R, Jones OM, Cunningham C, Lindsey I. Isolated colonic inertia is not usually the cause of chronic constipation. Colorectal Dis. 2011;13(11):1299–302. https://doi.org/10.1111/j.1463-1318.2010.02455.x.
58. Tantiphlachiva K, Rao P, Attaluri A, Rao SSC. Digital rectal examination is a useful tool for identifying patients with dyssynergia. Clin Gastroenterol Hepatol. 2010;8(11):955–60. https://doi.org/10.1016/j.cgh.2010.06.031.
59. Bernini A, Madoff RD, Lowry AC, et al. Should patients with combined colonic inertia and nonrelaxing pelvic floor undergo subtotal colectomy? Dis Colon Rectum. 1998;41(11):1363–6. https://doi.org/10.1007/bf02237050.
60. Lubowski DZ, Chen FC, Kennedy ML, King DW. Results of colectomy for severe slow transit constipation. Dis Colon Rectum. 1996;39(1):23–9. https://doi.org/10.1007/bf02048263.
61. Akervall S, Fasth S, Nordgren S, Oresland T, Hultén L. The functional results after colectomy and ileorectal anastomosis for severe constipation (Arbuthnot Lane's disease) as related to rectal sensory function. Int J Color Dis. 1988;3(2):96–101. https://doi.org/10.1007/bf01645313.
62. Reshef A, Alves-Ferreira P, Zutshi M, Hull T, Gurland B. Colectomy for slow transit constipation: effective for patients with coexistent obstructed defecation. Int J Color Dis. 2013;28(6):841–7. https://doi.org/10.1007/s00384-012-1498-3.
63. Gila A. Outcome of colectomy for slow-transit constipation in relation to presence of small-bowel dysmotility. Dis Colon Rectum. 2004;47(1):96–102.
64. Redmond JM, Smith GW, Barofsky I, Ratych RE, Goldsborough DC, Schuster MM. Physiological tests to predict long-term outcome of total abdominal colectomy for intractable constipation. Am J Gastroenterol. 1995;90(5):748–53.
65. Ghosh S, Papachrysostomou M, Batool M, Eastwood MA. Long-term results of subtotal colectomy and evidence of noncolonic involvement in patients with idiopathic slow-transit constipation. Scand J Gastroenterol. 1996;31(11):1083–91. https://doi.org/10.3109/00365529609036891.
66. Zmora O, Colquhoun P, Katz J, et al. Small bowel transit does not correlate with outcome of surgery in patients with colonic inertia. Surg Innov. 2005;12(3):215–8. https://doi.org/10.1177/155335060501200305.
67. Kamm MA, Hawley PR, Lennard-Jones JE. Outcome of colectomy for severe idiopathic constipation. Gut. 1988;29(7):969–73. https://doi.org/10.1136/gut.29.7.969.
68. O'brien S. Sexual abuse: a strong predictor of outcomes after colectomy for slow-transit constipation. Dis Colon Rectum. 2009;52(11):1844–7.
69. Vergara-Fernandez O, Mejía-Ovalle R, Salgado-Nesme N, et al. Functional outcomes and quality of life in patients treated with laparoscopic total colectomy for colonic inertia. Surg Today. 2014;44(1):34–8. https://doi.org/10.1007/s00595-012-0464-6.
70. Jang TY, Yu CS, Kim CW, et al. Surgical outcomes after total colectomy with ileorectal anastomosis in patients with medically intractable slow transit constipation. J Korean Soc Coloproctol. 2011;27(4):180–7. https://doi.org/10.3393/jksc.2011.27.4.180.
71. Ding Z, Sun K-L, Chen W-H, et al. Surgical outcomes of subtotal colectomy with antiperistaltic caecorectal anastomosis vs total colectomy with ileorectal anastomosis for intractable slow-transit constipation. Gastroenterol Rep. 2019;7(6):449–54. https://doi.org/10.1093/gastro/goz014.
72. FitzHarris GP, Garcia-Aguilar J, Parker SC, et al. Quality of life after subtotal colectomy for slow-transit constipation: both quality and quantity count. Dis Colon Rectum. 2003;46(4):433–40. https://doi.org/10.1007/s10350-004-6576-3.
73. Paquette IM, Varma M, Ternent C, et al. The American Society of Colon and Rectal Surgeons' Clinical Practice Guideline for the Evaluation and Management of Constipation. Dis Colon Rectum. 2016;59(6):479–92. https://doi.org/10.1097/DCR.0000000000000599.
74. Knowles CH, Grossi U, Chapman M, Mason J, NIHR CapaCiTY working group, Pelvic floor Society. Surgery for constipation: systematic review and practice recommendations: Results I: Colonic resection. Colorectal Dis. 2017;19 Suppl 3:17–36. https://doi.org/10.1111/codi.13779.
75. Ripetti V, Caputo D, Greco S, Alloni R, Coppola R. Is total colectomy the right choice in intractable slow-transit constipation? Surgery. 2006;140(3):435–40. https://doi.org/10.1016/j.surg.2006.02.009.
76. Zutshi M, Hull TL, Trzcinski R, Arvelakis A, Xu M. Surgery for slow transit constipation: are we helping patients? Int J Color Dis. 2007;22(3):265–9. https://doi.org/10.1007/s00384-006-0189-3.
77. Patton V, Balakrishnan V, Pieri C, et al. Subtotal colectomy and ileorectal anastomosis for slow transit constipation: clinical follow-up at median of 15 years. Tech Coloproctol. 2020;24(2):173–9. https://doi.org/10.1007/s10151-019-02140-5.
78. Iannelli A, Fabiani P, Mouiel J, Gugenheim J. Laparoscopic subtotal colectomy with cecorectal anastomosis for slow-transit constipation. Surg Endosc. 2006;20(1):171–3. https://doi.org/10.1007/s00464-005-0099-4.
79. Marchesi F, Percalli L, Pinna F, Cecchini S, Ricco' M, Roncoroni L. Laparoscopic subtotal colectomy with antiperistaltic cecorectal anastomosis: a new step in the treatment of slow-transit constipation. Surg Endosc. 2012;26(6):1528–33. https://doi.org/10.1007/s00464-011-2092-4.
80. Yang Y, Cao Y-L, Wang W-H, Zhang Y-Y, Zhao N, Wei D. Subtotal colonic bypass plus colostomy with antiperistaltic cecoproctostomy for the treatment of slow transit constipation in an aged population: a retrospective control study. World J Gastroenterol. 2018;24(23):2491–500. https://doi.org/10.3748/wjg.v24.i23.2491.
81. Li N, Jiang J, Feng X, Ding W, Liu J, Li J. Long-term follow-up of the Jinling procedure for combined slow-transit constipation and obstructive defecation. Dis Colon Rectum. 2013;56(1):103–12. https://doi.org/10.1097/DCR.0b013e318273a182.
82. Gladman MA, Scott SM, Lunniss PJ, Williams NS. Systematic review of surgical options for idiopathic megarectum and megacolon. Ann Surg. 2005;241(4):562–74. https://doi.org/10.1097/01.sla.0000157140.69695.d3.

83. Thakur A, Fonkalsrud EW, Buchmiller T, French S. Surgical treatment of severe colonic inertia with restorative proctocolectomy. Am Surg. 2001;67(1):36–40.
84. Kalbassi MR, Winter DC, Deasy JM. Quality-of-life assessment of patients after ileal pouch-anal anastomosis for slow-transit constipation with rectal inertia. Dis Colon Rectum. 2003;46(11):1508–12. https://doi.org/10.1007/s10350-004-6804-x.
85. Christensen P, Krogh K. Transanal irrigation for disordered defecation: a systematic review. Scand J Gastroenterol. 2010;45(5):517–27. https://doi.org/10.3109/00365520903583855.
86. Tod AM, Stringer E, Levery C, Dean J, Brown J. Rectal irrigation in the management of functional bowel disorders: a review. Br J Nurs Mark Allen Publ. 2007;16(14):858–64. https://doi.org/10.12968/bjon.2007.16.14.24323.
87. Etherson KJ, Minty I, Bain IM, Cundall J, Yiannakou Y. Transanal irrigation for refractory chronic idiopathic constipation: patients perceive a safe and effective therapy. Gastroenterol Res Pract. 2017;2017:3826087. https://doi.org/10.1155/2017/3826087.
88. Christensen P, Krogh K, Buntzen S, Payandeh F, Laurberg S. Long-term outcome and safety of transanal irrigation for constipation and fecal incontinence. Dis Colon Rectum. 2009;52(2):286–92. https://doi.org/10.1007/DCR.0b013e3181979341.
89. Bildstein C, Melchior C, Gourcerol G, et al. Predictive factors for compliance with transanal irrigation for the treatment of defecation disorders. World J Gastroenterol. 2017;23(11):2029–36. https://doi.org/10.3748/wjg.v23.i11.2029.
90. Chan DSY, Delicata RJ. Meta-analysis of antegrade continence enema in adults with faecal incontinence and constipation. Br J Surg. 2016;103(4):322–7. https://doi.org/10.1002/bjs.10051.
91. Sturkenboom R, van der Wilt AA, van Kuijk SMJ, et al. Long-term outcomes of a Malone antegrade continence enema (MACE) for the treatment of fecal incontinence or constipation in adults. Int J Color Dis. 2018;33(10):1341–8. https://doi.org/10.1007/s00384-018-3088-5.
92. Lees NP, Hodson P, Hill J, Pearson RC, MacLennan I. Long-term results of the antegrade continent enema procedure for constipation in adults. Colorectal Dis. 2004;6(5):362–8. https://doi.org/10.1111/j.1463-1318.2004.00669.x.
93. Pilkington SA, Emmett C, Knowles CH, et al. Surgery for constipation: systematic review and practice recommendations: Results V: Sacral Nerve Stimulation. Colorectal Dis. 2017;19 Suppl 3:92–100. https://doi.org/10.1111/codi.13780.
94. Falletto E, Brown S, Gagliardi G. Sacral nerve stimulation for faecal incontinence and constipation in adults. Tech Coloproctol. 2018;22(2):125–7. https://doi.org/10.1007/s10151-017-1744-3.
95. Gortazar de Las Casas S, Rubio-Pérez I, Saavedra Ambrosy J, et al. Sacral nerve stimulation for constipation: long-term outcomes. Tech Coloproctol. 2019;23(6):559–64. https://doi.org/10.1007/s10151-019-02011-z.
96. Schiano di Visconte M, Pasquali A, Cipolat Mis T, Brusciano L, Docimo L, Bellio G. Sacral nerve stimulation in slow-transit constipation: effectiveness at 5-year follow-up. Int J Color Dis. 2019;34(9):1529–40. https://doi.org/10.1007/s00384-019-03351-w.
97. El-Tawil AM. Reasons for creation of permanent ileostomy for the management of idiopathic chronic constipation. J Gastroenterol Hepatol. 2004;19(8):844–6. https://doi.org/10.1111/j.1440-1746.2003.03309.x.
98. Iqbal F, van der Ploeg V, Adaba F, et al. Patient-reported outcome after ostomy surgery for chronic constipation. J Wound Ostomy Cont Nurs. 2018;45(4):319–25. https://doi.org/10.1097/WON.0000000000000445.
99. Scarpa M, Barollo M, Keighley MRB. Ileostomy for constipation: long-term postoperative outcome. Colorectal Dis. 2005;7(3):224–7. https://doi.org/10.1111/j.1463-1318.2005.00810.x.

Treatment of Difficult/Obstructive Defecation

59

Massarat Zutshi and Lucia Camara Castro Oliveira

Key Concepts

- Obstructed defecation syndrome is a subtype of constipation wherein patients usually complain of straining; incomplete, unsuccessful, or painful evacuation; bowel infrequency; abdominal pain and bloating; and the possible need for digitation.
- Initial management is lifestyle advice, laxatives, and bowel retraining programs, including biofeedback and psychological support.
- Diagnostic testing may point to a diagnosis, but clinical correlation should always be used.
- Dyssynergic defecation is a clinical diagnosis and requires knowledge of anatomy and physiology for management.
- Patients with overt rectal or anterior compartment prolapse and symptoms of obstructed defecation should be managed surgically.
- Rectoceles, when symptomatic, require a surgical option.
- Enteroceles and sigmoidoceles need a multimodal approach for effective symptom relief.

Introduction

As the general population is aging in most of the occidental world, pelvic floor disorders are increasingly seen, especially within the elderly female population [1]. The effects of a lifetime of damage to the pelvic floor such as from parity, obesity, and surgical trauma to the pelvic ligaments may directly lead to evacuation and voiding disorders. In the USA, 16% and 9% of women, respectively, will experience bladder or bowel incontinence. Pelvic organ prolapse affects 3% of women [1]. Constipation is a general term that involves a complex variety of clinical scenarios, commonly divided into three major groups: colonic inertia (abdominal), pelvic (obstructed defecation), and constipation with normal transit time associated with irritable bowel syndrome. In this chapter, we will discuss patients with pelvic constipation and obstructed defecation symptoms.

Physiology of Defecation

The process of defecation is determined by complex and multifactorial mechanisms, involving the integration of somatic and visceral functions, under the control of the central nervous system [2]. Therefore, there is an interaction between the brain, spinal cord, enteric neurons, and the muscle of the colon, rectum, anus, and pelvic floor. The structures that require coordination are dependent on conscious control. The defecation process is very complex and not very well understood.

Defecation is triggered by the entry of feces into the rectum as a result of the peristaltic movements of the colon. As the peristaltic movements increase, the rectum receives a larger quantity of feces, thus triggering the defecation reflex. Involuntary passage of feces and gas are controlled through the voluntary contraction of the external sphincter muscle and the puborectalis muscle and the change in the anorectal angle. At the appropriate time, the defecation reflex initiates the process of elimination of the rectal contents, causing the abdominal muscles to contract, the pelvic floor to relax, and the anal canal angle changes, opening it and allowing the passage of feces.

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Definition and Etiology

Individuals who present with a clinical condition of difficult evacuation are frequently labeled as being constipated although they may have a normal transit. As constipation is a poorly defined symptom, an international working group standardized its meaning creating a consensus document frequently referred to as the Rome Criteria. Using common symptoms described by the patients, this consensus usually requires two or more complaints for at least 12 months without the use of laxatives to qualify. According to the Rome IV criteria [3], functional constipation must include ≥2 of the following symptoms (refer also to Table 59.1):

1. Straining during >25% of defecations
2. Lumpy or hard stools in >25% of defecations
3. Sensation of incomplete evacuation >25% of the time
4. Sensation of anorectal obstruction/blockage >25% of the time
5. Manual maneuvers to facilitate defecation >25% of the time
6. Less than three bowel movements per week

Dyssynergic Defecation

Obstructed defecation as a result of a paradoxical contraction or inadequate relaxation of the pelvic floor muscles during attempted defecation and/or inadequate propulsive forces during attempted defecation can occur in up to 40% of all constipated patients [4]. This condition has been variously named dyssynergic defecation, anismus, or paradoxical contraction of the puborectalis. Patient complaints are dominated by a feeling of incomplete evacuation and excessive straining. Physiological testing in these patients shows pathological patterns in inappropriate contraction of the pelvic floor muscles or incomplete relaxation of the anal sphincter or a combination of both [5].

This functional obstructed defecation syndrome is clinically defined by either clinically observing nonrelaxation of the puborectalis or paradoxical contraction of the puborectalis at the anorectal junction during Valsalva or evacuation. This is best done clinically with a digital rectal examination [6]. Testing includes anorectal manometry and/or cinedefecography.

Dyssynergic defecation can be categorized into four types based on anorectal manometry (see Chap. 57). This utilizes the patient's ability to generate an adequate pushing force and the type of sphincter contraction.

Obstructed defecation symptoms may also be a consequence of a structural abnormality within the pelvis such as a rectocele, enterocele, and sigmoidocele. In addition, internal and overt prolapse can lead to obstructive defecation symptoms.

Table 59.1 Physiological and imaging testing for obstructed defecation syndrome

Test	Purpose	Message
Anorectal manometry/ high-resolution anal manometry (HRAM)	Measurement of pressures in the anal canal Assessment of the rectoanal inhibitory reflex (RAIR), rectal sensitivity and compliance Assessment of anismus	Resting pressure = function of the internal anal sphincter Squeeze pressure = function of the external anal sphincter Loss of the reflex typically in Hirschsprung patients HRAM: Color differentiated waveform
Cinedefecography	Evaluation of the dynamic of evacuation after filling the rectum with a barium paste and the bowel with barium and/or the vagina with jelly	Evaluation of rectocele, enterocele, internal prolapse, perineal descent, anorectal angle
Echodefecography	Dynamic ultrasonography evaluation of the anal canal. Evaluation of rectocele, enterocele, internal prolapse, perineal descent after filling the rectum with ultrasound gel	Judgment of the integrity of sphincter muscles (defect?) Hypertrophy of the internal anal sphincter? Structural abnormalities
Colonic transit time study with radiopaque markers	Evaluation of the pattern of evacuation and demonstration of retention of the radiopaque markers	Diffuse spread of radiopaque markers typically for STC Collection of markers in the pelvis as sign for ODS
MR defecography	Functional judgment of the pelvic floor and the internal organs and their mobility	Structural substrate (e.g., rectocele) or only functional disorder (e.g., anismus)
EMG of the pelvic floor	Judgment of the motor unit potentials (MUP) Interference pattern	Loss or alteration or signs of denervation or reinnervation; Malfunction of muscle groups (e.g., anismus)
Pudendal nerve terminal motor latency (PNTML)	Function of the nerve supplying the pelvic floor	Useful for prognosis, if surgery is planned

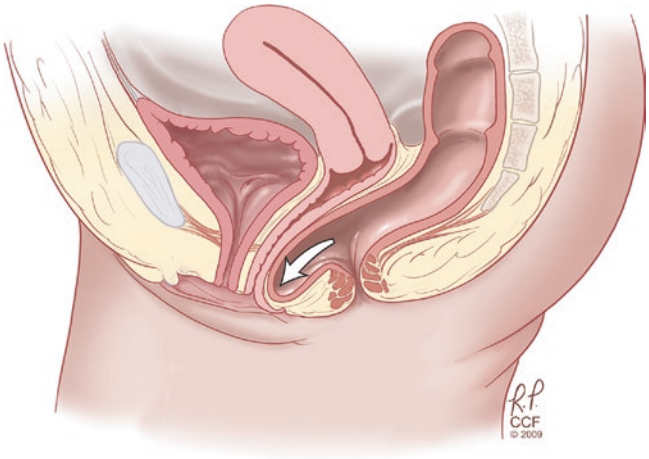

Fig. 59.1 Rectocele: Invagination of the anterior wall of the rectum into the vagina. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2020. All Rights Reserved)

Rectocele

A rectocele is a herniation of the rectal wall typically into the vagina (Fig. 59.1). Risk factors for developing a rectocele are age, obesity, obstetric injury, and/or multiple vaginal deliveries. On cinedefecography, a rectocele is a bulging of the rectal wall into the vagina. An observation regarding its size and whether the rectocele empties with defecation with or without digitation can help to guide treatment. Radiologically, rectoceles are graded as small (<2 cm), moderate (2–4 cm), and large (>4 cm) based on size [7]. Non-emptying or emptying with digitation are those that are considered for a surgical option based on symptoms.

Enterocele

On defecography, an enterocele is classified as presence of the small bowel between the rectum and vagina, reaching lower than the upper third of the vagina during the evacuation effort (Fig. 59.2). A first-degree enterocele lies above the pubococcygeal line. A second-degree enterocele is that which lies below the pubococcygeal line but above the ischiococcygeal line, and a third-degree enterocele lies below the ischiococcygeal line. Herniations of the peritoneal sac with other organs/structures contained can result in peritoneoceles, omentoceles, sigmoidoceles, and enteroceles. These can be graded as small (<3 cm), moderate (3–6 cm), and large (>6 cm) by measuring the largest distance between the pubococcygeal line and the most inferior point of the sac on cinedefecography [7] or dynamic MRI.

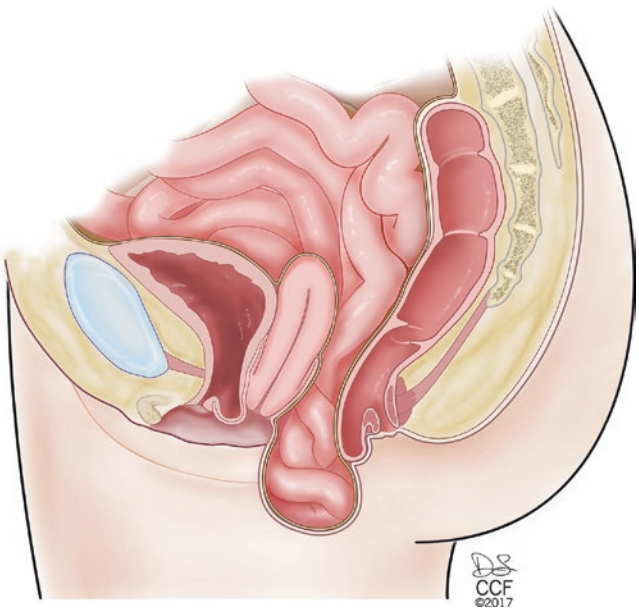

Fig. 59.2 Anatomical depiction of an enterocele. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2020. All Rights Reserved)

Internal Prolapse

Internal or occult rectal prolapse or rectal intussusception is a funnel-shaped infolding of the rectal wall that occurs during defecation. This infolding does not protrude out the anus.

Rectal Prolapse

Rectal prolapse is a circumferential full-thickness intussusception of the rectal wall with protrusion beyond the anal canal.

Scoring Systems

The Constipation Severity Instrument (CSI) [8] is a tool consisting of 78 items which aims at identifying and quantifying different subtypes of constipation. Another scoring system worth mentioning is the obstructed defecation syndrome score (ODS) [9] which has been prospectively validated. To assess the quality of life of constipated patients, the Constipation-Related Quality of Life (CRQOL) is a statistically validated questionnaire [10]. For patients with symptoms of both the anterior and posterior pelvic compartments, the Pelvic Floor Distress Inventory (PFDI) utilizes a pelvic

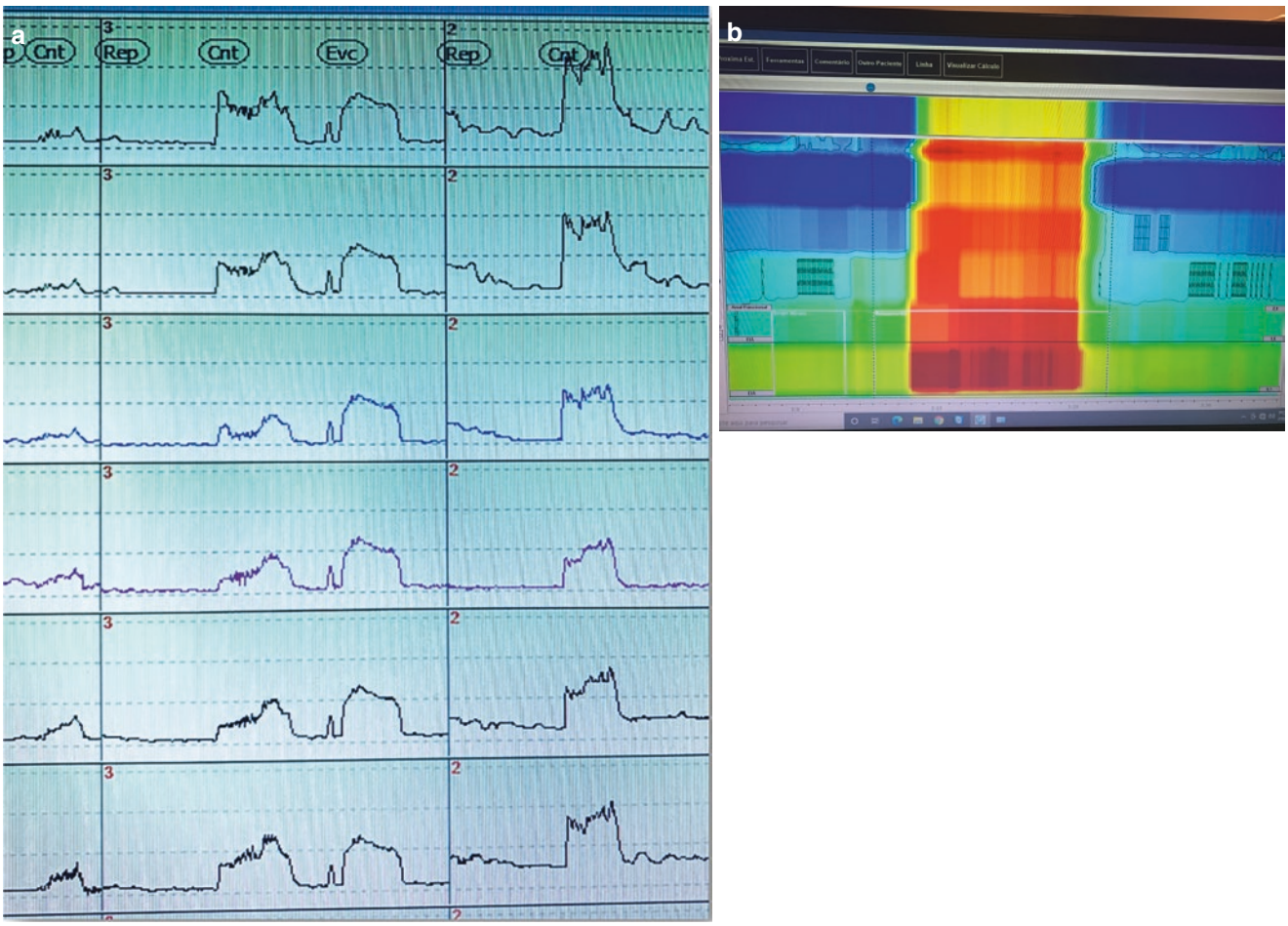

Fig. 59.3 (**a**) Water perfused anal manometry with patient simulating evacuation (bearing down) with non-relaxation of the puborectalis. (**b**) High-resolution manometry when patients bear down with non-relaxation of the puborectalis

organ prolapse score and a Colorectal-Anal Distress Inventory (CRADI) score [11].

It is essential to evaluate the number of evacuations, stool consistency, presence of mucus or blood in the stool, evacuation pain, sensation of incomplete evacuation, and the necessity of digital maneuvers to aid in defecation. It should be noted that most patients with dyssynergic defecation have greater difficulty evacuating soft stool. Detailed information about laxative and diet habits must also be obtained. Other bowel problems (e.g., irritable bowel syndrome, cancer, celiac, and diverticular disease) should be considered in patients that have symptoms such as abdominal pain particularly if located in the left lower quadrant. Abdominal bloating and recent altered bowel habits may also be related to other bowel disorders. Painful evacuation can be present in patients with anorectal inflammatory pathologies.

Physical exam should include the inspection of the anorectal area in order to exclude rectal tumors, anal stenosis, internal prolapse, thrombosed hemorrhoids, or anal fissures. A complete proctologic exam may reveal the presence of melanosis coli (which indicates chronic abuse of laxatives), solitary rectal ulcer, rectal prolapse, descending perineal syndrome, and rectoceles. The presence of fecal impaction requires further investigation in the elderly and children.

Testing for Obstructed Defecation Syndrome

Although a medical history and physical examination may provide an adequate evaluation of patients with symptoms of obstructed defecation, anorectal physiology testing and imaging modalities may aid in defining functional situations from a structural abnormality. Testing may also be helpful in planning a surgical option [4, 8, 12–15]. Anorectal manometry (Fig. 59.3), static and dynamic endoanal ultrasound (Fig. 59.4), colonic transit study (Fig. 59.5), cinedefecography [7] (Fig. 59.6), and electromyography and pelvic MRI (Fig. 59.7) are commonly utilized tests (Table 59.1).

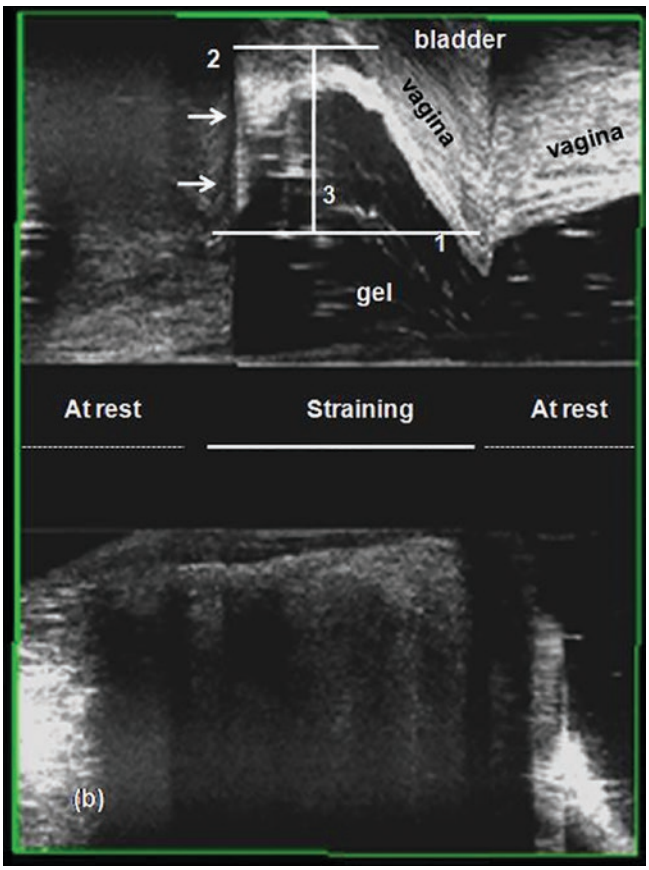

Fig. 59.4 Dynamic 360-degree endoanal ultrasound with ultrasound gel in the rectum showing an anterior rectocele

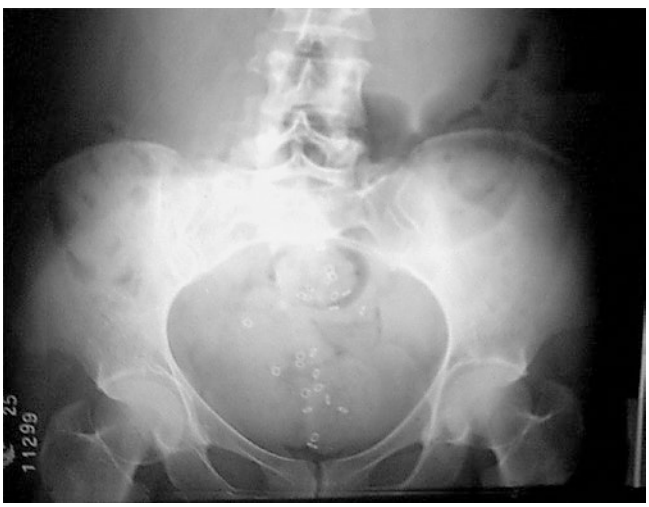

Fig. 59.5 Colonic transit study showing radiopaque markers in the rectum and rectosigmoid

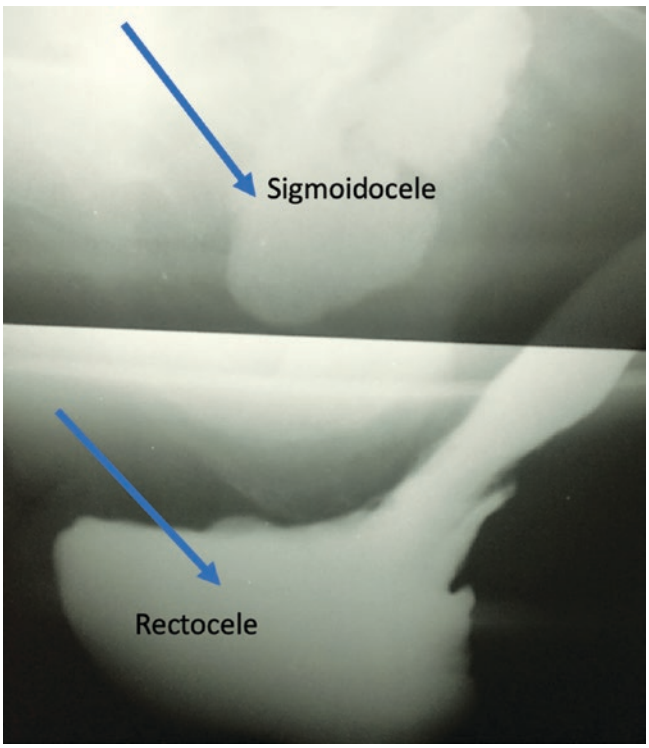

Fig. 59.6 Cinedefecography with barium paste showing a rectocele and sigmoidocele

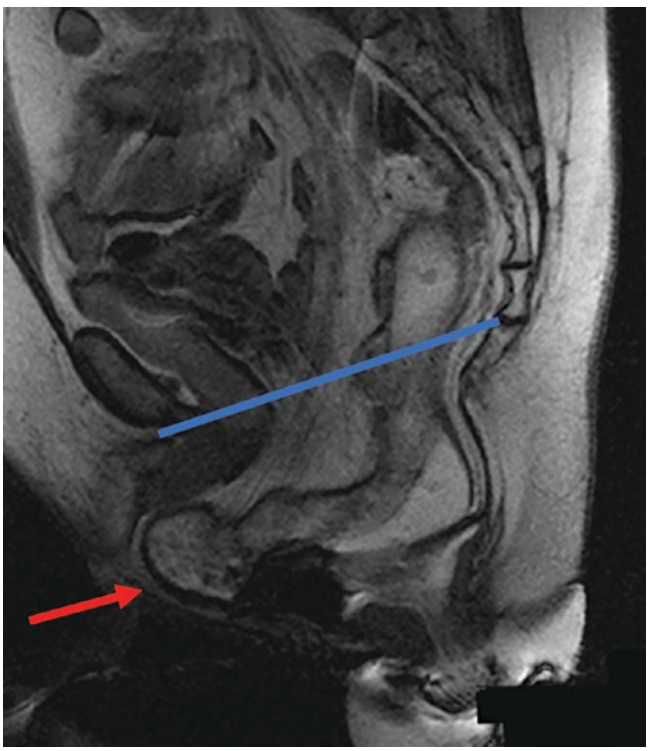

Fig. 59.7 Dynamic MRI in evacuation phase showing an enterocele (red arrow). There is herniation of small bowel loops in the middle compartment, between the bladder and vagina and rectum, due to rupture of the endopelvic fascia and the retovaginal septum. Blue line represents pubococcygeal line

Treatment of Obstructed Defecation

Treatment is individualized and based on a detailed history and physical with additional testing as needed. An algorithm is presented in Fig. 59.8 as a guide to possible therapy.

Treatment of Obstructed Defecation Syndrome Due to Puborectalis Pathology

A tight or dysfunctional puborectalis or levator ani muscle can give rise to dyssynergia leading to paradoxical contractions as described by the Rome IV criteria. The incidence is about 4.6% in patients without IBS [9]. These patients are diagnosed clinically and tested as described above. Many of these patients may have concurrent constipation and may need bowel management as part of their treatment. This is especially problematic as one may lead to the other; however both problems need to be addressed simultaneously for effective results.

An honest discussion with the patient, highlighting the etiology and allaying fears that patients may have, is the initial step. It is important to emphasize that this abnormal muscle contraction can be "unlearned." The next step is physical therapy with a trained pelvic floor physical therapist. Often the patient returns to the referring physician, and when questioned it becomes apparent that the physical therapy was actually focused on Kegel exercises, which is the exact opposite of the intended treatment; therefore, it is important to question the patient on what they actually did during physical therapy. In order to teach relaxation of the pelvic muscles, physical therapy may use sensory biofeedback, electrical stimulation, visual manometry, and simulated defecation techniques to aid the patient in understanding when their muscles are paradoxically contracting [10]. This should involve diaphragmatic breathing and relaxation for efficient relaxation. Patients should continue with physical therapy for multiple visits before considering this therapy a failure. In patients with no access to a trained physical therapist, home-based physical therapy may be offered [16]. If physical therapy is unsuccessful, the next available options are either injections of botulinum toxin A (BOTOX™) or electrogalvanic stimulation (EGS).

EGS is an office procedure where a rectal probe attached to an electrical stimulating device is inserted into the anal canal. The muscle is stimulated transanally at different current amplitudes using galvanic current as tolerated by the patient with an aim to fatigue the muscle. Multiple treatments are required to achieve the desired result [17]. Recommended treatment is three times a week for the first week, two times for the next week, and once a week for several weeks. Maintenance treatments as indicated are provided based on response to treatment and patient tolerance. Most studies have not shown a greater result of EGS over biofeedback, and this may be in part due to nonstandardization of the method of administration. At the Cleveland Clinic,

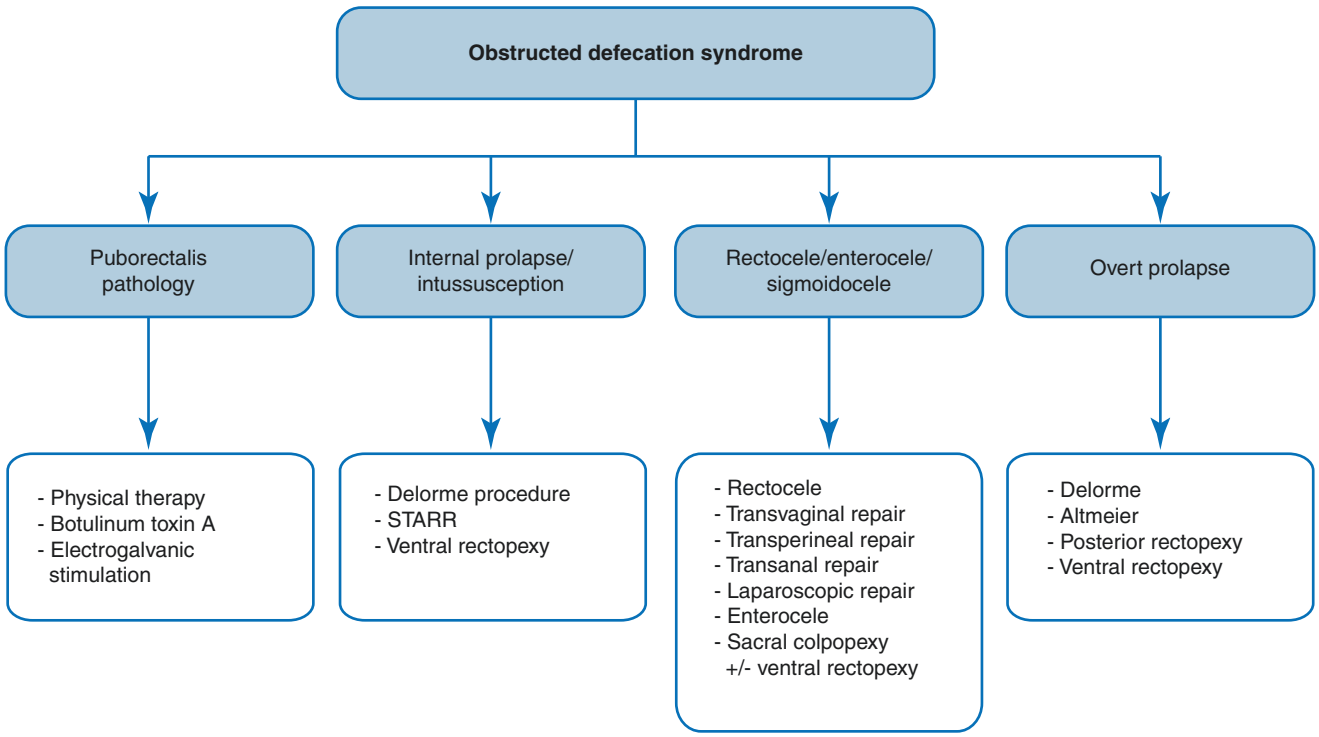

Fig. 59.8 Treatment algorithm for patients with obstructed defecation

EGS is administered over 1 hour and at the frequency described above with anecdotal good results in a selected population. The adverse effects of the treatment are increased pain, rectal irritation, and bleeding. EGS treatment results are varied and few centers offer this treatment.

Botulinum toxin A injections may be given to patients with refractory symptoms. Botulinum toxin A acts by binding to nerves which use acetylcholine. This blocks its release, so the nerve is not signaled to contract and leads to paralysis. The process is reversible and results in temporary paralysis of the muscle fibers. The injections are given under anesthesia followed by an aggressive anal massage [18]. Briefly, 200 units of botulinum toxin A is diluted in 6–7 cc of saline and loaded in six tuberculin syringes. The injections are carried out from the perineum with a finger in the rectum guiding the needle into the levator muscle. The mixture is injected posteriorly, posterior-laterally, laterally, and anterolaterally in the direction of the fibers of the levator muscle (Fig. 59.9). If digital examination reveals a tight internal anal sphincter, this may be included. However, if the internal sphincter is injected, the patient should be warned about temporary fecal incontinence.

Results of botulinum toxin A injections are varied. No consistent dose nor technique is used across various centers. We recommended to continue physical therapy while the effects of botulinum toxin A are in effect. The injections may be repeated at 3-month intervals if good results are obtained. It is unclear if repeated injections dilute the effects over time.

Another treatment with uncertain results is a myomectomy of the puborectalis muscle. This technique has been described but not popularized [19].

Patients who fail all treatments may be offered fecal diversion as a last resort. Patients with both slow transit constipation and dyssynergia and have failed medical treatments are a challenging group to treat. They may be offered colectomy for slow transit constipation (possibly with an ileostomy) followed by treatment of dyssynergia after surgery.

Treatment of ODS Due to Internal Prolapse/ Rectal Intussusception

Internal intussusception may be clinically suspected and demonstrated on cinedefecography. The radiological results should be correlated with the clinical findings. Symptomatic patients may be offered surgery and many treatment options have been described. A decade ago stapled transanal rectal resection or the STARR procedure was popularized. Initially after acceptable results, the procedure has lost favor in the

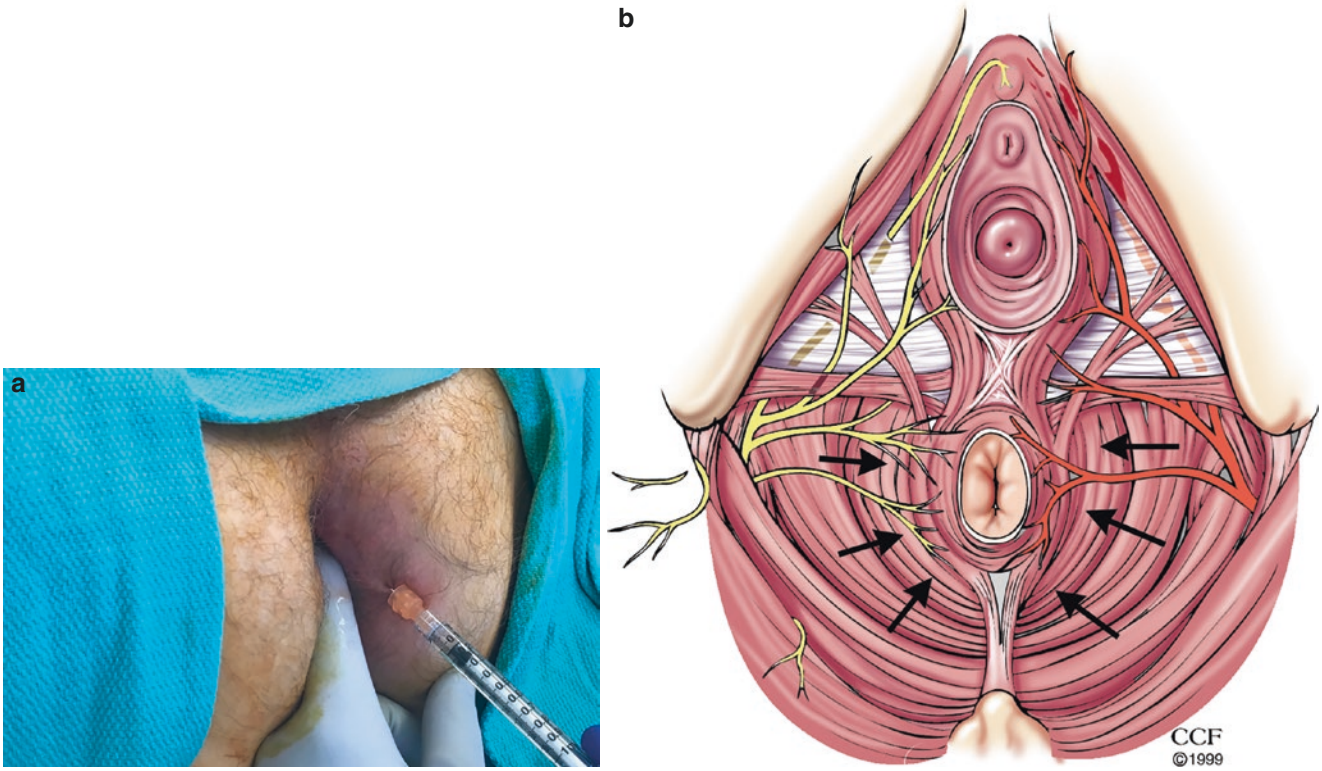

Fig. 59.9 (**a**) Injection technique of botulinum toxin A into the levator ani muscle. (**b**) Diagrammatic representation of the levator ani muscle with other pelvic floor muscle. Arrows indicate the sites of injection of botulinum toxin A. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2020. All Rights Reserved)

USA. Currently few centers offer it. Although results were good, it has been postulated that the positive effect is overestimated due to the variety of patient-reported outcome measures used to calculate ODS [20]. The procedure is still popular in some countries, and variations have been described and include using different stapling techniques like the Transtar™ [21, 22].

Ventral rectopexy has emerged as the newest technique to address symptomatic internal intussusception. Complications related to nonabsorbable mesh have been published [23]. Similar outcomes have been reported using absorbable/biodegradable mesh. The procedure will be discussed in detail in Chap. 60 which focuses on rectal prolapse.

Treatment of ODS Due to Overt Rectal Prolapse

The approach for surgical treatment of rectal prolapse is based on surgeon preference and patient characteristics. Based on this data, it is either a perineal or abdominal approach. Patients who have constipation associated with rectal prolapse may need further testing and further consideration of a sigmoid resection based on findings. The decision-making details and surgical procedures will be discussed in Chap. 60 (rectal prolapse).

Treatment of ODS Due to Rectocele/Enterocele/Sigmoidocele

Optimal therapy for ODS due to a rectocele, enterocele, or sigmoidocele may involve a team approach which includes urogynecologists and colorectal surgeons. Diagnosis is based on a thorough history and physical examination. Further investigations with a cinedefecography and anal physiology interpreted in a multidisciplinary manner guide therapy.

Rectoceles may be treated surgically when symptomatic, usually manifested by requiring vaginal support to aid defecation. Defecography may demonstrate that the rectocele does not empty. Rectoceles may be treated surgically via a laparoscopic, vaginal, transperineal, or transanal approach. Most of these patients may have associated urological/gynecologic issues which should be addressed at the same time.

Transanal repairs require an incision in the anterior wall of the rectum with excision of the mucosa over the rectocele and plication of the rectovaginal septum. The mucosal defect is then closed (Fig. 59.10). Results show a 30–90 percent decrease in the symptoms; however there may be a recurrence of symptoms in about 48 months [24, 25]. Complications include dyspareunia, fecal incontinence, and rectovaginal fistulas.

The STARR procedure has been extensively studied as a treatment for rectoceles. The procedure is done under general anesthesia in the lithotomy position. It consists of full-thickness excision of the rectal wall using two staplers (PPH01) one used anteriorly and one posteriorly. Care should be taken to prevent drawing the vaginal wall in the purse string suture or including it in the staple line. Complications include bleeding, anastomotic leak, rectovaginal fistula, and rectal pain. In the short term good results were reported, but long-term data shows that recurrence of symptoms occurs in about 40% of patients [26]. Currently the STARR procedure is on the decline in Europe [27].

Repairs through the transperineal route have an advantage of not breaching the vaginal mucosa. This involves a transperineal incision with dissection up to the vaginal apex. The surgical procedure is a simple fascial repair from the apex to the perineum. The repair may be augmented using mesh although the use of synthetic mesh has been controversial.

The transvaginal route starts with a vaginal incision followed by separation of the vaginal mucosa from the fascia. Several fascial stitches close the rectocele. The repair may be augmented as in the transperineal repair with mesh. Excess mucosa is trimmed (Fig. 59.11). Recurrence rates are about 7.1% [28]. Complications include dyspareunia, bleeding, and wound infection. In a meta-analysis native tissue transvaginal repairs are preferentially recommended over other repairs [29].

Treatment of an Enterocele/Sigmoidocele

Enteroceles and sigmoidoceles are described as a pelvic floor herniation of the bowel into the pouch of Douglas. Treatment is not recommended on the basis of radiological diagnosis alone. Demonstration of an outlet obstruction along with a substantial hernia warrants surgical consideration. The treatment plan is usually made in conjunction with a urogynecologist. All pelvic surgical problems may be addressed at the same procedure. The preferred repair is a sacrocolpopexy using a monofilament nylon mesh (Fig. 59.12).

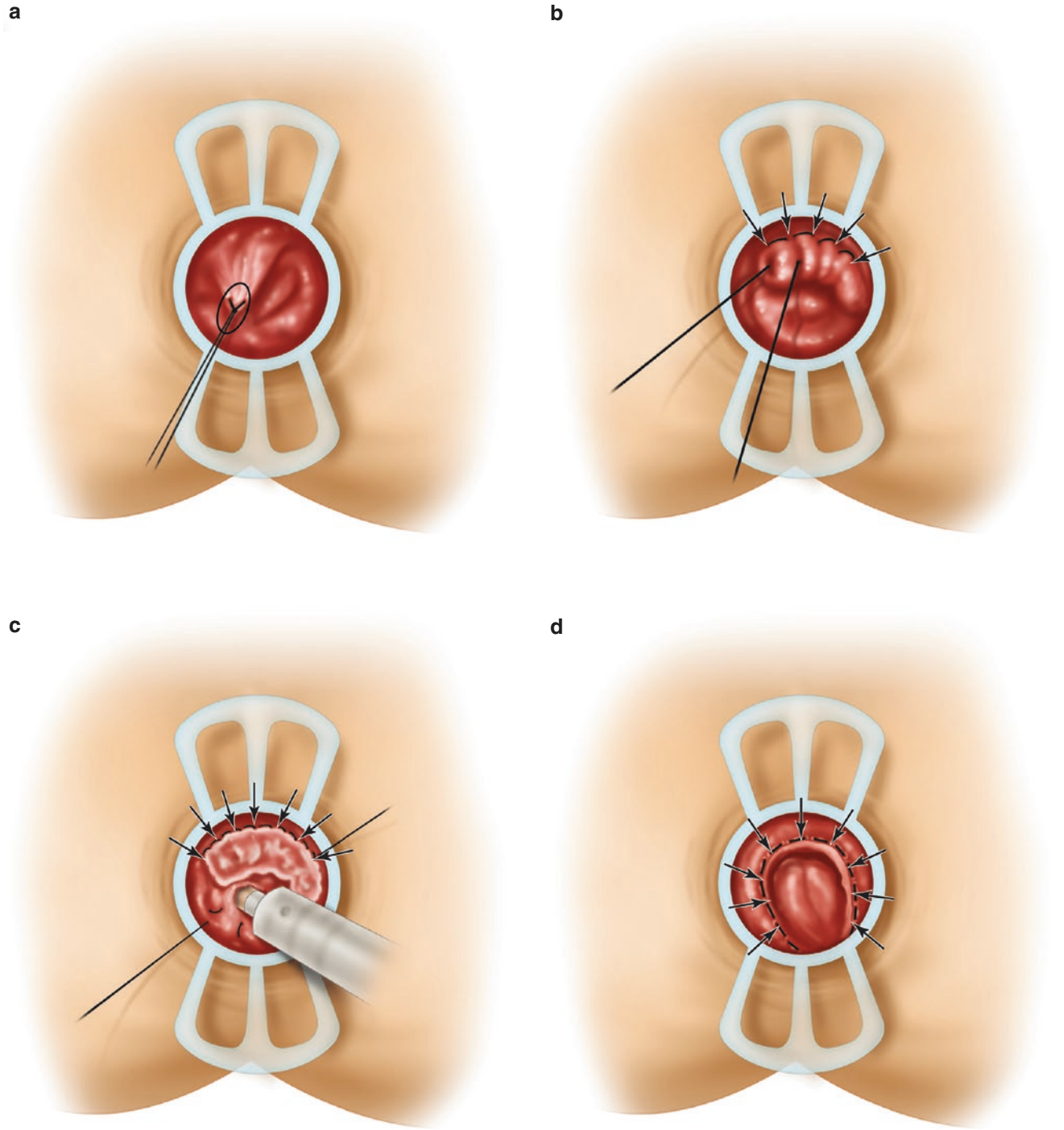

Fig. 59.10 Transanal rectocele repair and mucosectomy (with a circular stapler). (**a**) The apex of the rectocele is identified and pulled down through a stitch (circle). (**b**) A running horizontal suture is placed through the base of the rectocele (arrows). (**c**) The exceeded prolapsed mucosa and the muscular layer were excised, keeping an opened wound with the edges joined by the previous manual suture (arrows). The purse-string suture is tied around the stapler's center rod. (**d**) The remaining stapled suture line (*arrows*). (From 3rd Edition ASCRS Textbook)

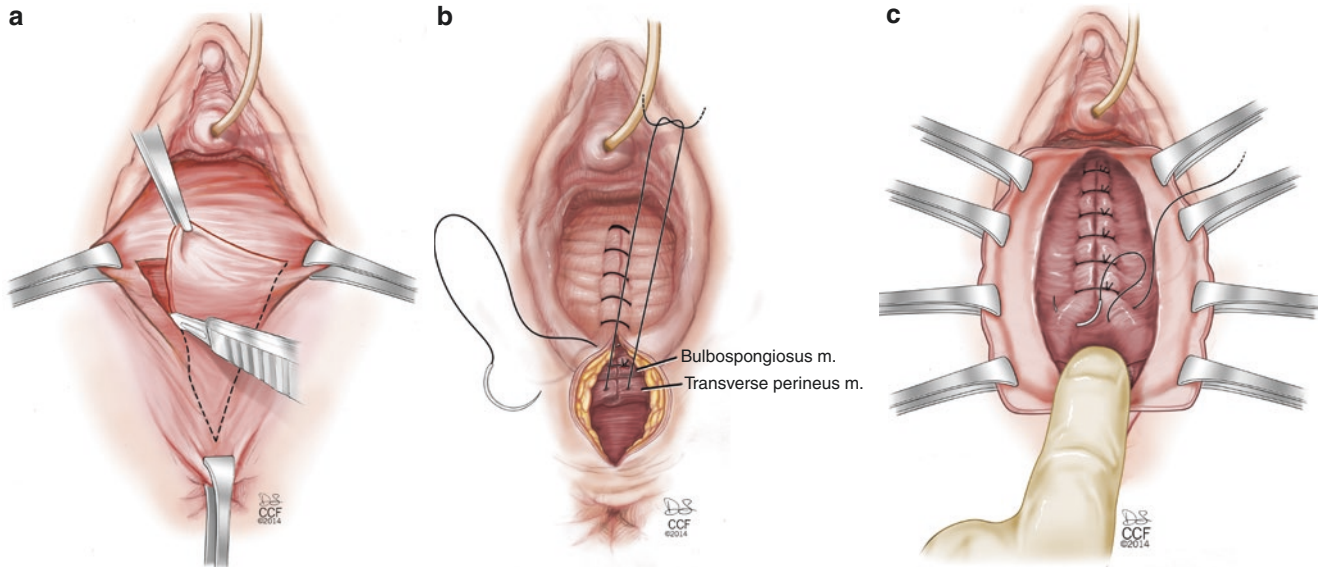

Fig. 59.11 Transvaginal rectocele repair. (**a**) Incision in the vagina. (**b**) Excision of redundant vaginal mucosa after dissection from fascia. (**c**) Plication of the rectovaginal fascia and transverse perinei and bulbospongiosus muscle and suture of the defect in layers

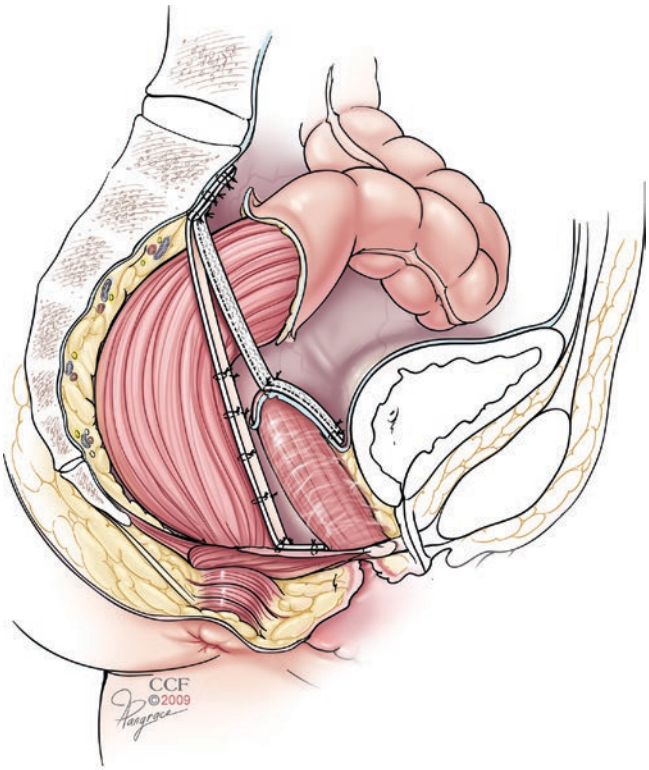

Fig. 59.12 Mesh placement in a sacrocolpopexy and ventral mesh rectopexy showing mesh placement in the pelvis from the vagina and rectum to the sacrum. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2020. All Rights Reserved)

Conclusions

Patients who suffer from obstructed defecation are a special category of patients. Knowledge of normal pelvic anatomy and physiology are essential to make a clinical diagnosis. A detailed history and physical examination are essential. Testing should be complementary to aid in diagnosis or to plan a surgical option. Radiological evidence of mild structural abnormalities may not necessarily be associated with a successful surgical outcome. Recurrent symptoms after a surgical repair or complications may lead to patient dissatisfaction. Patient education and obtaining the patient's trust is an important aspect of treatment.

References

1. Nygaard I, Barber MD, Burgio KL, Kenton K, et al. Prevalence of symptomatic pelvic floor disorders in US women. JAMA. 2008;300:1311–6.
2. Rasmussen OO. Anorectal function. Dis Colon Rectum. 1994;37:386–403.
3. Simren M, Palsson OS, Whitehead WE. Update on Rome IV criteria for colorectal disorders: implications for clinical practice. Curr Gastroenterol Rep. 2017;19:15.
4. Bordeianou LG, Carmichael JC, Paquette IM, Wexner S, et al. Consensus statement of definitions for anorectal physiology testing and pelvic floor terminology (revised). Dis Colon Rectum. 2018;61:421–7.

5. Rao SS, Bharucha AE, Chiarioni G, Felt-Bersma R, et al. Functional anorectal disorders. Gastroenterology. 2016;150:1430–42.
6. Tantiphlachiva K, Rao P, Attaluri A, Rao SS. Digital rectal examination is a useful tool for identifying patients with dyssynergia. Clin Gastroenterol Hepatol. 2010;8:955–60.
7. Karasick S, Karasick D, Karasick SR. Functional disorders of the anus and rectum: findings on defecography. AJR Am J Roentgenol. 1993;160:777–82.
8. Martin M. G, Garcia Armengol, J, Roig Vila, JV, Garcia Coret, MJ, et al., [analysis of experience in the use of dynamic pelvic magnetic resonance imaging in the assessment of obstructive defaecation syndrome]. Cir Esp. 2012;90:292–7.
9. Stewart WF, Liberman JN, Sandler RS, Woods MS, et al. Epidemiology of constipation (EPOC) study in the United States: relation of clinical subtypes to sociodemographic features. Am J Gastroenterol. 1999;94:3530–40.
10. Rao SS, Patcharatrakul T. Diagnosis and treatment of dyssynergic defecation. J Neurogastroenterol Motil. 2016;22:423–35.
11. Barber MD, Kuchibhatla MN, Pieper CF, Bump RC. Psychometric evaluation of 2 comprehensive condition-specific quality of life instruments for women with pelvic floor disorders. Am J Obstet Gynecol. 2001;185:1388–95.
12. Jorge JM, Habr-Gama A, Wexner SD. Clinical applications and techniques of cinedefecography. Am J Surg. 2001;182:93–101.
13. Regadas FS, Haas EM, Abbas MA, Marcio Jorge J, et al. Prospective multicenter trial comparing echodefecography with defecography in the assessment of anorectal dysfunction in patients with obstructed defecation. Dis Colon Rectum. 2011;54:686–92.
14. Lee TH, Bharucha AE. How to perform and interpret a high-resolution anorectal manometry test. J Neurogastroenterol Motil. 2016;22:46–59.
15. Seong MK, Kim TW. Significance of defecographic parameters in diagnosing pelvic floor dyssynergia. J Korean Surg Soc. 2013;84:225–30.
16. Rao SSC, Valestin JA, Xiang X, Hamdy S, et al. Home-based versus office-based biofeedback therapy for constipation with dyssynergic defecation: a randomised controlled trial. Lancet Gastroenterol Hepatol. 2018;3:768–77.
17. Nugent E, Beal M, Sun G, Zutshi M. Botulinum toxin a versus electrogalvanic stimulation for levator ani syndrome: is one a more effective therapy? Tech Coloproctol. 2020;24:545–51.
18. Bolshinsky V, Gurland B, Hull TL, Zutshi M. Levator ani syndrome: transperineal botox injections. Tech Coloproctol. 2018;22:465–6.
19. Faried M, El Nakeeb A, Youssef M, Omar W, et al. Comparative study between surgical and non-surgical treatment of anismus in patients with symptoms of obstructed defecation: a prospective randomized study. J Gastrointest Surg. 2010;14:1235–43.
20. Van Geluwe B, Stuto A, Da Pozzo F, Fieuws S, et al. Relief of obstructed defecation syndrome after stapled transanal rectal resection (STARR): a meta-analysis. Acta Chir Belg. 2014;114:189–97.
21. Naldini G, Martellucci J, Rea R, Lucchini S, et al. Tailored prolapse surgery for the treatment of haemorrhoids and obstructed defecation syndrome with a new dedicated device: TST STARR plus. Int J Color Dis. 2014;29:623–9.
22. Ren XH, Yaseen SM, Cao YL, Liu WC, et al. A transanal procedure using TST STARR plus for the treatment of obstructed defecation syndrome: 'a mid-term study'. Int J Surg. 2016;32:58–64.
23. Riss S, Winstanley J, Collie M. Laparoscopic ventral mesh rectopexy for obstructive defecation syndrome: still the way to go? Int Urogynecol J. 2017;28:979–81.
24. Khubchandani IT, Clancy JP 3rd, Rosen L, Riether RD, et al. Endorectal repair of rectocele revisited. Br J Surg. 1997;84:89–91.
25. Tjandra JJ, Ooi BS, Tang CL, Dwyer P, et al. Transanal repair of rectocele corrects obstructed defecation if it is not associated with anismus. Dis Colon Rectum. 1999;42:1544–50.
26. di Visconte MS, Nicoli F, Pasquali A, Bellio G. Clinical outcomes of stapled transanal rectal resection for obstructed defaecation syndrome at 10-year follow-up. Color Dis. 2018;20:614–22.
27. Kim M, Meurette G, Ragu R, Lehur PA. Current surgical treatment of obstructed defecation among selected European opinion leaders in pelvic floor surgery. Tech Coloproctol. 2016;20:395–9.
28. Marks BK, Goldman HB. What is the gold standard for posterior vaginal wall prolapse repair: mesh or native tissue? Curr Urol Rep. 2012;13:216–21.
29. Grimes CL, Schimpf MO, Wieslander CK, Sleemi A, et al. Surgical interventions for posterior compartment prolapse and obstructed defecation symptoms: a systematic review with clinical practice recommendations. Int Urogynecol J. 2019;30:1433–54.

Rectal Prolapse

60

Margarita Murphy and Sarah A. Vogler

Key Concepts

- Full-thickness rectal prolapse can present with many symptoms including rectal/pelvic pressure, bowel habit irregularity, incomplete evacuation of stool with defecation, seepage of mucous, occasional blood on stool or toilet paper, fecal urgency, and outlet dysfunction constipation. Additionally questions directed at symptoms from the middle and anterior compartments should be asked to plan treatment. A multidisciplinary approach can enhance the outcomes.
- Testing is done to gain insight into the strength, coordination, and anatomic pelvic deficits associated with the prolapse.
- Treatment is nearly always surgical with over 100 procedures reported to treat rectal prolapse. The approach is either perineal or abdominal.
- Ventral mesh rectopexy facilitated by a laparoscopic or robotic approach has rapidly gained acceptance as a favored surgical therapy for rectal prolapse.

Introduction

Rectal prolapse is full-thickness protrusion of the concentric rings of the rectum through the anal canal. It can occur in men and women of all ages but most commonly presents in parous women in the seventh to eighth decade of life. The anatomic changes that occur with rectal prolapse lead to symptoms that are not life threatening but can be lifestyle limiting for patients. These symptoms can span from fecal incontinence and urgency to constipation and outlet dysfunction. Rectal prolapse is a surgically correctable problem. There are over 100 surgical techniques that have been described to repair rectal prolapse. All of these techniques have a risk of developing recurrent rectal prolapse, and none have been declared as a gold standard. Choosing the optimal surgical repair for a patient can involve many factors, including general health, bowel function, bothersome symptoms, and concomitant pelvic organ prolapse.

Multidisciplinary Approach

The female pelvis can be divided into three anatomic compartments: anterior, middle, and posterior. The rectovaginal space and rectum are considered the posterior compartment. Historically, rectal prolapse has been considered a problem that is isolated to the posterior compartment, and colorectal surgeons have focused their repair on this compartment in isolation. A multidisciplinary approach that evaluates all the pelvic compartments is increasingly recommended. Literature has shown that an anatomic defect in a single pelvic compartment is frequently present with symptoms or defects in other pelvic compartments [1, 2]. For example, a patient with rectal prolapse may also present with urinary incontinence or vaginal bulging. This concomitant pelvic organ prolapse (POP) may include enterocele, genital, and bladder prolapses. This correlation increases with age, higher BMI, and in those who have undergone a hysterectomy [3–6]. Overlooking this association during treatment planning may result in exacerbation of symptoms in another pelvic compartment after an isolated repair. This is of particular importance because patients with POP have earlier and higher recurrence rate after rectopexy alone and a higher number of reoperations both for the rectal prolapse and for

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repair of the other compartments [3, 4]. A multidisciplinary approach may offer a more robust surgical plan and avoidance of sequential surgeries [7–9].

Pathophysiology

The mechanism by which full-thickness rectal prolapse occurs remains poorly understood. There have been multiple theories. Broden and Snellman and others have suggested that full-thickness rectal prolapse is initiated by mid-rectal intussusception that progresses down through the anal canal [10, 11]. Connective tissue disorders have also been proposed as a contributing factor in developing rectal prolapse, especially in younger patients. Associated symptoms that may contribute to the development of prolapse include constipation with repeated straining during defecation and solitary rectal ulcer. Intestinal motility abnormalities which include slow transit constipation and malabsorptive diarrhea have also been associated with an incidence of rectal prolapse. Finally, multicompartment pelvic organ prolapse, suggesting weakness in the tissues throughout the pelvis, may also contribute to progressive deterioration in posterior compartment support and eventual development of rectal prolapse.

It is important to differentiate full thickness rectal prolapse from internal rectal intussusception and rectal mucosal prolapse. The underlying mechanism of developing each of these anatomic abnormalities might be the same, but the treatment options may vary. Rectal mucosal prolapse refers to only the rectal or anal mucosal protruding from the anal opening. Internal rectal intussusception involves telescoping of the full rectal wall down toward the anal canal but without full protrusion through the anal opening. The Oxford group has developed a grading system for rectal prolapse (Table 60.1) [12, 13]. This grading system is useful in discerning the severity of rectal intussusception on defecography or exam. The degree of rectal intussusception or rectal prolapse can be correlated to a patient's clinical symptoms and subsequently helpful in developing a surgical plan.

Table 60.1 Oxford rectal prolapse grading system

Oxford rectal prolapse grade	Radiological characteristics of rectal prolapse
Internal rectal prolapse/intussusception	
I (low grade)	Descends no lower than proximal limit of the rectocele
II (low grade)	Descends into the level of the rectocele, but not into anal canal
III (high grade)	Descends into proximal anal canal
IV (high grade)	Descends into distal anal canal
External rectal prolapse	
V (overt rectal prolapse)	Protrudes from anus

Patients with symptomatic deep rectal intussusception may benefit from surgical repair, similar to full-thickness rectal prolapse [13, 14]. However, rectal intussusception may be present in patients who are relatively asymptomatic, and a repair should not be considered in these patients.

Solitary Rectal Ulcer Syndrome

Solitary rectal ulcer syndrome (SRUS) is a disorder of defecation which is often associated with rectal prolapse or internal intussusception. Patients may present with rectal bleeding, difficult defecation, tenesmus, mucus discharge, and anal or pelvic pain. On occasion, the rectal bleeding can be severe enough to require transfusion. The mucosal ulcerations and thickening are due to intussusception of the rectum, which traumatizes the mucosa as it invaginates downward. This repeated trauma my lead to transient ischemia which has been speculated to be part of the etiology.

On examination, there is typically thickened mucosa located on the anterior rectal wall with ulcers seen in about 23% of cases and polyps or masses in 74% [15]. If present, rectal ulcers can be single or multiple shallow ulcers with hyperemic margins and a pale base. This uncommon condition may be misdiagnosed as a polyp or even a cancer because of the alarming appearance seen in some with SRUS. Colitis cystica profunda (CCP) is considered a related disorder that produces similar symptoms to SRUS and may have a similar gross appearance.

Characteristically on biopsy, SRUS has fibrotic obliteration of the lamina propria. There can be a thickened muscularis mucosa. Biopsies of CCP demonstrate mucous cysts lined by columnar epithelium deep in the muscularis mucosa. It is conceivable that with trauma from a cephalad prolapsing area of the rectum, mucosa may be forced beneath the surface to produce these mucous cysts. A correct diagnosis of both these conditions is made with accurate pathologic evaluation.

The workup for both SRUS and CCP includes an in-depth history assessing for straining to defecate, rectal bleeding, and other anal symptoms. Endoscopy with biopsy is essential to make an accurate diagnosis. Treatment of these conditions is challenging, and defecography and anal manometry may be useful to guide choices. Interestingly in SRUS, a thickened internal anal sphincter has been reported as a typical finding on endoanal ultrasonography [16]. Treatment is primarily directed toward normalizing the defecatory disorder with diet modifications and bowel retraining utilizing pelvic floor physical therapy [17, 18]. Argon plasma coagulation has also been described as a potential treatment modality, particularly to control bleeding [19].

In those patients who have a deep rectal intussusception, Oxford grades 3–4, secondary to pelvic floor weakness, and

multicompartment pelvic organ prolapse, surgical correction of the prolapse with a rectopexy can be offered [20–25]. A careful history, physical exam, and testing with manometry and defecography should be performed to differentiate individuals with SRUS secondary to weakness versus those with defecatory dysfunction and SRUS secondary to straining. Surgical correction in those with internal prolapse secondary to weakness and multicompartment prolapse could involve a form of rectopexy, either suture, mesh, or ventral rectopexy, and consideration of combined surgery with urogynecology [26, 27]. Surgical correction is not recommended in those patients who have defecatory dysfunction secondary to straining and pelvic floor dyssynergia. These patients benefit from pelvic floor physical therapy.

Evaluation of the Patient

History and Physical Exam

The evaluation of a patient with rectal prolapse should start with a careful history that includes an overview of general health and specific attention to pelvic floor symptoms and gastrointestinal complaints. Symptoms that occur commonly with rectal prolapse include rectal/pelvic pressure, bowel habit irregularity, incomplete evacuation of stool with defecation, seepage of mucous, occasional blood on stool or toilet paper, fecal urgency, and outlet dysfunction constipation. Reviewing if there is a prior history of rectal prolapse repair or other pelvic organ prolapse repair is important and can impact your surgical planning. Asking the patient about symptoms related to other pelvic compartments, such as urinary incontinence, urinary hesitancy, vaginal pressure, dyspareunia, or vaginal bulging, will help in determining if a multidisciplinary treatment team is necessary [28]. Jackson, et al. found that 20–35% of patients with rectal prolapse reported urinary incontinence. Additionally, 15–30% of patients with rectal prolapse also have significant vaginal vault prolapse [2].

A full physical exam should be performed with special attention to the abdomen and pelvis. A digital rectal exam will help in understanding anal sphincter tone and strength. Asking the patient to squeeze and bare down during digital rectal exam will help in assessing their pelvic floor coordination. Also, asking the patient to bare down while sitting upright on a commode and using a mirror to visualize their perineum will allow for visualization of rectal prolapse and vaginal protrusion or widening.

Since patients will commonly present with a change in their usual bowel habits, either constipation or incontinence, a review of their colonoscopy history should be performed. A colonoscopy should be considered to rule out any other cause for their change in bowel habits.

Patient Questionnaires

It is important to understand patients' bowel habits prior to surgical repair of rectal prolapse. This can be done as part of the history and also by using more objective measurement tools such as validated questionnaires. Capturing this information helps in setting patient expectations for their bowel habits after surgery and allows for counseling as to medical bowel regimens that can be started preoperatively and may help to alleviate some of these bothersome symptoms. While surgical correction of the rectal prolapse may improve or relieve these symptoms, it is also possible that these symptoms may be persistent or exacerbated by surgery. Changes in functional symptoms, such as incontinence or constipation, can evolve for several months after surgery. Standardized questionnaires can help in objectively following this evolution. Since rectal prolapse, and even more so multicompartment pelvic organ prolapse, can span a very broad range of patient reported symptoms, it is difficult to choose the single best questionnaire to recommend for routine clinical use. In 2019, the Pelvic Floor Disorders Consortium identified the validated surveys most highly recommended for several symptoms and combined these into a single validated instrumented labeled IMPACT (Initial Measurement of Patient-Reported Pelvic Floor Complaints Tool) [29]. IMPACT allows for capturing multiple patient-reported symptoms related to prolapse and how these symptoms improve, worsen, or develop over time.

Anorectal Physiology Testing

The size of the rectal prolapse or depth of rectal intussusception can result in changes that are seen on anal physiology studies such as manometry. Repeated stretching of the anal sphincter complex by protrusion of tissue through this canal results in low anal rectal pressures and diminished recruitment of anal squeeze pressures. Understanding the baseline strength of the anal sphincter complex prior to surgical repair of rectal prolapse may help in counseling patients as to expected postoperative continence or the potential need for postoperative physical therapy to regain strength.

EMG recruitment studies may have variable results in the setting of POP due to the pressure applied to the pelvic floor from prolapsing tissue with Valsalva or evacuation. The EMG tracing may show appropriate relaxation of the pelvic floor muscles. Interestingly, a paradoxical increase in EMG activity with Valsalva may occur due to the mounting pressure from prolapsing tissue. This can mimic the EMG recruitment results seen with dyssynergia of the pelvic floor, so clinical correlation to the test results is imperative.

Imaging

Fluoroscopic defecography imaging is the most helpful test to better understand the anatomic pelvic dynamics that are occurring during defecation. Full-thickness rectal prolapse can be easily seen on physical exam with the patient straining on a commode. However, physical exam is unable to determine the extent of internal pelvic organ collapse with evacuation, so defecography is used to capture this. Additional findings on defecography that may be contributing to the extent of rectal prolapse or the cause for rectal prolapse include anterior rectal wall weakness with rectocele, internal rectal intussusception, enterocele, sigmoidocele, uterovaginal prolapse, or cystocele (Fig. 60.1a–c).

An alternative is dynamic magnetic resonance imaging defecography (dMRD) [30]. This imaging technique is almost always performed with the patient in a supine position as opposed to the more physiologic sitting position used during fluoroscopic defecography. Ramage et al. [31] reported that the dMRD is less sensitive than fluoroscopic defecography. Miss rates for anorectal intussusception and rectal prolapse were significantly higher with dMRD than with the use of fluoroscopic defecography. Small rectoceles and vaginal vault descent were also less likely to be detected.

Treatment

In the vast majority of circumstances, treatment of rectal prolapse is surgical. Bowel habits can be improved by starting a bowel regimen prior to surgery to achieve optimal stool consistency and regularity. Pelvic floor physical therapy may also help to optimize pelvic floor coordination. However, only in rare cases of extreme constipation and straining causing rectal prolapse will these measures allow for full resolution of rectal prolapse.

There are two main categories of surgical repairs for rectal prolapse: abdominal and perineal. The surgical approach is chosen based on a patient's general health, prolapse-associated symptoms, concomitant pelvic organ prolapse, prior surgical history, and surgical urgency. Incarcerated rectal prolapse requires a perineal approach. Otherwise, a perineal repair generally has a higher risk of prolapse recurrence and is thus reserved for patients who are very poor surgical candidates [32, 33]. The newest surgical options include minimally invasive techniques and multidisciplinary surgical teams. Overall, the optimal operation for rectal prolapse is unclear [34, 35].

Perineal Repairs

Perineal repairs can be performed with the use of light anesthetic without paralysis and at times with spinal or local anesthetic. Avoidance of abdominal incisions also minimizes postoperative discomfort and can help to facilitate early ambulation, deep breathing, and coughing. The three main perineal procedures are anal encirclement, Delorme procedure, and Altemeier procedure.

Anal encirclement (Thiersch procedure) has generally fallen out of practice because of high failure and complication rates. Thus, it is reserved for patients with the most extreme comorbidities or those with prolapse and a permanent colostomy who cannot tolerate other options. The procedure involves reduction of the prolapse and placement of a permanent material that encircles the anus in the subcutaneous space. A thick suture, biologic mesh, permanent mesh, or wire has been used for the encirclement with the goal of nar-

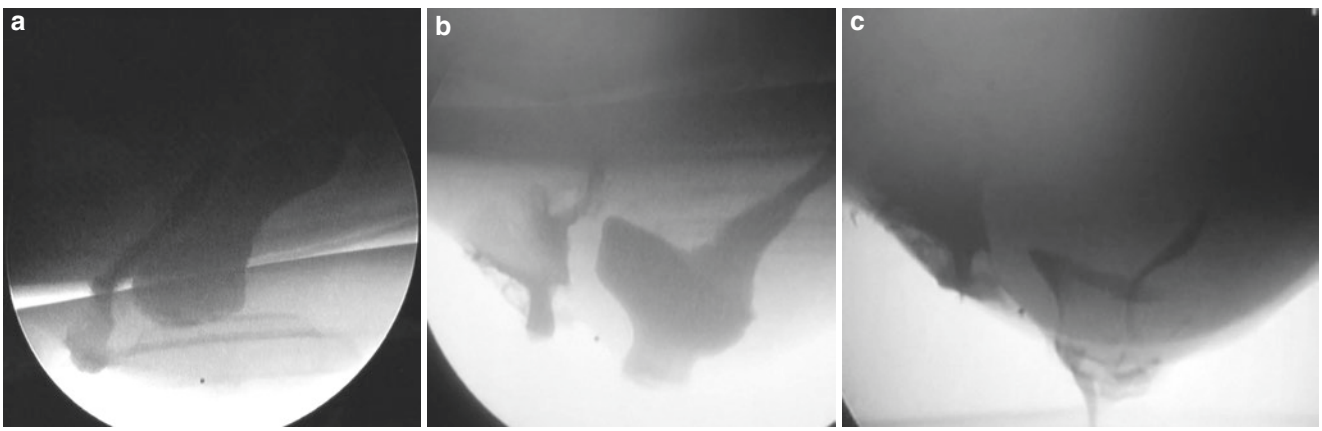

Fig. 60.1 Defecography images: (**a**) Pre-evacuation – vaginal silhouette and rectum prior to evacuation. (**b**) Mid-evacuation – development of rectocele and loss of vaginal apical support. (**c**) End of evacuation – rectal intussusception has progressed into short segment of full-thickness prolapse

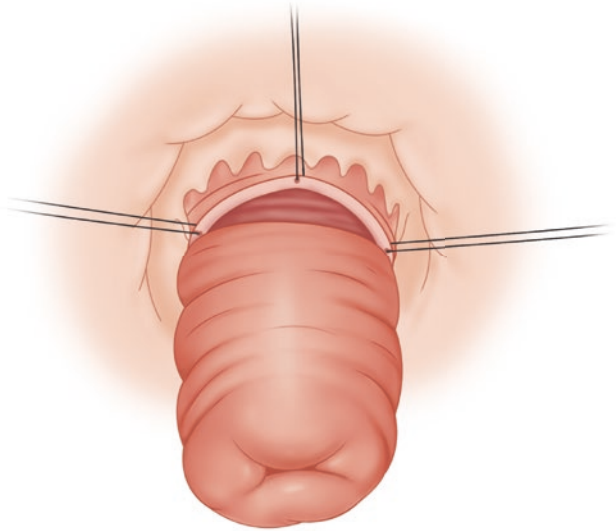

Fig. 60.2 Delorme procedure. Two centimeters proximal to the dentate line, a circular line is marked out in the mucosa with the bovie. The area is injected with a vasoconstricting agent. An incision is then made through the mucosa but not full thickness through the entire rectal wall. The bovie is an excellent means to make the mucosal incision

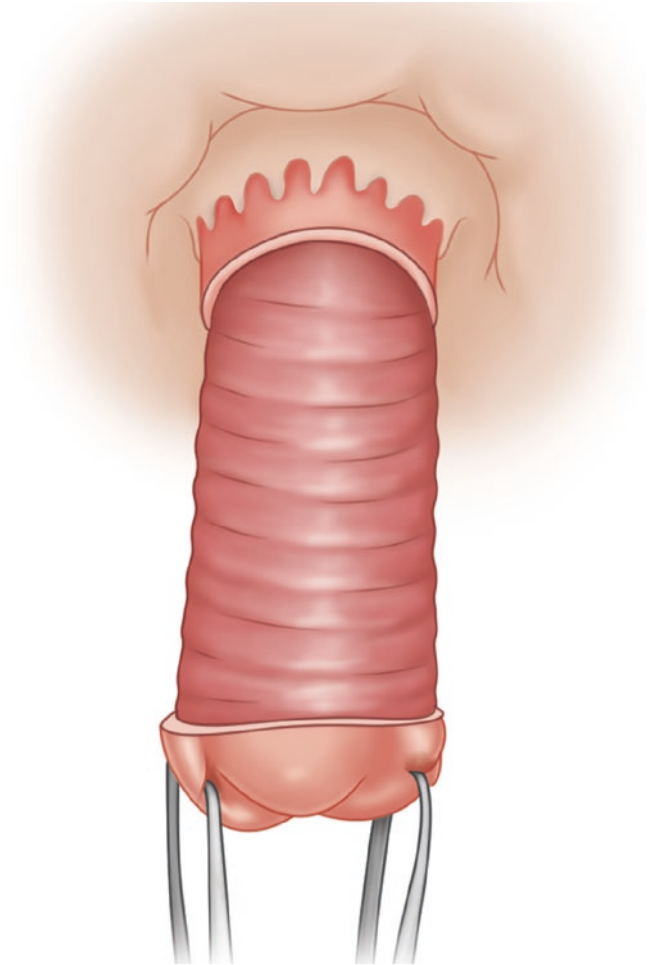

Fig. 60.3 Delorme procedure. Working cephalad, a sleeve of mucosa is dissected off the muscular layer of the rectal wall. Liberal injection of saline with or without a vasoconstricting agent assists in developing the correct plane. Care is taken to achieve meticulous hemostasis as there are penetrating vessels in this plane of dissection which will need to be tied or coagulated

rowing the anal canal to prevent recurrent prolapse. Complications include erosion of the encircling device, severe outlet dysfunction, and recurrent prolapse. The risk of recurrent prolapse ranges from 33 to 44% [36].

The Delorme procedure was first described by Delorme in 1900 and involves a mucosal sleeve resection. The mucosa of the prolapsed segment is stripped and resected (Figs. 60.2 and 60.3). Then the underlying muscle layers are plicated, and the proximal and distal mucosa is re-approximated (Figs. 60.4 and 60.5). This procedure is most commonly performed on patients who are poor abdominal surgical candidates and have a short segment of rectal prolapse. The morbidity and mortality associated with this procedure are very low; however, the prolapse recurrence rates are high and range from 16% to 30% [37–39]. For a description of the procedure, please see Fig. 60.6.

The Altemeier procedure is a perineal rectosigmoidectomy and was first described in the 1960s. To start this procedure, the rectum is prolapsed out of the anus, and a circumferential full-thickness incision is made, starting approximately 2 cm above the dentate line. Once the mesorectum is visible, it is systematically divided by identifying the point of maximal tension and working circumferentially to continue pulling the redundant rectum and sigmoid colon out through the anal canal. The peritoneal reflection in the rectovaginal septum is encountered anteriorly, and the peritoneal cavity is commonly entered as the dissection proceeds proximally. Once the rectal redundancy or redundant sigmoid colon loop is maximally pulled through the anal canal, the colon is divided at this proximal resection point, taking care to ensure adequate blood supply and lack of tension. A sutured coloanal anastomosis or low end-to-end stapled colorectal anastomosis is created. This procedure can be combined with a levatorplasty to help in supporting the weak pelvic floor muscles and possibly improve postoperative continence [40]. Since this procedure involves a full resection, it carries the risk of anastomotic bleeding, pelvic abscess, or anastomotic leak. Recurrence rates can range up to 20% (Figs. 60.7, 60.8, 60.9, 60.10, 60.11, 60.12, and 60.13) [41].

Concomitant pelvic organ prolapse and a history of prior prolapse repairs are important parts of surgical decision-making and planning. In patients with vaginal prolapse, a colpocleisis can be performed in combination with a Delorme or Altemeier procedure. A prior history of an abdominal surgery for prolapse repair does not preclude doing a perineal procedure for recurrent prolapse. However, an Altemeier

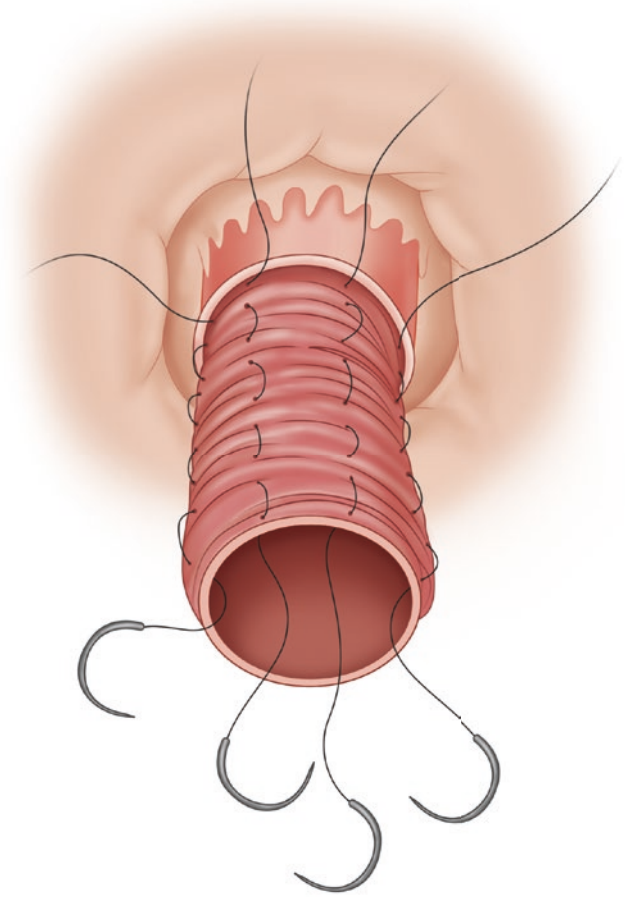

Fig. 60.4 Delorme procedure. When there is tension at the plane of the mucosal dissection, this is completed. After ensuring that complete hemostasis exists, the muscular layer (the rectal wall) is approximated using sutures starting at the proximal cut mucosal end and including bites of the rectal wall every few centimeters until the other cut edge is reached at the anal region. Placement of these sutures is along the longitudinal axis of the rectal wall and is not full thickness but deep enough to ensure when tied they do not tear through the tissue. As these sutures are placed, they compress the wall in an accordion (or concertina) like fashion. Four to six futures are typically required to stabilize the compressed rectal wall

procedure cannot be performed if there is a prior history of sigmoid resection due to the risk of vascular disruption to the coloanal anastomosis [42].

Incarcerated Rectal Prolapse

An attempt should be made to manually reduce rectal prolapse if the prolapsed rectum appears pink and well perfused. Coating the prolapse with granulated sugar may help to decrease the swelling which will facilitate manual reduction. If the prolapse cannot be reduced or appears gangrenous, then an Altemeier procedure should be performed to excise the incarcerated rectum (see Figs. 60.14 and 60.15). A

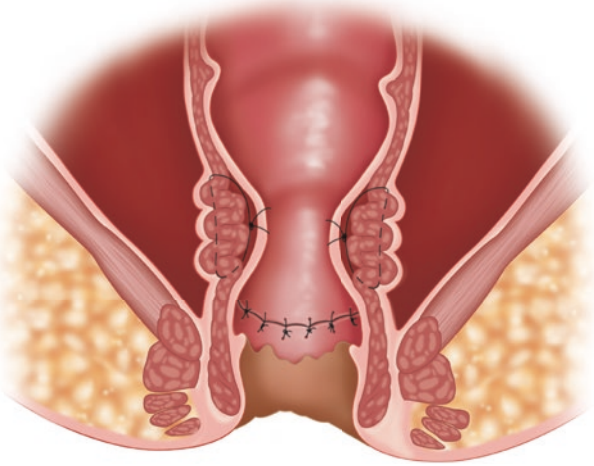

Fig. 60.5 Delorme procedure. After the sutures that have been placed in the rectal wall are tied down, the two cut ends of the mucosa will be in close proximity. The mucosa is then reapproximated with sutures to create a neo-anastomosis in the anal canal proximal to the dentate line

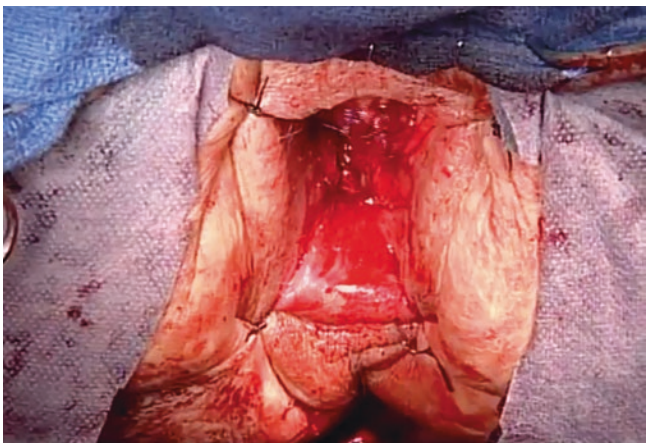

Fig. 60.6 Delorme procedure

tension-free coloanal anastomosis can be performed in this scenario if the proximal bowel appears healthy with a good blood supply.

Abdominal Repairs

Minimally invasive (laparoscopic and robotic) or open approaches can be used to perform a rectopexy during which the rectum is anchored to the anterior longitudinal ligament near the level of the sacral promontory, thereby correcting the telescoping of the prolapsing bowel. This approach has shown lower recurrence rate, better functional results, and low morbidity compared to perineal operations. Advanced age has been considered a factor to exclude abdominal surgeries as a possible treatment option. The

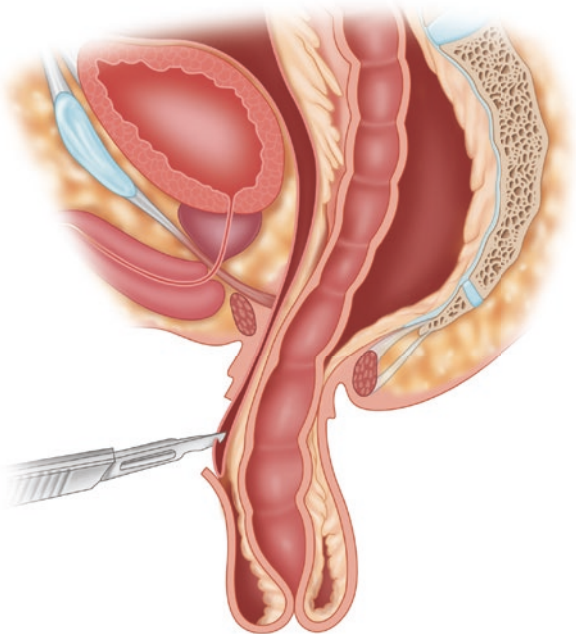

Fig. 60.7 Altemeier procedure. A circular incision is mapped out approximately 2–5 cm cephalad to the dentate line in the rectal mucosa

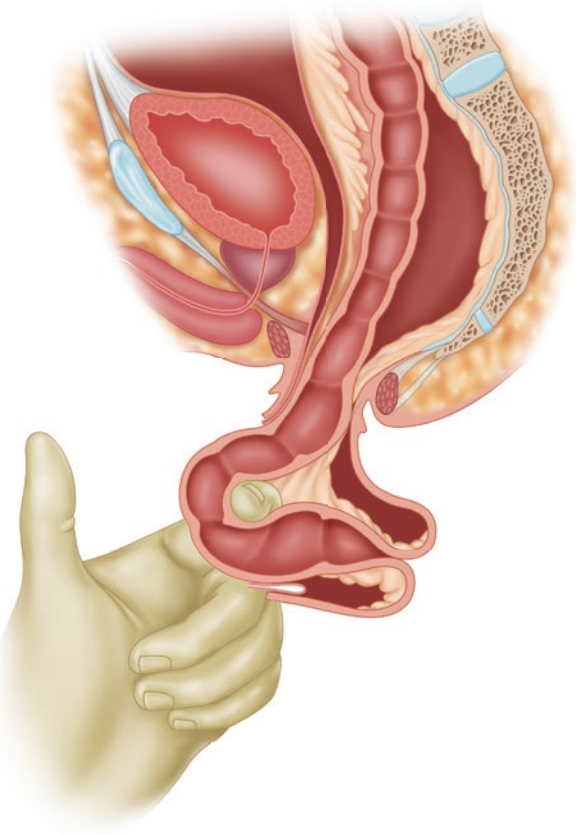

Fig. 60.8 Altemeier procedure. The rectum is pulled out of the anus and the mesentery divided stopping at a point just distal to where the rectum (or sigmoid) no longer easily can be pulled out of the anus

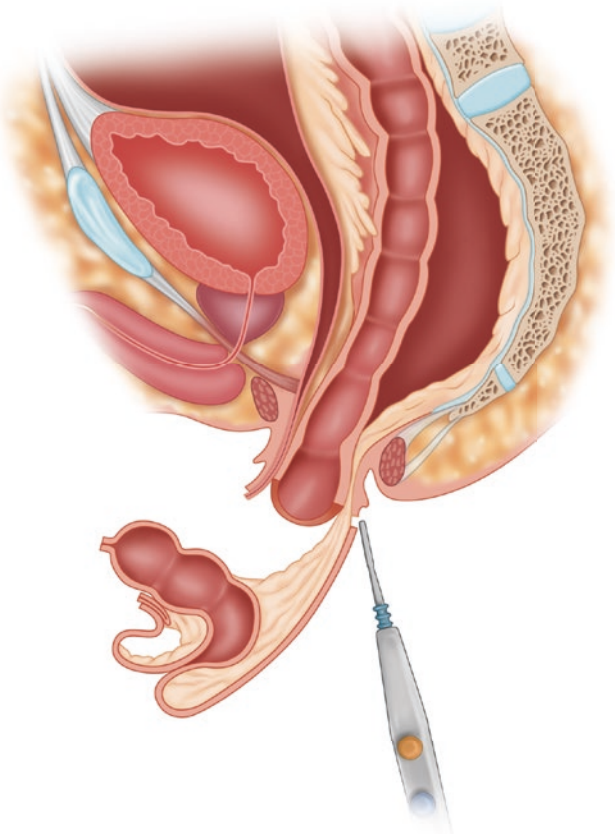

Fig. 60.9 Altemeier procedure. The redundant rectum and sigmoid colon are excised. It is important to ensure that the proximal bowel has sufficient mesentery to avoid ischemia to this segment

rationale is that perineal procedures can be performed on these elderly and frail patients without a general anesthetic and with lower morbidity and mortality. Fang et al. queried the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database in 2008 [43]. Results showed that in patients who were considered high risk, defined as ASA of 3 and 4, the relative risk for mortality was four times greater in the group that underwent perineal procedures than in the abdominal procedure group. Furthermore, the mortality in the laparoscopic approach was 0%. Bjenker and Mynster [44] reviewed the National Danish Registry data to include 2004 through 2014. The overall 30-day mortality rate was only 2.1% despite 41% of their patients being octogenarians. In this study, perineal procedures had a higher mortality rate when compared to abdominal procedures ($p < 0.0001$). Specifically, mortality was 3.3% after open rectopexy, 1.4% after laparoscopic rectopexy, 4.4% after Altemeier, and 2.3% after Delorme. Also, the recurrence rate was much higher for the perineal procedures with the highest being for that of the Altemeier operation (50%). Although these retrospective reviews have some inherent bias as to which patients underwent perineal versus abdominal sur-

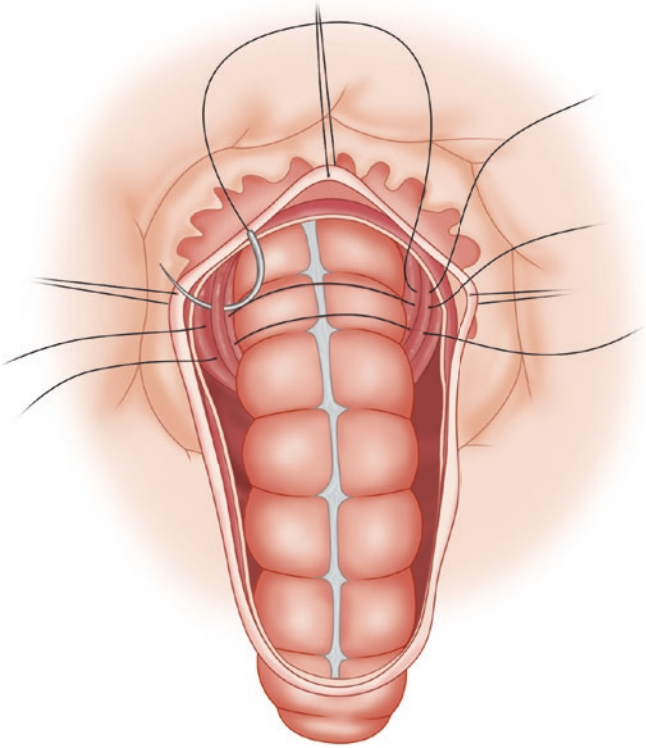

Fig. 60.10 Altemeier procedure. Anteriorly the levator ani muscles may be approximated with sutures (levatorplasty) which may improve fecal continence

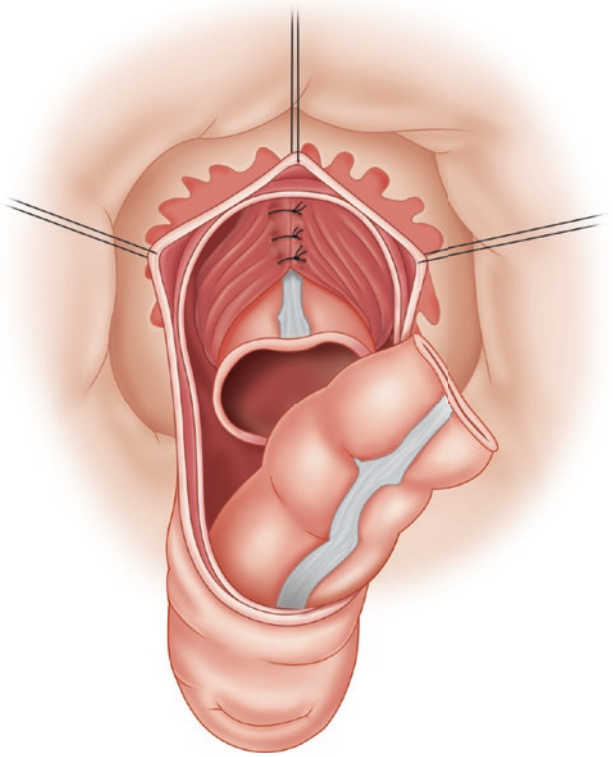

Fig. 60.11 Altemeier procedure. The redundant rectum and sigmoid colon are excised. It is important to ensure that the proximal bowel has sufficient mesentery to avoid ischemia to this segment. This figure also demonstrates the completed levatorplasty

geries, there is growing evidence that minimally invasive abdominal procedures can safely be performed on elderly patients with rectal prolapse.

Suture Rectopexy

This was first described by Dr. Daher Cutait in 1959 and was presented as a video at the Royal Academy of Medicine. For this approach, the rectum is mobilized anteriorly and posteriorly to the level of the levators with identification and preservation of the hypogastric nerves. The rectum is then pulled cephalad, and the mesorectum is sutured to the anterior longitudinal ligament at the sacral promontory with nonabsorbable suture. Some surgeons may use other fixation devices such as tacks. Long-term results have shown recurrence rates of up to 20% [45, 46]. Improvement in continence can be seen in up to 34–42% of patients; De Brujin et al. also reported new onset incontinence in 7% [46]. New onset constipation is seen in up to 50% percent of cases [35, 37]. Denervation of the rectum from the neural efferent nerves residing in the lateral ligaments is thought to contribute to worsening function and constipation. Unilateral pres-

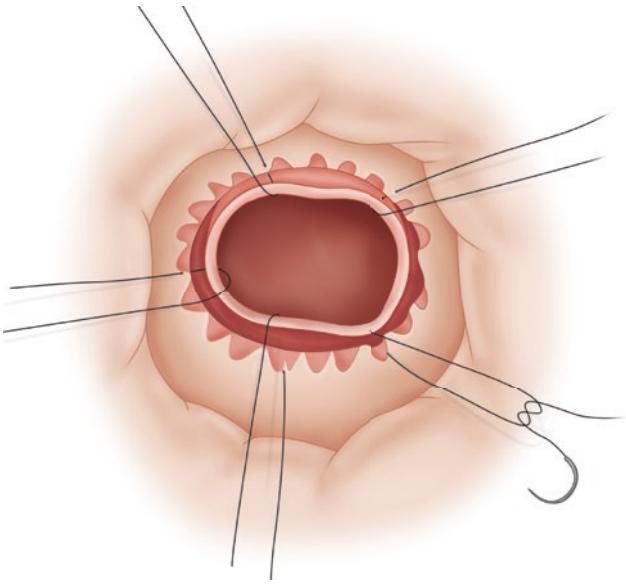

Fig. 60.12 Altemeier procedure. A tension-free end-to-end anastomosis is carried out using sutures (a circular stapled anastomosis also can be done)

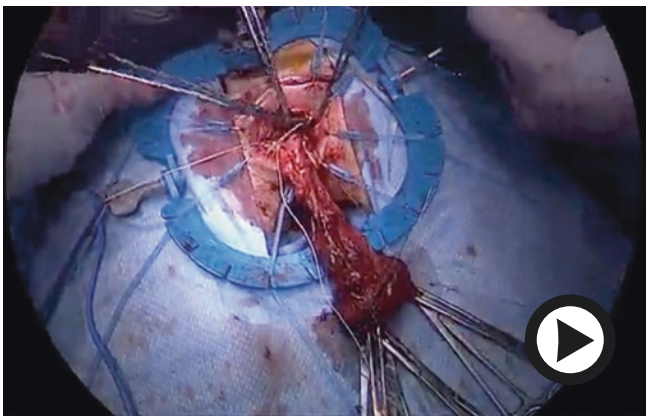

Fig. 60.13 Altemeier procedure. https://doi.org/10.1007/000-33t

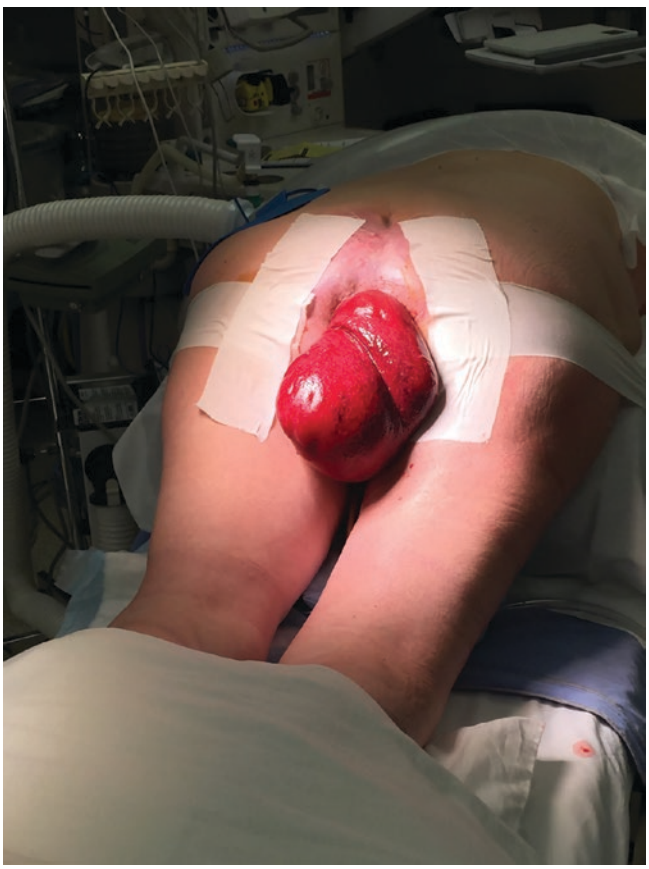

Fig. 60.14 Incarcerated rectal prolapse

ervation of a lateral stalk and unilateral fastening of the rectal mesentery to the sacrum can be considered to mitigate worsening function [47]. Hidaka et al. reported a 6-year follow up of a double-blind, randomized study comparing laparoscopic suture rectopexy versus laparoscopic ventral mesh rectopexy [48]. The recurrence rate was reported as 23.3% in the suture rectopexy group compared to 8.2% in the ventral rectopexy group. The functional outcomes, including obstructive defecation symptoms, incontinence, constipation, and quality of life, also favored laparoscopic ventral mesh rectopexy.

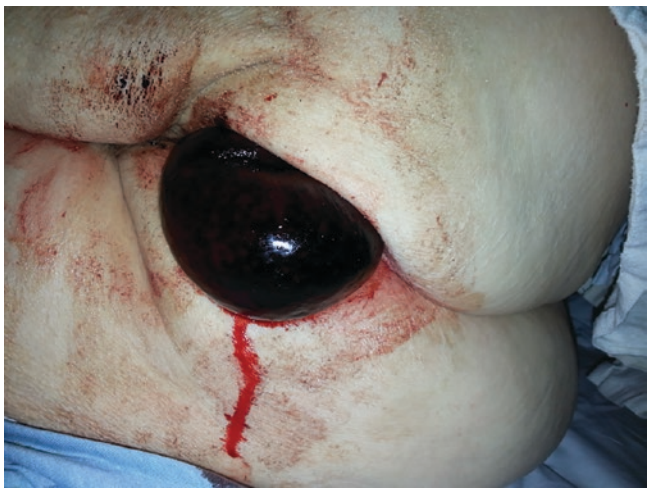

Fig. 60.15 Strangulated rectal prolapse with compromised blood supply

Suture Rectopexy with Sigmoid Resection

As described by Frykman and Goldberg in 1969, [49] adding a sigmoid resection to the rectopexy decreases postoperative constipation, especially in those patients who present with this complaint preoperatively [50]. The possibility of anastomotic leak was thought to add unnecessary morbidity to the treatment of what is otherwise a quality of life, benign pathology. This, however, has not proven to be the case. The number of anastomotic complications reported in the literature is low, varying from 0% to 2.3% [51–53]. Laubert et al. [51] noticed an overall improvement in incontinence symptoms in 64% of the patients and improvement in constipation in 77% of their patients. Formijne et al. [24] had similar findings and found that when compared with laparoscopic ventral rectopexy, both techniques achieved the same improvement in constipation and obstructive defecation symptoms. Rectal prolapse recurrence rate is lower than that of rectopexy alone, between 10% and 13% (Fig. 60.16) [52].

Posterior Rectopexy with Mesh

Professor Charles Wells first described this procedure in 1959 when he reported using a polyvinyl alcohol sponge (Ivalon) in 15 patients [54]. Pelvic sepsis in up to 16% of patients forced the evolution of the technique to the use of mesh and avoidance of the sponge [55].

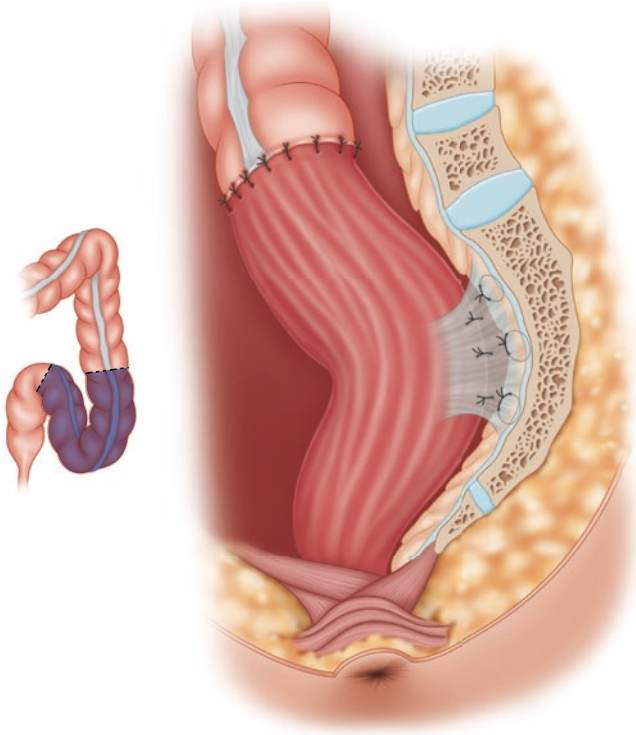

Fig. 60.16 Resection/rectopexy. The sigmoid colon is excised and an end-to-end anastomosis performed. The rectum is mobilized, and non-absorbable sutures are placed in the lateral rectal ligament. The suture is then placed in the anterior sacral ligament (tacks can also be used) to anchor the rectum securely to the sacrum at about the S1 level. It is important to position the needle to enter the sacrum at a right angle. The needle is pushed into the bone and minutely pulled back. Then the curve of the needle is followed when continuing the suture placement at the sacrum. This ensures the suture will be in the anterior sacral ligament. Two sutures on the right are typically placed. Sutures can be placed also on the left side of the rectum, but when tying them down, it is crucial to ensure the rectum is not kinked/occluded

The rectum is mobilized anteriorly and posteriorly to the level of the levator muscles. The sacral promontory is exposed, and a piece of mesh is sutured to the anterior longitudinal ligament. The rectum is then pulled cephalad, and the mesh is wrapped around the rectum leaving the anterior wall of the rectum open. The mesh is attached to the lateral stalks. Constipation is significantly worse postoperatively, and the recurrence rate has been reported to be 6% for a complete rectal prolapse and 12% for mucosal prolapse, but with longer follow-up, the recurrence rate increases [56–59]. Even with mesh, as opposed to the sponge, the morbidity secondary to pelvic sepsis is still high [58].

Ripstein Procedure

The Ripstein procedure, also known as anterior sling rectopexy, was first described by Ripstein in 1952 [60]. Multiple variations of the technique have since been described. After complete mobilization of the rectum, an anterior sling made with fascia lata or mesh is fixated to the anterior rectum and then to the anterior longitudinal ligament on both sides. Recurrence rate has been described up to 13%. Roberts et al. reported recurrence was three times higher in males (24%) than in females [61]. Reports show some improvement in continence but not in constipation symptoms. De novo constipation is seen in 14% of patients and fecal impaction requiring hospital admission for management in 5%. To decrease the incidence of obstruction, Ripstein himself modified the procedure such that the sling would not go all the way around the anterior portion of the rectum, but rather a gap is left between the two edges [56, 58, 61]. Roberts et al. reported a 52% complication rate [62]. Due to the high morbidity of this procedure and the risk of rectal outlet dysfunction, this procedure is performed much less frequently.

Ventral Mesh Rectopexy

The ventral mesh rectopexy (VMR) technique was first described by D'Hoore and has rapidly become an important option in the armamentarium for the treatment of rectal and pelvic organ prolapse [63]. The dissection is purely an anterior dissection and thus avoids potential complications of a posterior rectal dissection. To begin, the sacral promontory is exposed,s and then the rectum is mobilized anteriorly, opening the rectovaginal septum all the way to the pelvic floor (Fig. 60.17). The visualization and extent of this dissection is facilitated by a laparoscopic or robotic approach. Mesh, either biologic or synthetic, is cut to the appropriate size and is sutured to the rectum and sometimes the pelvic floor itself (Fig. 60.18). Typically, 8–12 stitches are placed between the mesh and to the distal and mid-anterior rectum. The mesh is then sutured to the anterior longitudinal ligament at the level of the sacral promontory (Fig. 60.19 and 60.20). This allows for elevation of the pelvic floor and correction of rectocele, rectal prolapse, and intussusception. In those patients with

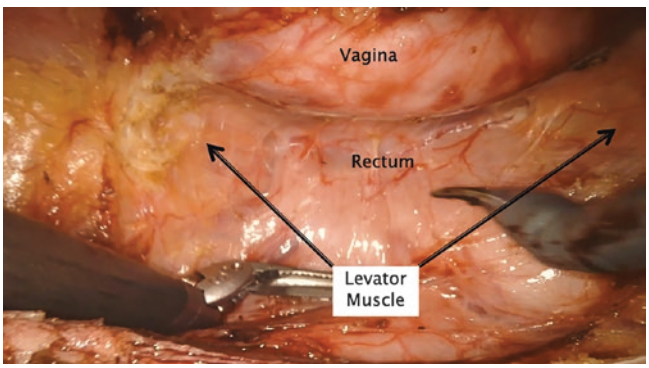

Fig. 60.17 VMR dissection down to the pelvic floor in preparation for mesh placement

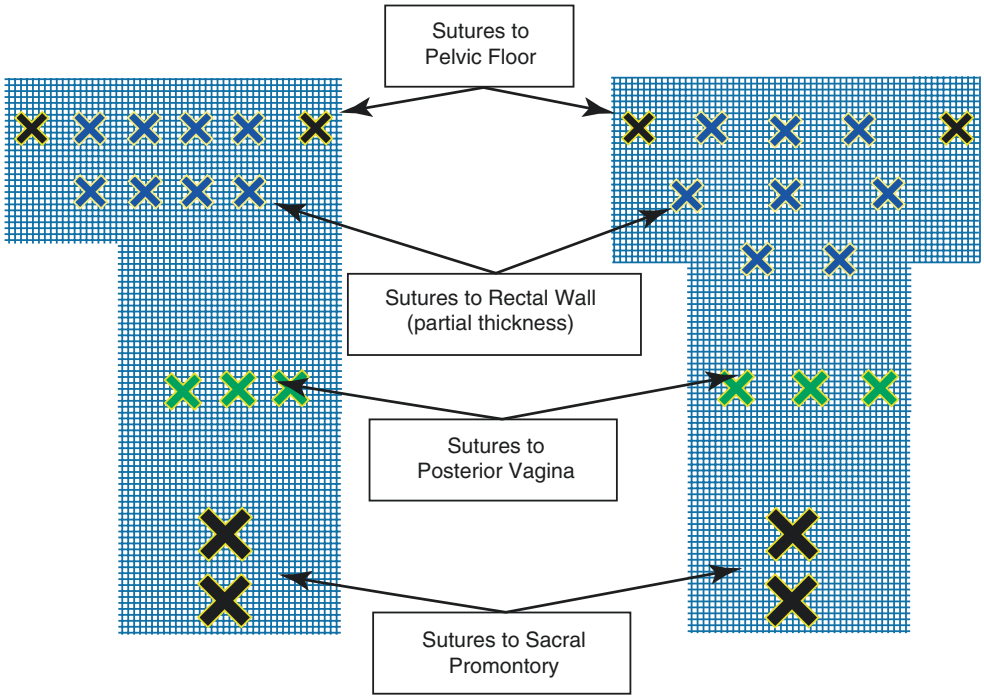

Fig. 60.18 Mesh used for VMR can be cut to various configurations and sizes depending on surgeon preference and pelvic anatomy. This diagram shows two possible mesh configurations and suture locations

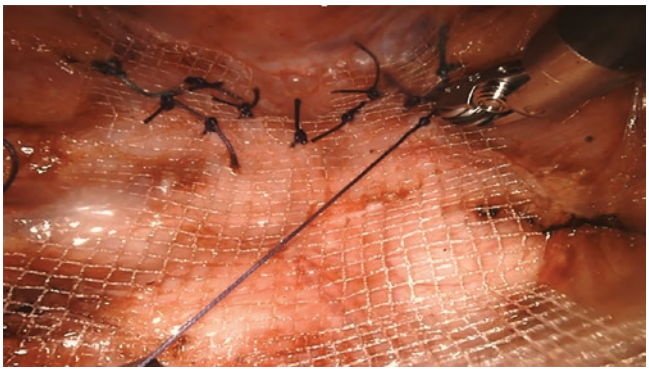

Fig. 60.19 Securing mesh to the anterior rectal wall during VMR

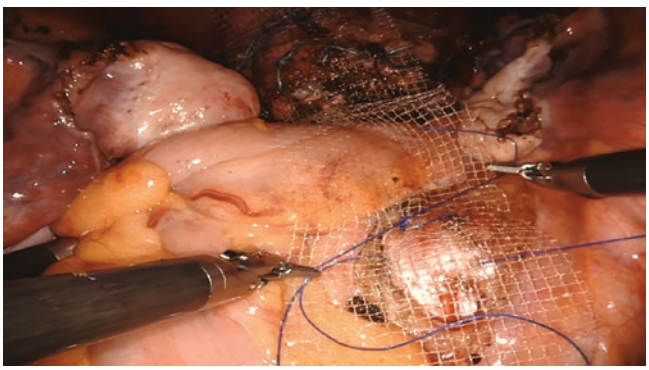

Fig. 60.20 Securing mesh to the sacral promontory during VMR

severe pelvic floor laxity, stitches may be placed between the mesh and the levator ani and the pubococcygeus muscles [64]. Once the mesh is completely secured in place, the peritoneum is reapproximated over the mesh (Fig. 60.21).

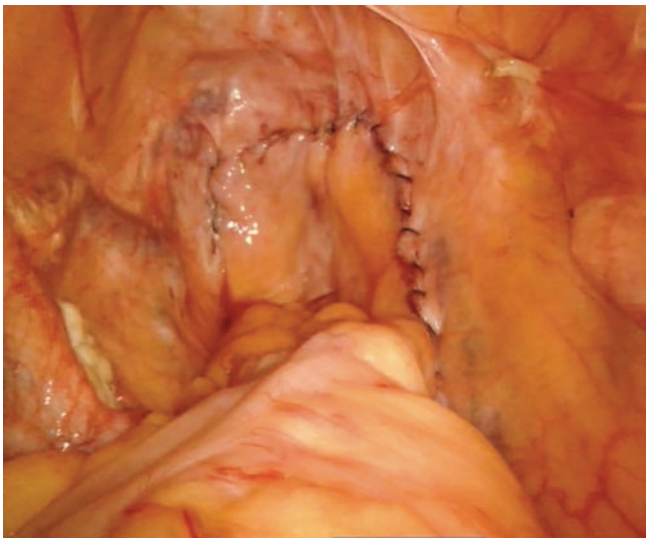

Fig. 60.21 Closure of peritoneum over mesh at completion of VMR

One advantage to VMR is that it avoids autonomic nerve damage that can occur with posterior rectal mobilization and division of the lateral stalks. But the greatest advantage is that VMR allows the opportunity to correct the anatomic defects or laxity of the middle and anterior pelvic compartments. This approach also makes operating with a multidisciplinary team easy since the entire dissection remains in the rectovaginal septum with a large portion of the dissection being identical for both VMR and sacrocolpopexy. Additionally, the same surgical port sites and similar instruments, i.e., mesh and sutures, are used by both surgical teams.

D'Hoore initially described placing stitches between the mesh and posterior vaginal wall (posterior colpopexy) to

obliterate the rectovaginal septum prior to anchoring the mesh to the sacral promontory [63]. The goal is to fix an enterocele or sigmoidocele and provide additional protection from pressure being applied to the anterior rectal wall. Several variations have been described for the colpopexy and/or hysteropexy. The vaginal fornix or vaginal vault is raised with a vaginal retractor, and the anterior side of the VMR mesh is sutured to the posterior vaginal wall, as described by D'Hoore. Alternatively, a separate piece of mesh may be attached to the posterior wall of the vagina and uterus and then attached to the sacrum. If the uterus is absent or a concomitant supracervical hysterectomy is performed at the same time as VMR, then a sacrocolpopexy may be performed which involves suturing mesh to the vagina anteriorly and posteriorly. The sacrocolpopexy will improve middle compartment support and also boost the bladder forward.

The use of mesh in VMR continues to be studied in regard to adverse events related to mesh fixation techniques and mesh material. Evans et al. reported mesh erosions after laparoscopic VMR in only 2% of 2203 patients [65]. Of these, 42 (2.4%) occurred in the synthetic mesh group and 3 (0.7%) in the biological mesh group. Of the three cases of biologic mesh erosion, two were actually non-absorbable suture (Ethibond®) sinuses as opposed to full mesh erosion. In the synthetic group, the use of polyester mesh was associated with much higher risk of erosion (6.5%), and the risk of erosion for polypropylene mesh was only 1.6%.

The type of suture used to secure mesh to the rectum and vagina may also impact the risk of mesh erosion. Tejedor et al. looked retrospectively at 495 cases of laparoscopic VMR with synthetic mesh (polypropylene) to compare the use of absorbable (PDS®) versus non-absorbable suture (Ethibond®) [66]. There was a 4% erosion in the non-absorbable suture group as opposed to 0% in the control group. Four erosions occurred into the rectum and two into the vagina.

Other than the concerns for mesh erosion, discitis has been described as a complication of any procedure that uses sacral fixation [52, 67–69]. Specifically for ventral rectopexy, it has been described in 0.1–2% of cases [25, 64, 65, 67]. It should be suspected in a patient with back pain radiating to the lower extremities and immediate evaluation and aggressive therapy initiated.

In general, VMR has been shown to improve functional symptoms of constipation and fecal incontinence. There is significant improvement in fecal incontinence in 60–80.2% of patients undergoing VMR [25, 70–72]; similarly the improvement in constipation is reported to occur in 58%–85% of patients [59]. In particular, symptoms of obstructive defecation syndrome (ODS) are reported to improve in 78.6% of patients. There are significant benefits in the function of the whole pelvic floor when combined with sacrocolpopexy as shown by improvement of the three axial perineal evaluation (TAPE) scores [73]. TAPE is an assessment that includes two questionnaires for each compartment. Improvement in stress urinary incontinence is seen in 53% of patients, gynecological prolapse symptoms in up to 93.75%, and statistically significant improvement in sexual dysfunction [67]. New onset or worsening of fecal incontinence after VMR has been reported in 1–3.9% [74], and new onset or worsening of constipation has been described in 1.4–12.9%.

The published recurrence rate of rectal prolapse after VMR varies from 0% to 15%, and the recurrence rate for pelvic organ prolapse is 8.5% [52, 64, 67, 70, 75]. Due to these low recurrence rates and symptomatic improvement in constipation and fecal incontinence, minimally invasive VMR is now considered the gold standard treatment for rectal prolapse in Europe. Laparoscopic VR is technically demanding and requires a complete ventral dissection of the rectovaginal septum (rectovesical in men) down to the pelvic floor and suturing skills within a confined space that further maximizes the difficulty. Mackenzie and Dixon reported that the proficiency gain learning curve for the relevant clinical and quality-of-life outcomes for laparoscopic VR was between 82 and 105 cases [74]. Proficiency with respect to reduced operating time was reached at 54 cases. Poor technique minimizes the functional benefit and increases the risk for complications.

Ventral rectopexy is ideally suited for robotic surgery. There is some evidence that the use of the robot may have better functional results possibly because of the better opportunity to overcome the difficulties of operating in the deep pelvis and of suturing on the distal rectum and the pelvic floor muscles. [70] Systematic review and meta-analysis comparing the outcomes of robotic VMR versus laparoscopic VMR reveal similar recurrence, conversion, and reoperation rates [76]. The meta-analysis shows that operative time is significantly longer for robotic VMR, but the robotic approach is associated with a significantly lower blood loss, fewer postoperative complications, and shorter hospital course.

Recurrent Rectal Prolapse

Deciding how to manage recurrent rectal prolapse is difficult, and the current quality of evidence is insufficient to create an algorithm. That being said, female patients with multicompartment POP at the time of their rectal prolapse recurrence should have a multidisciplinary evaluation and treatment plan that minimizes the risk of recurrent prolapse. Gurland et al. reported recurrence rates after ventral rectopexy to be much higher and occurring sooner on patients who had prior prolapse surgeries (25% at 5-year follow-up) compared to those who had VMR for their primary repair (9.7% at 5-year follow-up) [77]. This study also found the risk of full-thickness rectal prolapse recurrence to be even higher if the initial oper-

ation had been a Delorme procedure. Similarly, Hotouras et al. reported that patients who were treated for a rectal prolapse recurrence with a perineal approach had a much higher risk of a second recurrence [78]. This has been reported to be as high as 50%. Given the lower rates of re-recurrences with abdominal procedures, a recurrence should ideally be managed with an abdominal approach. An important consideration is that of vascular supply when performing a resection rectopexy on a patient with a prior Altemeier procedure. The possibility of leaving a devascularized segment of rectum in between the two anastomosis is more than theoretical as reported by Fengler et al. and Steele et al. [33, 79]. These reports included one patient who had sloughing of the rectal mucosa and two patients with postoperative strictures. The same warning would apply for those patients who had a resection rectopexy initially; an Altemeier procedure with a second anastomosis should be avoided unless the prior anastomosis can be included in the specimen. In VMR, if a recurrence occurs early, detachment of the mesh from the sacral promontory should be suspected and reattachment considered. In some situations, a more extensive dissection even to include a posterior dissection may be performed. Overall, based on the current literature, patients with recurrence should be warned of their much higher risk of re-recurrences no matter which operation is performed.

Conclusion

The ideal operation for rectal prolapse would be one with the lowest morbidity, best functional results, and lowest recurrence rate. The single, most ideal surgical repair has not yet been determined. A careful history and physical exam can help in understanding the patient's symptoms and their expectations from undergoing surgical repair. Additional evaluation with validated questionnaires, pelvic floor physiology testing, and defecography imaging can provide deeper insight into the strength, coordination, and anatomic pelvic deficits associated with the prolapse. Thus, several factors influence the exact surgery offered to a patient. In those patients who do not have prohibitive comorbidities, an abdominal repair seems to have the best anatomical and functional results with the lowest mortality. As with other surgeries, there is higher morbidity and mortality with open approaches as opposed to minimally invasive surgical approaches. Robotic surgery may provide some technical benefits in performing ventral mesh rectopexy.

There is growing evidence that a multidisciplinary evaluation is necessary in women presenting with rectal prolapse, and surgical planning should treat the pelvis as a single functional unit. As such, the choice of operation should be one that encompasses all three compartments if necessary. Women who have pelvic organ prolapse have a higher recurrence rate after isolated rectal prolapse repair; furthermore, there is evidence that correcting only one of the pelvic floor compartments often worsens symptoms in the other compartments [71, 80, 81].

In male patients, and females without multicompartment POP, the choice of operation maybe more difficult to determine. The current level of evidence does not provide a single, clear recommendation. Regardless, better functional outcomes and lower recurrence rates are seen with sigmoid resection with rectopexy and with ventral mesh rectopexy. Ultimately, surgical correction of rectal prolapse can allow for significant improvement in life-altering symptoms such as fecal incontinence, constipation, pelvic pressure, and outlet obstruction, but all surgical options carry a risk of developing recurrent rectal prolapse.

References

1. Ellerkmann RM, Cundiff GW, Melick CF, Nihira MA, Leffler K, Bent AE. Correlation of symptoms with location and severity of pelvic organ prolapse. Am J Obstet Gynecol. 2001;185(6):1332–7. discussion 1337-8
2. Jackson SL, Weber AM, Hull TL, Mitchinson AR, Walters MD. Fecal incontinence in women with urinary incontinence and pelvic organ prolapse. Obstet Gynecol. 1997;89(3):423–7.
3. Altman D, Zetterstrom J, Schultz I, Nordenstam J, Hjern F, Lopez A, Mellgren A. Pelvic organ prolapse and urinary incontinence in women with surgically managed rectal prolapse: a population-based case-control study. Dis Colon Rectum. 2006;49(1):28–35.
4. Catanzarite Tatiana T. Recurrence of rectal prolapse after surgical repair in women with pelvic organ prolapse. Dis Colon Rectum. 2018;61(7):861–7.
5. Gonzalez-Argente FX, Jain A, Nogueras JJ, Davila GW, Weiss EG, Wexner SD. Prevalence and severity of urinary incontinence and pelvic genital prolapse in females with anal incontinence or rectal prolapse. Dis Colon Rectum. 2001;44(7):920–6.
6. Nygaard I, Barber MD, Burgio KL, Kenton K, Meikle S, Schaffer J, Spino C, Whitehead WE, Wu J, Brody DJ. Prevalence of symptomatic pelvic floor disorders in US women. JAMA. 2008;300(11):1311–6.
7. Jallad K, Gurland B. Multidisciplinary approach to the treatment of concomitant rectal and vaginal prolapse. Clin Colon Rectal Surg. 2016;29(2):101–5.
8. Kapoor DS, Sultan AH, Thakar R, Abulafi MA, Swift RI, Ness W. Management of complex pelvic floor disorders in a multidisciplinary pelvic floor clinic. Color Dis. 2008;10(2):118–23.
9. Lim M, Sagar PM, Gonsalves S, Thekkinkattil D, Landon C. Surgical management of pelvic organ prolapse in females: functional outcome of mesh sacrocolpopexy and rectopexy as a combined procedure. Dis Colon Rectum. 2007;50(9):1412–21.
10. Broden B, Snellman B. Procidentia of the rectum studied with cineradiography. A contribution to the discussion of causative mechanism. Dis Colon Rectum. 1968;11(5):330–47.
11. Wijffels NA, Collinson R, Cunningham C, Lindsey I. What is the natural history of internal rectal prolapse? Color Dis. 2010;12(8):822–30.
12. Lindsey I, Nugent K, Dixon T. Pelvic floor disorders for the colorectal surgeon. Oxford [England]: Oxford University Press; 2011.
13. Gosselink MP, Adusumilli S, Gorissen KJ, Fourie S, Tuynman JB, Jones OM, Cunningham C, Lindsey I. Laparoscopic ventral rec-

topexy for fecal incontinence associated with high-grade internal rectal prolapse. Dis Colon Rectum. 2013;56(12):1409–14.
14. Ris F, Gorissen KJ, Ragg J, Gosselink MP, Buchs NC, Hompes R, Cunningham C, Jones O, Slater A, Lindsey I. Rectal axis and enterocele on proctogram may predict laparoscopic ventral mesh rectopexy outcomes for rectal intussusception. Tech Coloproctol. 2017;21(8):627–32.
15. Ortega AE, Klipfel N, Kelso R, Petrone P, Roman I, Diaz A, Avalos B, Kaufman HS. Changing concepts in the pathogenesis, evaluation, and management of solitary rectal ulcer syndrome. Am Surg. 2008;74(10):967–72.
16. Lee TH, Hong SJ, Lee JS. Thickened internal anal sphincter has been reported to be a typical finding in solitary rectal ulcer syndrome. J Neurogastroenterol Motil. 2015;21(1):140–1.
17. Rao SS, Benninga MA, Bharucha AE, Chiarioni G, Di Lorenzo C, Whitehead WE. ANMS-ESNM position paper and consensus guidelines on biofeedback therapy for anorectal disorders. Neurogastroenterol Motil. 2015;27(5):594–609.
18. Vaizey CJ, van den Bogaerde JB, Emmanuel AV, Talbot IC, Nicholls RJ, Kamm MA. Solitary rectal ulcer syndrome. Br J Surg. 1998;85(12):1617–23.
19. Waniczek D, Rdes J, Rudzki MK, Piecuch J, Rubicz N, Arendt J. Effective treatment of solitary rectal ulcer syndrome using argon plasma coagulation. Prz Gastroenterol. 2014;9(4):249–53.
20. Collinson R, Wijffels N, Cunningham C, Lindsey I. Laparoscopic ventral rectopexy for internal rectal prolapse: short-term functional results. Color Dis. 2010;12(2):97–104.
21. Wahed S, Ahmad M, Mohiuddin K, Katory M, Mercer-Jones M. Short-term results for laparoscopic ventral rectopexy using biological mesh for pelvic organ prolapse. Color Dis. 2012;14(10):1242–7.
22. Sileri P, Franceschilli L, de Luca E, Lazzaro S, Angelucci GP, Fiaschetti V, Pasecenic C, Gaspari AL. Laparoscopic ventral rectopexy for internal rectal prolapse using biological mesh: postoperative and short-term functional results. J Gastrointest Surg. 2012;16(3):622–8.
23. van Iersel JJ, Paulides TJ, Verheijen PM, Lumley JW, Broeders IA, Consten EC. Current status of laparoscopic and robotic ventral mesh rectopexy for external and internal rectal prolapse. World J Gastroenterol. 2016;22(21):4977–87.
24. Formijne Jonkers HA, Maya A, Draaisma WA, Bemelman WA, Broeders IA, Consten EC, Wexner SD. Laparoscopic resection rectopexy versus laparoscopic ventral rectopexy for complete rectal prolapse. Tech Coloproctol. 2014;18(7):641–6.
25. Consten EC, van Iersel JJ, Verheijen PM, Broeders IA, Wolthuis AM, D'Hoore A. Long-term outcome after laparoscopic ventral mesh rectopexy: an observational study of 919 consecutive patients. Ann Surg. 2015;262(5):742–7. discussion 747-8
26. Evans C, Ong E, Jones OM, Cunningham C, Lindsey I. Laparoscopic ventral rectopexy is effective for solitary rectal ulcer syndrome when associated with rectal prolapse. Color Dis. 2014;16(3):O112–6.
27. Badrek-Amoudi AH, Roe T, Mabey K, Carter H, Mills A, Dixon AR. Laparoscopic ventral mesh rectopexy in the management of solitary rectal ulcer syndrome: a cause for optimism? Color Dis. 2013;15(5):575–81.
28. Karjalainen PK, Mattsson NK, Nieminen K, Tolppanen AM, Jalkanen JT. The relationship of defecation symptoms and posterior vaginal wall prolapse in women undergoing pelvic organ prolapse surgery. Am J Obstet Gynecol. 2019;221(5):480 e1–480 e10.
29. Bordeianou LG, Anger JT, Boutros M, Birnbaum E, Carmichael JC, Connell KA, De EJB, Mellgren A, Staller K, Vogler SA, Weinstein MM, Yafi FA, Hull TL. Measuring pelvic floor disorder symptoms using patient-reported instruments: proceedings of the consensus meeting of the pelvic floor consortium of the American Society of Colon and Rectal Surgeons, the international continence society, the American Urogynecologic Society, and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction. Dis Colon Rectum. 2020;63(1):6–23.
30. Lin FC, Funk JT, Tiwari HA, Kalb BT, Twiss CO. Dynamic pelvic magnetic resonance imaging evaluation of pelvic organ prolapse compared to physical examination findings. Urology. 2018;119:49–54.
31. Ramage L, Simillis C, Yen C, Lutterodt C, Qiu S, Tan E, Kontovounisios C, Tekkis P. Magnetic resonance defecography versus clinical examination and fluoroscopy: a systematic review and meta-analysis. Tech Coloproctol. 2017;21(12):915–27.
32. Williams JG, Rothenberger DA, Madoff RD, Goldberg SM. Treatment of rectal prolapse in the elderly by perineal rectosigmoidectomy. Dis Colon Rectum. 1992;35(9):830–4.
33. Steele SR, Goetz LH, Minami S, Madoff RD, Mellgren AF, Parker SC. Management of recurrent rectal prolapse: surgical approach influences outcome. Dis Colon Rectum. 2006;49(4):440–5.
34. Senapati A, Gray RG, Middleton LJ, Harding J, Hills RK, Armitage NC, Buckley L, Northover JM. PROSPER: a randomised comparison of surgical treatments for rectal prolapse. Color Dis. 2013;15(7):858–68.
35. Tou S, Brown SR, Nelson RL. Surgery for complete (full-thickness) rectal prolapse in adults. Cochrane Database Syst Rev. 2015;(11):Cd001758.
36. Kuijpers HC. Treatment of complete rectal prolapse: to narrow, to wrap, to suspend, to fix, to encircle, to plicate or to resect? World J Surg. 1992;16(5):826–30.
37. Lieberth M, Kondylis LA, Reilly JC, Kondylis PD. The Delorme repair for full-thickness rectal prolapse: a retrospective review. Am J Surg. 2009;197(3):418–23.
38. Tsunoda A, Yasuda N, Yokoyama N, Kamiyama G, Kusano M. Delorme's procedure for rectal prolapse: clinical and physiological analysis. Dis Colon Rectum. 2003;46(9):1260–5.
39. Liberman H, Hughes C, Dippolito A. Evaluation and outcome of the delorme procedure in the treatment of rectal outlet obstruction. Dis Colon Rectum. 2000;43(2):188–92.
40. Chun SW, Pikarsky AJ, You SY, Gervaz P, Efron J, Weiss E, Nogueras JJ, Wexner SD. Perineal rectosigmoidectomy for rectal prolapse: role of levatorplasty. Tech Coloproctol. 2004;8(1):3–8. discussion 8-9
41. Altomare DF, Binda G, Ganio E, De Nardi P, Giamundo P, Pescatori M. Long-term outcome of Altemeier's procedure for rectal prolapse. Dis Colon Rectum. 2009;52(4):698–703.
42. Bordeianou L, Hicks CW, Kaiser AM, Alavi K, Sudan R, Wise PE. Rectal prolapse: an overview of clinical features, diagnosis, and patient-specific management strategies. J Gastrointest Surg. 2014;18(5):1059–69.
43. Fang SH, Cromwell JW, Wilkins KB, Eisenstat TE, Notaro JR, Alva S, Bustami R, Chinn BT. Is the abdominal repair of rectal prolapse safer than perineal repair in the highest risk patients? An NSQIP analysis. Dis Colon Rectum. 2012;55(11):1167–72.
44. Bjerke T, Mynster T. One decade of rectal prolapse surgery: a national study. Int J Color Dis. 2018;33(3):299–304.
45. Foppa C, Martinek L, Arnaud JP, Bergamaschi R. Ten-year follow up after laparoscopic suture rectopexy for full-thickness rectal prolapse. Color Dis. 2014;16(10):809–14.
46. de Bruijn H, Maeda Y, Tan KN, Jenkins JT, Kennedy RH. Long-term outcome of laparoscopic rectopexy for full-thickness rectal prolapse. Tech Coloproctol. 2019;23(1):25–31.
47. Varma M, Rafferty J, Buie WD. Practice parameters for the management of rectal prolapse. Dis Colon Rectum. 2011;54(11):1339–46.
48. Hidaka J, Elfeki H, Duelund-Jakobsen J, Laurberg S, Lundby L. Functional outcome after laparoscopic posterior sutured rectopexy versus ventral mesh rectopexy for rectal prolapse: six-year follow-up of a double-blind, randomized single-center study. E Clin Med. 2019;16:18–22.

49. Frykman HM, Goldberg SM. The surgical treatment of rectal procidentia. Surg Gynecol Obstet. 1969;129(6):1225–30.
50. Brown AJ, Anderson JH, McKee RF, Finlay IG. Strategy for selection of type of operation for rectal prolapse based on clinical criteria. Dis Colon Rectum. 2004;47(1):103–7.
51. Laubert T, Bader FG, Kleemann M, Esnaashari H, Bouchard R, Hildebrand P, Schloricke E, Bruch HP, Roblick UJ. Outcome analysis of elderly patients undergoing laparoscopic resection rectopexy for rectal prolapse. Int J Color Dis. 2012;27(6):789–95.
52. Carvalho ECME, Hull T, Zutshi M, Gurland BH. Resection rectopexy is still an acceptable operation for rectal prolapse. Am Surg. 2018;84(9):1470–5.
53. Ashari LH, Lumley JW, Stevenson AR, Stitz RW. Laparoscopically-assisted resection rectopexy for rectal prolapse: ten years' experience. Dis Colon Rectum. 2005;48(5):982–7.
54. Wells C. New operation for rectal prolapse. Proc R Soc Med. 1959;52:602–3.
55. Lake SP, Hancock BD, Lewis AAM. Management of pelvic sepsis after ivalon rectopexy. Dis Colon Rectum. 1984;27(9):589–90.
56. Scaglia M, Fasth S, Hallgren T, Nordgren S, Oresland T, Hulten L. Abdominal rectopexy for rectal prolapse. Influence of surgical technique on functional outcome. Dis Colon Rectum. 1994;37(8):805–13.
57. Aitola PT, Hiltunen KM, Matikainen MJ. Functional results of operative treatment of rectal prolapse over an 11-year period: emphasis on transabdominal approach. Dis Colon Rectum. 1999;42(5):655–60.
58. Madiba TE, Baig MK, Wexner SD. Surgical management of rectal prolapse. Arch Surg. 2005;140(1):63–73.
59. Dyrberg DL, Nordentoft T, Rosenstock S. Laparoscopic posterior mesh rectopexy for rectal prolapse is a safe procedure in older patients: a prospective follow-up study. Scand J Surg. 2015;104(4):227–32.
60. Ripstein CB, Lanter B. Etiology and surgical therapy of massive prolapse of the rectum. Ann Surg. 1963;157:259–64.
61. Tjandra JJ, Fazio VW, Church JM, Milsom JW, Oakley JR, Lavery IC. Ripstein procedure is an effective treatment for rectal prolapse without constipation. Dis Colon Rectum. 1993;36(5):501–7.
62. Roberts PL, Schoetz DJ Jr, Coller JA, Veidenheimer MC. Ripstein procedure. Lahey clinic experience: 1963–1985. Arch Surg. 1988;123(5):554–7.
63. D'Hoore A, Cadoni R, Penninckx F. Long-term outcome of laparoscopic ventral rectopexy for total rectal prolapse. Br J Surg. 2004;91(11):1500–5.
64. Jallad K, Ridgeway B, Paraiso MFR, Gurland B, Unger CA. Long-term outcomes after ventral rectopexy with sacrocolpo- or hysteropexy for the treatment of concurrent rectal and pelvic organ prolapse. Female Pelvic Med Reconstr Surg. 2018;24(5):336–40.
65. Evans C, Stevenson AR, Sileri P, Mercer-Jones MA, Dixon AR, Cunningham C, Jones OM, Lindsey I. A Multicenter collaboration to assess the safety of laparoscopic ventral rectopexy. Dis Colon Rectum. 2015;58(8):799–807.
66. Tejedor P, Lindsey I, Jones OM, Jones HJS, Gorissen K, Penna M, Cunningham C. Impact of suture type on erosion rate after laparoscopic ventral mesh rectopexy: a case-matched study. Dis Colon Rectum. 2019;62(12):1512–7.
67. Gouvas N, Georgiou PA, Agalianos C, Tan E, Tekkis P, Dervenis C, Xynos E. Ventral colporectopexy for overt rectal prolapse and obstructed defaecation syndrome: a systematic review. Color Dis. 2015;17(2):O34–46.
68. Florian-Rodriguez ME, Hamner JJ, Corton MM. First sacral nerve and anterior longitudinal ligament anatomy: clinical applications during sacrocolpopexy. Am J Obstet Gynecol. 2017;217(5):607.e1–4.
69. Muller PC, Berchtold C, Kuemmerli C, Ruzza C, Z'Graggen K, Steinemann DC. Spondylodiscitis after minimally invasive recto- and colpo-sacropexy: report of a case and systematic review of the literature. J Minim Access Surg. 2020;16(1):5–12.
70. Postillon A, Perrenot C, Germain A, Scherrer ML, Buisset C, Brunaud L, Ayav A, Bresler L. Long-term outcomes of robotic ventral mesh rectopexy for external rectal prolapse. Surg Endosc. 2020;34(2):930–9.
71. Martin Del Olmo JC, Toledano M, Martin Esteban ML, Montenegro MA, Gomez JR, Concejo P, Rodriguez de Castro M, Del Rio F. Outcomes of laparoscopic management of multicompartmental pelvic organ prolapse. Surg Endosc. 2019;33(4):1075–9.
72. van Iersel JJ, Formijne Jonkers HA, Paulides TJC, Verheijen PM, Draaisma WA, Consten ECJ, Broeders I. Robot-assisted ventral mesh rectopexy for rectal prolapse: a 5-year experience at a tertiary referral center. Dis Colon Rectum. 2017;60(11):1215–23.
73. Altomare DF, Picciariello A, Memeo R, Fanelli M, Digennaro R, Chetta N, De Fazio M. Pelvic floor function following ventral rectopexy versus STARR in the treatment of obstructed defecation. Tech Coloproctol. 2018;22(4):289–94.
74. Mackenzie H, Dixon AR. Proficiency gain curve and predictors of outcome for laparoscopic ventral mesh rectopexy. Surgery. 2014;156(1):158–67.
75. Makela-Kaikkonen J, Rautio T, Kairaluoma M, Carpelan-Holmstrom M, Kossi J, Rautio A, Ohtonen P, Makela J. Does ventral rectopexy improve pelvic floor function in the long term? Dis Colon Rectum. 2018;61(2):230–8.
76. Rondelli F, Bugiantella W, Villa F, Sanguinetti A, Boni M, Mariani E, et al. Robot-assisted or conventional laparoscopic rectopexy for rectal prolapse? Systematic review and meta-analysis. Int J Surg. 2014;12 Suppl 2:S153–9.
77. Gurland B, E Carvalho MEC, Ridgeway B, Paraiso MFR, Hull T, Zutshi M. Should we offer ventral rectopexy to patients with recurrent external rectal prolapse? Int J Color Dis. 2017;32(11):1561–7.
78. Hotouras A, Ribas Y, Zakeri S, Bhan C, Wexner SD, Chan CL, Murphy J. A systematic review of the literature on the surgical management of recurrent rectal prolapse. Colorectal Dis. 2015;17(8):657–64.
79. Fengler SA, Pearl RK, Prasad ML, Orsay CP, Cintron JR, Hambrick E, Abcarian H. Management of recurrent rectal prolapse. Dis Colon Rectum. 1997;40(7):832–4.
80. Crafoord K, Sydsjo A, Johansson T, Brynhildsen J, Kjolhede P. Factors associated with symptoms of pelvic floor dysfunction six years after primary operation of genital prolapse. Acta Obstet Gynecol Scand. 2008;87(9):910–5.
81. Forsgren C, Zetterstrom J, Zhang A, Iliadou A, Lopez A, Altman D. Anal incontinence and bowel dysfunction after sacrocolpopexy for vaginal vault prolapse. Int Urogynecol J. 2010;21(9):1079–84.

Fecal Incontinence: Evaluation and Treatment

61

Giovanna da Silva and Anders Mellgren

Key Concepts

- A thorough history and physical examination and conservative management measures should be the initial step in managing fecal incontinence.
- Preoperative physiology testing can assist the surgeon in selecting the optimal treatment modality.
- Sacral neuromodulation is successful for patients with and without sphincter defects; however, reinterventions are not uncommon.
- Biomaterial injection may provide limited benefits.
- Overlapping sphincteroplasty is an option for younger patients with an isolated sphincter injury, as after obstetric injury.

Introduction

Fecal incontinence (FI) is a distressing and embarrassing condition, which is usually defined as uncontrolled passage of feces or gas (anal incontinence) over at least 1 month's duration in an individual who had previously achieved control. The estimated prevalence varies in the literature, according to the definition, methods used, and population studied. An up-to-date systematic review of 4840 articles showed an estimate rate ranging from 1% to 19% [1]. The severity of FI varies widely but can have a significant negative impact on affected individuals with reduced quality of life, depression, and associated social stigma [2].

Continence is a complex mechanism which depends on the interaction between stool consistency, anal sphincter function, rectal compliance, neurologic function, and pelvic floor muscle coordination. FI is frequently multifactorial and caused by disruption of one or more of these components (Table 61.1).

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Evaluation

History and Physical Exam

Evaluation starts with a detailed history and physical exam, which allows the physician to identify potential cause(s) of FI and direct counseling and management. Bowel habits should be assessed for frequency of bowel movements, presence of diarrhea or constipation, and any recent changes. Medications should be carefully reviewed. Comorbidities, such as diabetes, neurologic conditions, irritable bowel syndrome, inflammatory bowel disease, previous radiation inflammatory bowel disease, rectal prolapse and previous radiation can contribute to FI. Concomitant urinary symptoms or anterior prolapse should be inquired can contribute to FI. Past obstetric and surgical history, including episiotomy, colectomy, and/or anorectal procedures, should be documented. A proper history can determine the severity of FI and its impact on patient's

Table 61.1 Etiology of fecal incontinence

Anatomical abnormalities	Sphincter trauma: obstetric, accidental, anorectal surgery Rectal prolapse/intussusception Imperforate anus
Neurologic	Pudendal neuropathy (stretch injury, diabetes mellitus, radiation, chemotherapy) Central nervous system (stroke, dementia, spinal cord injury, trauma, tumor, multiple sclerosis, cauda equina)
Stool characteristics	Diarrhea (infectious, IBS, inflammatory bowel disease, malabsorption, laxative abuse, radiation enteritis) Constipation (overflow incontinence)
Rectum	Radiation proctitis, LAR/coloanal anastomosis, etc.

S. R. Steele et al. (eds.), *The ASCRS Textbook of Colon and Rectal Surgery*, https://doi.org/10.1007/978-3-030-66049-9_61

Table 61.2 Cleveland Clinic Florida-Fecal Incontinence Score (CCF-FIS) [44]

	Frequency				
Type of incontinence	Never	Rarely	Sometimes	Usually	Always
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Gas	0	1	2	3	4
Wears pad	0	1	2	3	4
Lifestyle alteration	0	1	2	3	4

Never, 0; rarely, <1/month; sometimes, <1/week, ≥1/month; usually, <1/day, ≥1/week; always, ≥1/day. Minimum score 0 (perfect continence), maximum score 20 (complete incontinence)

quality of life. Several scoring systems have been developed to help in the evaluation of these patients. The Cleveland Clinic Florida Fecal-Incontinence Scoring System (CCF-FIS) is a validated tool that is simple and helpful in the evaluation of these patients (Table 61.2).

Physical examination starts with inspection of the perianal skin for rash, scars, trauma, deformities, fistula, excoriation, patulous anus, prolapsing hemorrhoids, and rectal prolapse. The patient should be asked to bear down to further examine for rectal prolapse and descending perineum, which is a sign of pelvic floor weakness. Sensation is assessed by using a cotton ball and/or a sharp object to touch the perianal skin. The presence of the anocutaneous reflex ("anal wink") suggests an intact sacral reflex arc and pudendal nerve innervation of the external anal sphincter. On digital rectal exam, the resting tone and voluntary squeeze increase are noted. Attention to whether the gluteus is used to help in contraction, presence of rectocele, and thickness of the perineal body are noted.

Anorectal Manometry

Anorectal physiology testing can give insight and objectively document pelvic floor function. Although manometry may not always correlate with clinical examination or predict response of treatment, the assessment can be helpful to guide therapy [3]. Anorectal manometry measures the internal (resting) and external (squeeze increase) sphincter pressures, sphincter length, anorectal sensation, rectal compliance, and anorectal inhibitory reflex. Sphincter pressures are usually low in FI; however they might be normal or increased in the presence of anismus or incomplete evacuation, especially in men with FI [4]. Low internal sphincter pressures are seen in patients with leakage or passive incontinence, whereas the external sphincter pressures are associated with urgent, active incontinence. Rectal hyposensitivity can lead to constipation associated with incontinence [5], whereas rectal hypersensitivity is seen in patients with urgency, diarrhea, IBS, low anterior resection syndrome, or radiation. The lack of rectoanal inhibitory reflex is seen in Hirschsprung's disease, after anorectal surgery, or in patients with connective tissue disorders. The rectoanal inhibitory reflex can be difficult to see/ evaluate in patients with low anal resting pressures. Compliance can be decreased in inflammatory bowel disease, after radiation, or in patients with scleroderma.

Ultrasound

Anal ultrasound provides an objective assessment of the sphincter integrity and can readily diagnose injuries or anatomic deficiencies of the internal and external anal sphincters. Ultrasound is relatively cheap, is conveniently available for the surgeon, and offers the best imaging of the internal sphincter. MRI can be an alternative for imaging, especially for the anterior part of the external sphincter or imaging of concomitant pelvic prolapse. In experienced hands, complete pelvic floor ultrasound with transperineal and transvaginal techniques can offer excellent imaging of all pelvic compartments. Pelvic floor ultrasound can identify pelvic organ prolapse and other anatomical abnormalities that may contribute to FI.

Neurophysiology Testing

Anorectal neurophysiology testing of the pelvic floor can be achieved with pudendal nerve terminal motor latency (PNTML) testing and electromyography (EMG). PNTML evaluates the neuromuscular integrity between the pudendal nerve and the anal sphincter. A finger is introduced into the rectum, with an electrode mounted on a glove, and electrical impulses are delivered to the pudendal nerve. The latency between the electrical impulse and the muscle response is measured as PNTML, and a prolonged latency can be indicative of neuropathy. Recent data indicates that a prolonged PNTML does not independently predict the success of treatment and the technique [6–8] and the technique has slowly faded away as a diagnostic modality [9].

Sphincter mapping with EMG can identify sphincter defects and identify signs of nerve injury. The technique involves placing a needle into the sphincter muscle, which may cause significant discomfort and is nowadays infrequently used [10].

Defecography

Defecography evaluates the dynamic of defecation and can be performed with fluoroscopic or MRI technique. For FI, the exam can be valuable to confirm the inability to retain stool, which is a measurement of the severity of the FI, and to identify impaired evacuation and/or pelvic organ prolapse contributing to FI. The presence of a rectal intussusception is

a negative predictive factor for sacral nerve neuromodulation [11], and these patients may be possible candidates for ventral rectopexy. Incomplete evacuation and anismus have been associated with anal leakage, especially in men.

Colonoscopy

Colonoscopy is indicated according to the screening guidelines and in patients with bowel symptoms. Colonoscopy can exclude underlying pathology, such as malignancy and IBD, in patients with FI. In patients with diarrhea, especially older women, colonoscopy with biopsies should be performed to rule out microscopic colitis.

Treatment

Goals of treatment include decreasing the frequency and severity of FI accidents and improve quality of life. Most patients benefit from starting with conservative treatment modalities, especially since the below treatment alternatives rarely can offer complete resolution of incontinence symptoms. Conservative treatment and regulation of bowel habits can be combined with pelvic floor exercises or a rectal or vaginal insertion device.

Patients who don't respond to conservative treatment or biofeedback can benefit from minimally invasive treatment options or surgery. The most common minimally invasive treatment option is sacral neuromodulation (SNM). Alternative minimally invasive treatments include injection of a bulking agent injection, percutaneous tibial nerve stimulation, and radiofrequency remodeling (SECCA). There are also other minimally invasive therapies, including stem cell therapy and anal sling, but they are currently not available in the USA.

Patients with a defined sphincter disruption may be potential candidates for surgical sphincter repair (sphincteroplasty). Another surgical alternative, in patients with rectal intussusception or rectal prolapse, is ventral rectopexy. Gracilis muscle transposition can potentially help to strengthen the anal sphincters. Electrical stimulation of the gracilis muscle has been advocated to achieve improved results, but this treatment alternative is currently not available. Other treatment alternatives, which are currently not available in the USA, include the magnetic anal sphincter (MAS) and artificial bowel sphincter (ABS).

Conservative Treatment

First-line therapy should include dietary modifications avoiding sweeteners, dairy, caffeine, and medications known to aggravate FI. Antidiarrheal, cholestyramine, and/or fiber supplement to bulk the stool can lead to improvement in a significant portion of patients.

Bowel management may consist of enemas or suppositories to reduce the volume of stool in the rectum (and thereby decrease FI episodes). More recently, an anal irrigation system (Peristeen™) has been used in adults with low anterior resection syndrome with an improvement of symptoms quality of life [12]. The device consists in a balloon that is introduced into the rectum, a pump, pressure control unit, and a water container. Patients are trained to irrigate the colon with up to 1.5 L of water a few times per week.

Pelvic Floor Exercises

Pelvic floor exercise, or biofeedback, is a first-line therapy in FI patients. Although some studies have shown biofeedback results to be no different from advice and education [13], a Cochrane review found some evidence that biofeedback and electrical stimulation may enhance the outcomes of treatment compared to electrical stimulation alone or exercises alone [14]. Biofeedback therapy can improve rectal sensation and may enhance coordination between perception of rectal distention and external sphincter contraction in patients with reduced rectal sensation. In a study including 124 patients, Regadas et al. [15] found a 50% reduction in FI score in approximately 50% of the patients. Patients less likely to respond to biofeedback were those with CCF-FI score $\geq$10, previous vaginal delivery, and anorectal and/or colorectal surgery and those unable to maintain a squeezing effort.

Anal Insertion Device

Anal plug (Fig. 61.1) is an adjunct to conservative therapy. The plug is inserted into the distal rectum by the patient, with the goal of blocking the involuntary passage of stool. A Cochrane review noted that plugs can be difficult to tolerate [16]. A multicenter prospective study [17] evaluating a soft silicone anal insert found that 77% of the 73 patients who completed the study (62% of 91 intention-to-treat patients) achieved a $\geq$50% reduction in incontinence frequency over a 12-week period. The insert might be of greater benefit for patients with mild FI [18].

Vaginal Bowel Control System

The vaginal bowel control system (Fig. 61.2) is another supplementary tool that consists of a vaginally introduced insert with a balloon and a pressure-regulated pump designed to

temporarily occlude the rectum from the vagina. The device is deflated for defecation. Some patients find the device difficult to fit and uncomfortable. In a recent multicenter study [19], an open label trial with 137 patients, 62% could be fitted with the device. In this study, 73 patients with moderate FI (mean CCF-IS of 14.1) and who were able to keep the device had a success rate of 94% at 12 months. In these patients there was a significant improvement in the Fecal Incontinence Quality of Life score, and the satisfaction rate reached over 94% at 12 months.

Fig. 61.1 Renew anal insertion device

Sacral Neuromodulation

SNM has become a popular treatment for patients with moderate or severe FI. Initially, SNM was offered to patients with an intact external anal sphincter or patients with a limited sphincter defect. Over time, however, the treatment indications have widened. Today SNM treatment is offered to patients with or without a sphincter defect, and both groups achieve similar treatment results (Fig. 61.3).

The mechanism of action is not clearly understood. Postulated mechanisms include stimulation of the somatovisceral reflex, direct effect on anal sphincter complex, and afferent neuromodulation. The SNM procedure is performed in two stages. The first stage consists placing a lead to evaluate the treatment effect over a 1–2-week period. Patients who achieve a ≥50% improvement of the number of FI episodes qualify for the stage 2. The trial period can be performed by placing a unipolar stimulation lead percutaneously (PNE) in the office, which is later removed, or by inserting a quadripolar lead in the operating room. Whereas PNE might have a slightly higher failure rate [20], testing with a quadripolar lead may have a slightly higher risk of infection [21].

The US multicenter trial that led to FDA approval demonstrated the efficacy of SNM [22]. Of the 120 patients who underwent permanent implantation, 83% had ≥50% reduction of incontinent episodes at 1 year, and 41% achieved 100% continence. The success was maintained at 5-year follow-up, with 89% (64/72) of patients achieving ≥50%

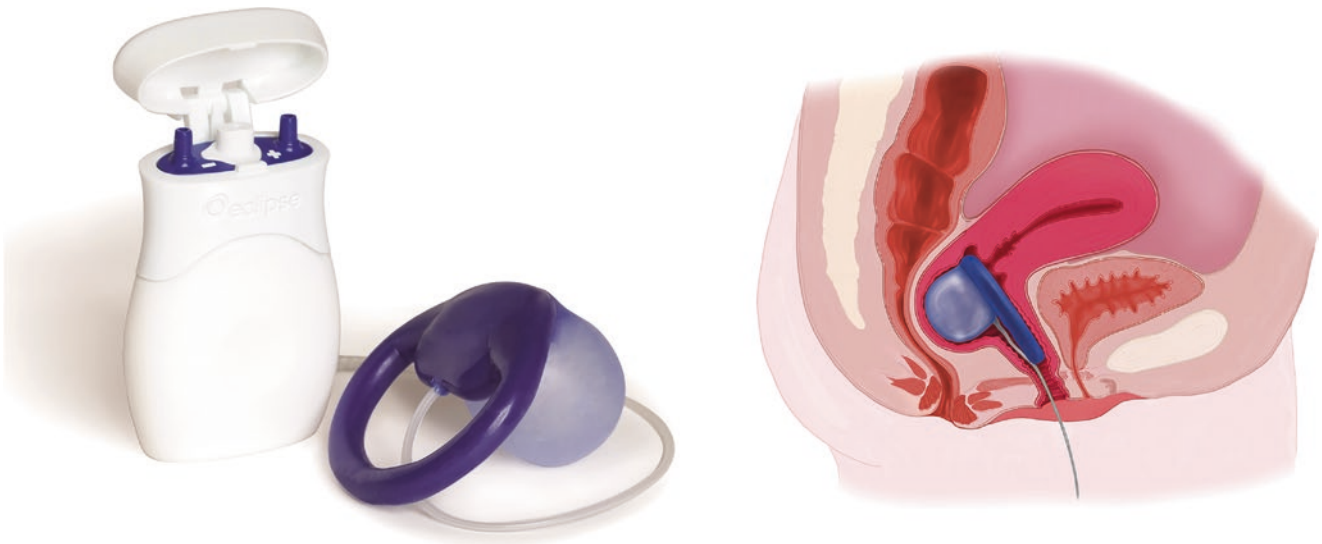

Fig. 61.2 Vaginal bowel control system (Eclipse). The vaginal bowel control insert is folded and deflated for insertion (right) and inflated as it would sit in the vagina; the insert is inflated with a handheld pressure-regulated pump. (Reused with permission from Pelvalon Inc.)

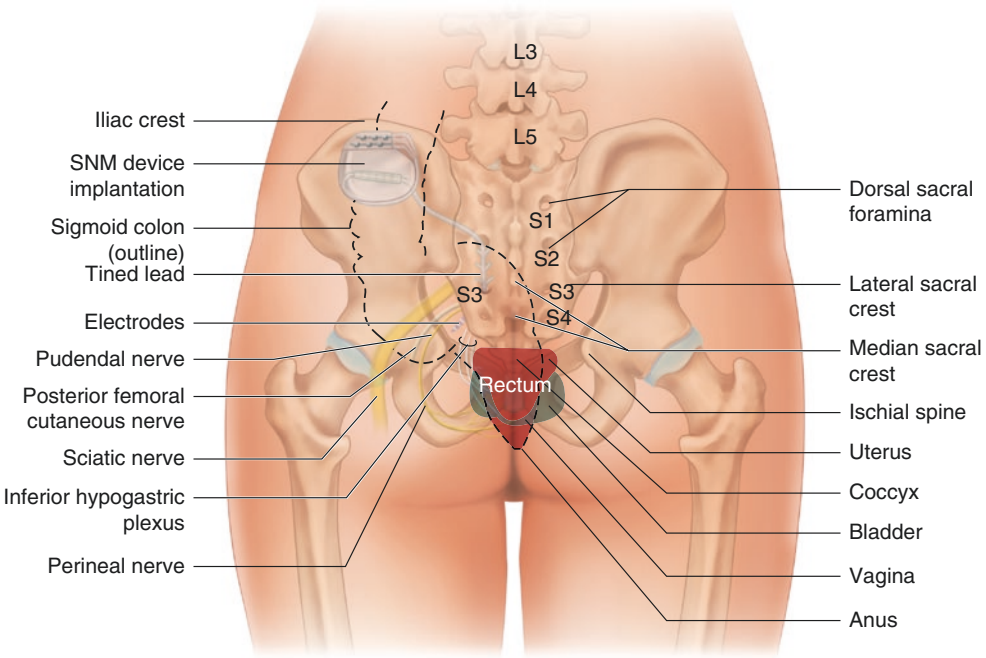

Fig. 61.3 Sacral nerve stimulation. Sacral nerve modulation: the lead is placed through the S3 foramen, and the implantable pulse generator is placed below the iliac crest and lateral to the sacrum

improvement ($p < 0.0001$) and 36% ($n = 26/72$) of patients reporting complete continence. Fecal Incontinence Quality of Life scores also significantly improved [23]. In a longer follow-up of 7 years, the European SNS group reported sustained success in 71.3% of patients who retained the device, and half of the patients sustained success on intention-to-treat analysis [24].

Complications related to sacral nerve stimulator placement include pocket complications, lead complications, infection, pain, and loss of efficacy. Infection frequently requires an explant of the lead and stimulator. Otherwise, most complications can be managed or improved by conservative means including medication or reprogramming. The reoperation rate can however be as high as 42% [25, 26], and the stimulator needs to be changed every 3–5 years. Recently, a rechargeable device has been introduced for SNM. This device can be used for up to 15 years and patients can undergo full-body MRI conditionally safe. The results of this device seem comparable with the original InterStim [27].

Bulking Agents

Multiple agents have been proposed to increase the bulk of the anal canal. In 2011, the US Food and Drug Administration (FDA) approved a nonanimal stabilized hyaluronic acid/dextranomer gel for submucosal injection (NASHA Dx) for the treatment of FI (Fig. 61.4). The largest randomized controlled trial to date [28] compared NASHA Dx versus sham injection. The treatment arm demonstrated treatment success (a 50% decrease in the number of FI episodes) in 52% vs. 31% of patients in the placebo group ($P = 0.0089$). There was no significant difference in the FI scores between the groups at 2 months. At long-term follow-up (36 months), there was a sustained reduction in incontinence episodes (52%) with significant improvement in quality of life measures [29]. A randomized trial comparing NASHA Dx with biofeedback failed to show any difference in outcomes [30]. The final role of NASHA Dx in the treatment of fecal incontinence remains unclear. Most studies were not designed to evaluate if NASHA Dx works better in patients with minor or major symptoms of incontinence. In clinical practice indications have evolved and NASHA Dx is a treatment option more commonly for patients with mild or moderate incontinence, male patients with incontinence (especially if they have soiling), patients with residual incontinence after treatment with sacral neurostimulation, and for patients with postoperative key hole defects.

Percutaneous Tibial Nerve Stimulation

Percutaneous tibial nerve stimulation (PTNS) is thought to cause similar changes in anorectal neuromuscular function as SNM because of the shared sacral segmental innervation. Earlier studies reported success rates between 63% and 82%,

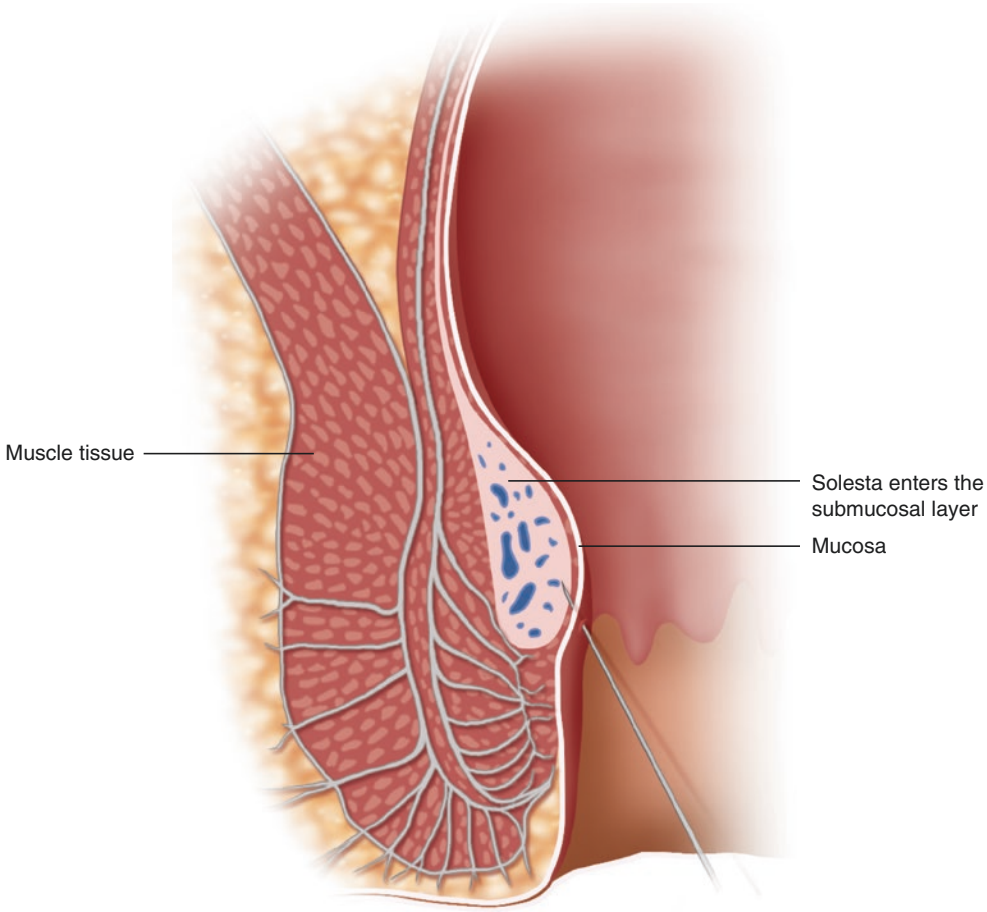

Fig. 61.4 Bulking agents. Biomaterial injection is performed by inserting the needle above the dentate line and into the submucosa

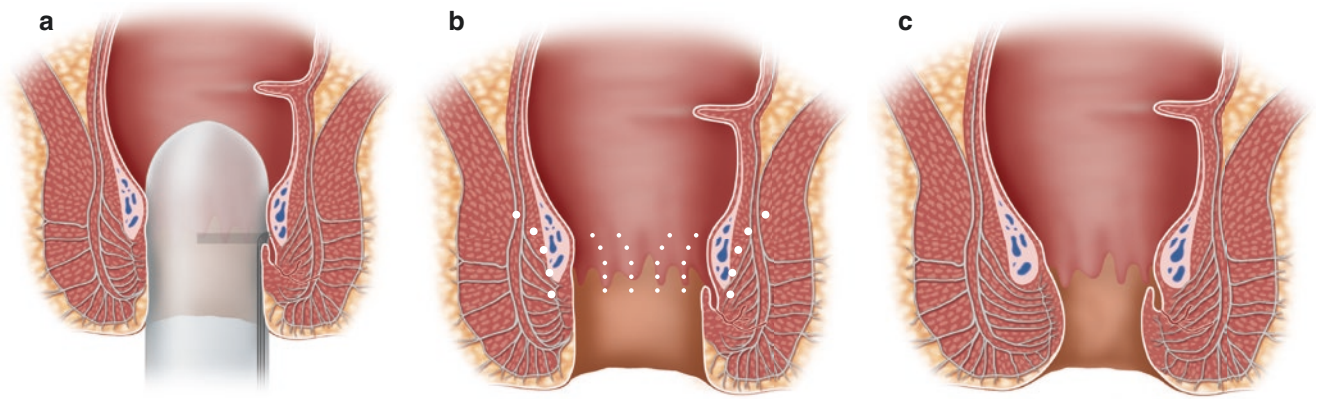

Fig. 61.5 Radiofrequency (SECCA) procedure. (**a**) Anoscope wires are deployed in three to four quadrants circumferentially and are meant to enter the internal anal sphincter. (**b**) Radiofrequency treatment is performed at four levels within anal canal, both above and below the dentate line. (**c**) Procedure leads to internal anal sphincter thickening

with different variability in the technique and frequency of stimulation [31]. A randomized double-blind controlled trial was performed in the UK [32]. The study included 227 patients, with 115 receiving PTNS and 112 sham stimulation. There was no significant difference between the groups at 12 weeks after treatment. A systematic review comparing PTNS with SNM demonstrated SNM to be associated with better functional outcomes and quality of life [33].

Radiofrequency Energy Delivery

Radiofrequency tissue remodeling (SECCA®) is a therapeutic option for patients with mild-to-moderate FI with intact or limited sphincter defects (Fig. 61.5). Radiofrequency energy is delivered into the internal anal sphincter to stimulate collagen deposition and thickening of the muscularis propria and thereby increase the outlet resistance.

Frascio et al. [34] reviewed the outcomes across several studies and found 55–80% of patients with mild-to-moderate FI were deemed responders at 12 months, showing limited improvement in CCF-FIS scores. Reported long-term results are variable [35–37]. One study reported a 3-year durability of improvement, without need for reintervention, in 22% of patients. Another study found that only 6% of patients maintained their results after the same time interval. A recent randomized controlled trial compared the clinical response of SECCA® to a sham procedure in 40 patients [38]. The authors demonstrated a statistically significant decrease in the Vaizey FI scores in patients undergoing the SECCA® procedure, although only two patients met the criteria for clinically relevant improvement (≥50% reduction in FI score or episodes). The ASCRS clinical practice guidelines state that SECCA® may be used to treat FI but recommend that alternative treatments be pursued before considering this therapy [9].

Stem Cell Therapy

The mechanism of action of stem cell injection is not fully understood, but is postulated as a means of providing recovery of sphincter function through regeneration of damaged striated sphincter muscle and/or expediting the healing process [39]. The most common studied stem cells in the treatment of FI are derived from muscle, bone marrow, and adipose tissue. In the first human study, ten women with FI from obstetric injury underwent injection of autologous myoblasts into the external sphincter [40]. At 12 months, the CCF-IS decreased by a mean of 13.7 points, anal squeeze pressures were unchanged, and overall quality of life scores improved. These results were sustained at 5-year follow-up [41]. Using myoblasts, Boyer et al. [42] reported the results of a phase II randomized, double-blind, placebo-controlled study. The authors enrolled 12 patients in the treatment arm and 12 in the control arm. At 6 months, CCF-IS score decreased in both groups, but at 12 months, the treatment group continued to show improvement in the CCF-IS score, while the control arm did not. No severe adverse events were reported. Stem cell is not FDA approved for FI at this time.

Anal Sling

Sling procedures involve correction of pelvic floor support with restoration of the appropriate anorectal angle, which is important for continence. Mellgren et al. [43] reported the results of a prospective, multicenter study involving 152 patients at 14 centers in the USA using the Transobturator Posterior Anal Sling (TOPAS, American Medical Systems). The TOPAS system involves looping a polypropylene mesh tape posterior to the anal canal using a minimally invasive needle-based delivery system. At 1-year follow-up, nearly 70 percent of women reported had ≥50% reduction in incontinent episodes as well as improvement in quality of life scores, with 19% reporting complete continence. Sixty-six patients reported one or more adverse events, the most common of which was pelvic pain. The TOPAS system is not available in the USA.

Surgical Sphincter Repair (Sphincteroplasty)

Anal sphincter damage sustained during childbirth is a common cause of fecal incontinence in women of childbearing age [44]. Occult sphincter defects during vaginal deliveries have been diagnosed by anal ultrasound in more than 30% of primiparous women and more than 40% of multiparous women and are especially common after forceps deliveries [45]. Sphincteroplasty may be an alternative for the younger patient with a defined sphincter defect as after an obstetric injury. Anal sphincteroplasty has the ability to also correct anatomical defects, such as a thinned perineal body or a rectovaginal fistula.

The operation is performed under general anesthesia and usually with the patient in the prone jackknife position. The operation starts with a curvilinear incision on the perineum, and the dissection is carried laterally to encounter the anal sphincter laterally on each side (Fig. 61.6a–d). A levatorplasty can be added to the procedure (Fig. 61.6e). Separate attention to the internal anal sphincter imbrication has not been demonstrated to add to the overall durability of sphincteroplasty [46, 47]. The ends of anal sphincter muscles are usually overlapped and repaired with mattress sutures, providing new bulk to the sphincter complex.

Short-term results (<5 years) are usually quite good, with improvement rates of about 70–90%. Few patients are completely relieved of their symptoms and results often deteriorate with time [48]. However, satisfaction remains relatively high despite deterioration of symptoms over time [48, 49].

Ventral Rectopexy

Patients with external rectal prolapse or significant rectal intussusception frequently have FI symptoms. Ventral mesh rectopexy (VMR) was first described by Andre D'Hoore et al. [50] in 2004. The initial idea for the procedure was derived from the cinegraphic data of Broden and Snellman [51], who demonstrated that the intussusception of the rectum starts usually in the anterior aspect. VMR aims to correct the descent of the posterior and middle compartment by mobilizing the rectovaginal septum down to the pelvic floor between the rectum and the vagina. Once the rectovaginal septum is dissected, it is reinforced with a mesh, and the mesh is fixed to the promontory.

The procedure carries a low rate of recurrence and offers good functional results in several studies. In a systematic review by Samaranayake et al. [52], the overall decrease in

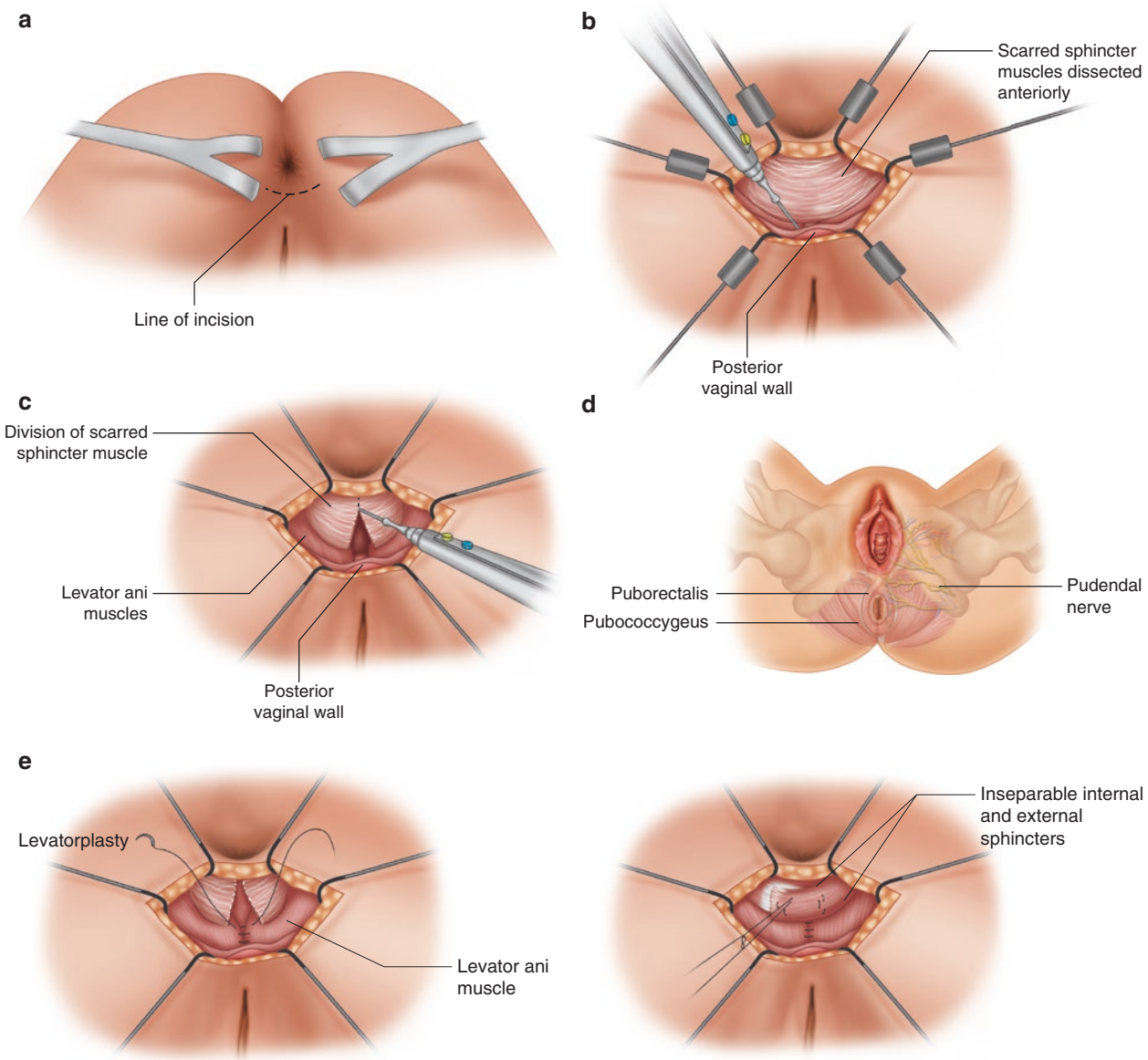

Fig. 61.6 Overlapping sphincteroplasty. (**a**) A curvilinear incision is made on the perineal body. (**b**) Scars with attached retracted sphincter muscles are dissected anteriorly. (**c**) Overlapping sphincteroplasty: anterior scan/sphincter complex is divided. (**d**) Surgeons must be aware of the course of the pudendal nerve and aim to minimize pudendal nerve injuries at the sphincter of sphincter repair by avoiding dissection beyond more than 180 degrees anteriorly. (**e**) Levatorplasty: (**a**) is performed when appropriate, (**b**) scar-sphincter complex is overlapped to allow the ends of the retracted muscles to be realigned as close as possible to each other

fecal incontinence score was 45% along with a significant decrease in constipation symptoms. VMR has therefore gained widespread acceptance in Europe as the treatment of choice for rectal prolapse. Some centers have expanded the indications to include patients with advanced internal prolapse (Oxford grades 3 and 4) with a combination of symptoms of FI and outlet obstruction symptoms [53, 54]. More studies comparing the functional outcome after VMR with other types of prolapse repair are still warranted.

Complication concerns include mesh complication, including mesh erosion into the vagina, bladder, or rectum, mid-rectal stricture, rectovaginal fistula, and chronic pelvic pain due to pudendal nerve irritation or chronic inflammation around the mesh. In most studies, the frequency of mesh-related complications seems to be low [55], but long-term follow-up is still limited.

Gracilis Muscle Transposition

Muscle transposition is usually performed with the gracilis muscle due to ease of harvest. The gracilis is located superficial in the medial thigh and can be transposed without any sequelae for the patient. The muscle has a single vascular pedicle in the proximal part of the muscle, facilitating its transposition around the anus.

The transposed muscle can be stimulated with an intramuscular electrode linked to an impulse generator in subcutaneous tissues. This induces contractions, and the initial fast-twitch fatigable muscle is retrained to become a slow-twitch, fatigue-resistant muscle. The technique demonstrated good effect in some patients, but complications were common [56–58]. Complications included surgical site infection, pain, device problems, erosion, and outlet obstruction. Dynamic graciloplasty is currently not available.

Magnetic Anal Sphincter Augmentation

The Fenix™ Continence Restoration System (MAS) was approved by the FDA under a humanitarian device exemption for patients with FI who fail medical and other surgical management. MAS includes placement of a number of magnetic beads on a titanium string around the anal sphincter to provide improved outlet resistance of the anal canal. At defecation, the rectal pressure will dilate the

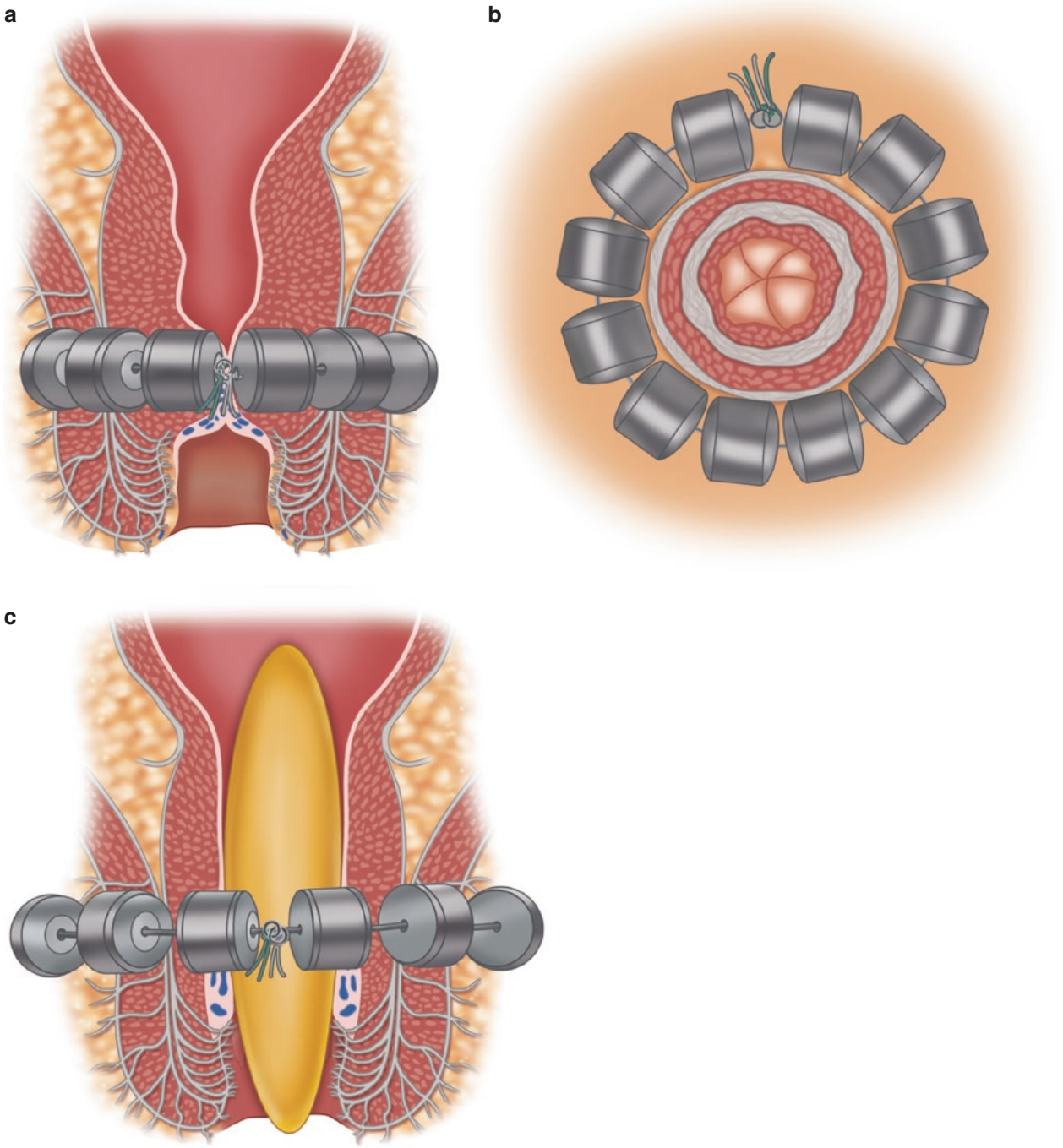

Fig. 61.7 Magnetic anal sphincter: (**a**) In the resting state, the magnets keep the anal canal closed. (**b**) Axial view to demonstrate placement of the magnetic sphincter outside the sphincter complex. (**c**) With bowel movements and Valsalva, the magnets expand to allow passage of stool

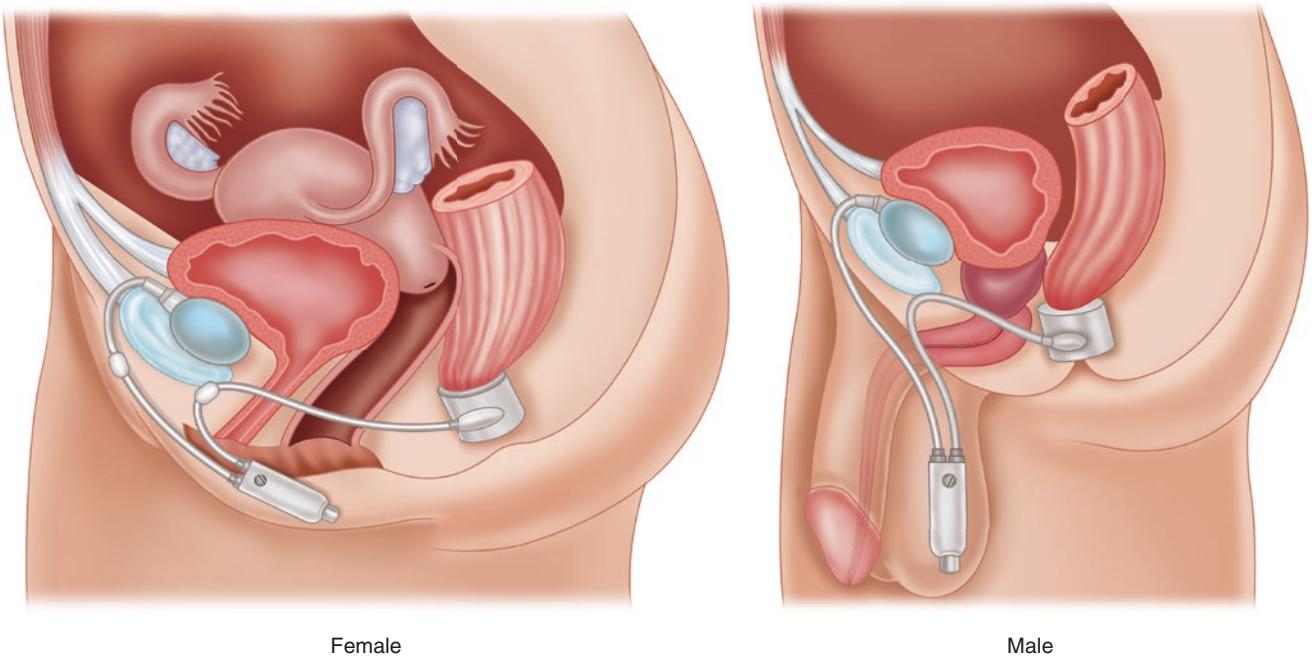

Fig. 61.8 Artificial bowel sphincter placement in males and females. The cuff is placed to encircle the anus, while the balloon is located in the space of Retzius. The button is placed in the labia in females and in the scrotum in males

anal canal with separation of the magnetic beads (Fig. 61.7).

Current literature, while limited, reports favorable outcomes in terms of improvement in FI scores with success in half of the patients at 5-year follow-up [59]. Complications include infection, pain, and gluteal swelling, and some patients will need to have the device explanted. The Fenix™ Continence Restoration System is currently not available.

Artificial Bowel Sphincter

The artificial bowel sphincter (ABS) system consists of an implanted cuff around the anus that is connected to a pump implanted within the subcutaneous tissues of the labia majora or scrotum. When defecation is required, the pump is compressed, deflating the implanted anal cuff and allowing the cuff fluid to drain into a balloon reservoir in the space of Retzius (Fig. 61.8). Though studies demonstrate solid results of approximately 60–70% in patients with end-stage FI, the device is associated with high rates of infection and erosion, which often required revisions and, ultimately, explantation [60, 61]. The ABS is no longer available in the USA.

Treatment Failure

When the above options fail, a well-constructed ileostomy or colostomy can lead to significant improvement in patients' quality of life. For selected motivated adult patients, the Malone antegrade colonic enema (MACE) procedure might be fashioned using a reverse appendicostomy or cecostomy. A catheter is introduced through the ostomy and the colon is flushed in an antegrade fashion.

A systematic review, including 374 patients who underwent MACE for FI and constipation, demonstrated that 47–100% of the patients still used their MACE stoma despite being time-consuming. Some patients report problems with soiling and leakage after usage of the MACE stoma. The rate of stoma stenosis varied from 8% to 50% and may require reintervention [62].

Conclusion

There are a variety of noninvasive and invasive options for the treatment of FI. Treatment should be tailored to the individual patient, based on the severity of the FI, anatomical abnormalities, and patients' expectations.

References

1. Sharma A, Yuan L, Marshall RJ, Merrie AEH, Bissett IP. Systematic review of the prevalence of faecal incontinence. BJS. 2016;103:1589–97.
2. Mazi B, Kaddour O, Al-Badr A. Depression symptoms in women with pelvic floor dysfunction: a case-control study. Int J Women's Health. 2019;11:143–8.
3. Quezada Y, Whiteside JL, Rice T, Karram M, Rafferty JF, Paquette IM. Does preoperative anal physiology testing or ultrasonography predict clinical outcome with sacral neuromodulation for fecal incontinence? Int Urogynecol J. 2015;26:1613–7.
4. Muñoz-Yagüe T, Solís-Muñoz P, de los Ríos CC, Muñoz-Garrido F, Vara J, Solís-Herruzo JA. Fecal incontinence in men: causes and clinical and manometric features. World J Gastroenterol. 2014;20(24):7933–40.
5. Burgell RE, Bhan C, Lunniss PJ, Scott SM. Fecal incontinence in men: coexistent constipation and impact of rectal hyposensitivity. Dis Colon Rectum. 2012;55(1):18–25.
6. Bravo Gutierrez A, Madoff RD, Lowry AC, Parker SC, Buie WD, Baxter NN. Long-term results of anterior sphincteroplasty. Dis Colon Rectum. 2004;47:727–31; discussion 731–2
7. Halverson AL, Hull TL. Long-term outcome of overlapping anal sphincter repair. Dis Colon Rectum. 2002;45:345–8.
8. Malouf AJ, Norton CS, Engel AF, Nicholls RJ, Kamm MA. Long-term results of overlapping anterior anal-sphincter repair for obstetric trauma. Lancet. 2000;355:260–5.
9. Paquette IM, Madhulika G, Varma MD, et al. The American Society of Colon and Rectal Surgeons' clinical practice guidelines for the treatment of fecal incontinence. Dis Colon Rectum. 2015;58:623–36.
10. Ferrara A, Lujan JH, Cebrian J, et al. Clinical, manometric, and EMG characteristics of patients with fecal incontinence. Tech Coloproctol. 2001;5(1):13–8.
11. Prapasrivorakul S, Gosselink M, Gorissen KJ, et al. Sacral neuromodulation for faecal incontinence: is the outcome compromised in patients with high-grade internal rectal prolapse? Int J Color Dis. 2015;30:229–34.
12. Martellucci J, Sturiale A, Bergamini C, Boni L, Cianchi F, Coratti A, Valeri A. Role of transanal irrigation in the treatment of anterior resection syndrome. Tech Coloproctol. 2018;22:519–27.
13. Norton C, Chelvanayagam S, Wilson-Barnett J, Redfern S, Kamm MA. Randomized controlled trial of biofeedback for fecal incontinence. Gastroenterology. 2003;125:1320–9.
14. Vonthein R, Heimerl T, Schwandner T, Ziegler A. Electrical stimulation and biofeedback for the treatment of fecal incontinence: a systematic review. Int J Color Dis. 2013;28:1567–77.
15. Murad-Regadas SM, Francisco Sergio P, Regadas FSP, Filho R, de Medonca JJ, Andrade Filho RS, da Silva Vilarinho A. Predictors of unsuccessful of treatment for fecal incontinence biofeedback for fecal incontinence in female. Arq Gastroenterol. 2019;56(1):61–5.
16. Deutekom M, Dobben AC. Plugs for containing faecal incontinence. Cochrane Database Sys Rev. 2015;(17):CD005086.
17. Lukacz ES, Segall MM, Wexner SD. Evaluation of an anal insert device for the conservative Management of Fecal Incontinence. Dis Colon Rectum. 2015;58:892–8.
18. Leo CA, Thomas GP, Hodgkinson JD, Segal JP, Maeda Y, Murphy J, Vaizey CJ. The Renew® anal insert for passive faecal incontinence: a retrospective audit of our use of a novel device. Colorectal Dis. 2019;21(6):684–8.
19. Richter HE, Dunivan G, Brown HW, Andy U, Dyer KY, Rardin C, Muir T, McNevin S, Paquette I, Gutman RE, Quiroz L, Wu J. A 12-month clinical durability of effectiveness and safety evaluation of a vaginal bowel control system for the nonsurgical treatment of fecal incontinence. Female Pelvic Med Reconstr Surg. 2019;25(2):113–9.
20. Everaerta K, Kerckhaerta H, Caluwaertsa M, Audenaerta H, Vereeckeb G, De Cuyperec A, Boelaertd U, Van den Homberghe W, Oosterlinck A. Prospective randomized trial comparing the 1-stage with the 2-stage implantation of a pulse generator in patients with pelvic floor dysfunction selected for sacral nerve stimulation. Eur Urol. 2004;45:649–54.
21. Rice TC, Quezada Y, Rafferty JF, Paquette IM. Dynamic article: percutaneous nerve evaluation versus staged sacral nerve stimulation for fecal incontinence. Dis Colon Rectum. 2016;59(10):962–7.
22. Wexner SD, Coller JA, Devroede G, et al. Sacral nerve stimulation for fecal incontinence: results of a 120-patient prospective multicenter study. Ann Surg. 2010;251:441–9.
23. Hull T, Giese C, Wexner SD, Mellgren A, Devroede G, Madoff RD, Stromberg K, Coller JA. Long-term durability of sacral nerve stimulation therapy for chronic fecal incontinence. Dis Colon Rectum. 2013;56(2):234–45.
24. Thin NN, Horrocks EJ, Hotouras A, Palit S, Thaha MA, Chan CL, Matzel KE, Knowles CH. Systematic review of the clinical effectiveness of neuromodulation in the treatment of faecal incontinence. Br J Surg. 2013;100(11):1430–47.
25. Force L, da Silva G. Management of complications of sacral neuromodulation. Semin Colon Rectal Surg. 2017;28:173–6.
26. Varghese C, Wells CI, O'Grady G, Bissett IP. Costs and outcomes of sacral nerve stimulation for faecal incontinence in New Zealand: a 10-year observational study. ANZ J Surg. 2020;90(4):569–75.
27. De Wachter S, Knowles CH, Elterman DS, Kennelly MJ, Lehur PA, Matzel KE, Engelberg S, Van Kerrebroeck PEV. New technologies and applications in sacral neuromodulation: an update. Adv Ther. 2020;37:637–43.
28. Graf W, Mellgren A, Matzel KE, Hul T, Johansson C, Bernstein M, NASHA Dx Study Group. Efficacy of dextranomer in stabilized hyaluronic acid for treatment of faecal incontinence: a randomised, sham-controlled trial. Lancet. 2011;377:997–1003.
29. Mellgren A, Matzel KE, Pollack J, Hull T, Bernstein M, Graf W, NASHA Dx Study Group. Long-term efficacy of NASHA Dx injection therapy for treatment of fecal incontinence. Neurogastroenterol Motil. 2014;26:1087–94.
30. Dehli T, Stordahl A, Vatten LJ, Romundstad PR, Mevik K, Sahlin Y, Lindsetmo RO, Vonen B. Sphincter training or anal injections of dextranomer for treatment of anal incontinence: a randomized trial. Scand J Gastroenterol. 2013;48(3):302–10.
31. Horrocks EJ, Thin N, Thaha MA, Taylor SJ, Norton C, Knowles CH. Systematic review of tibial nerve stimulation to treat faecal incontinence. Br J Surg. 2014;101(5):457–68.
32. Knowles CH, Horrocks EJ, Bremner SA, Stevens N, Norton C, O-Connell PR, Eldridge S. Percutaneous tibial nerve stimulation versus sham electrical stimulation for the treatment of faecal incontinence in adults (CONFIDeNT): a double-blind, multicenter, pragmatic, parallel-group, randomised controlled trial. Lancet. 2015;386:1640–8.
33. Simillis C, Lal N, Qiu S, Kontovounisios C, Rasheed S, Tan E, Tekkis PP. Sacral nerve stimulation versus percutaneous tibial nerve stimulation for faecal incontinence: a systematic review and meta-analysis. Int J Color Dis. 2018;33(5):645–8.
34. Frascio M, Mandolfino F, Imperatore M, et al. The SECCA procedure for faecal incontinence: a review. Color Dis. 2014;16:167–72.
35. Abbas MA, Tam MS, Chun LJ. Radiofrequency treatment for fecal incontinence: is it effective long-term? Dis Colon Rectum. 2012;55(5):605–10.
36. Lam TJ, Visscher AP, Meurs-Szojda MM, Felt-Bersma RJ. Clinical response and sustainability of treatment with temperature-controlled

radiofrequency energy (Secca) in patients with faecal incontinence: 3 years follow-up. Int J Color Dis. 2014;29(6):755–61.
37. Takahashi-Monroy T, Morales M, Garcia-Osogobio S, Valdovinos MA, Belmonte C, Barreto C, et al. SECCA procedure for the treatment of fecal incontinence: results of five-year follow-up. Dis Colon Rectum. 2008;51(3):355–9.
38. Visscher AP, Lam TJ, Meurs-Szojda MM, Felt-Bersma RJF. Temperature-controlled delivery of radiofrequency energy in fecal incontinence: a randomized sham-controlled clinical trial. Dis Colon Rectum. 2017;60(8):860–5.
39. Trebol J, Carabias-Orgaz A, Gracia-Arranz M, Garcia-Olmo D. Stem cell therapy for faecal incontinence: Current state and future perspectives. World J Stem Cells. 2018;10:82–105.25.
40. Frudinger A, Kölle D, Schwaiger W, et al. Muscle-derived cell injection to treat anal incontinence due to obstetric trauma: pilot study with 1 year follow-up. Gut. 2010;59:55–61.
41. Frudinger A, Pfeifer J, Paede J, et al. Autologous skeletal-muscle-derived cell injection for anal incontinence due to obstetric trauma: a 5-year follow-up of an initial study of 10 patients. Color Dis. 2015;17:794–801.
42. Boyer O, Bridoux V, Giverne C, Bisson A, Koning E, Leroi AM, Chambon P, Déhayes J, Le Corre S, Jacquot S, Bastit D, Martinet J, Houivet E, Tuech JJ, Benichou J, Michot F, and the Study Group of Myoblast Therapy for Faecal Incontinence. Autologous myoblasts for the treatment of fecal incontinence: results of a phase 2 randomized placebo-controlled study (MIAS). Ann Surg. 2018;267:443–50.
43. Mellgren A, Zutshi M, Lucente VR, et al. A posterior anal sling for fecal incontinence: results of a 152-patient prospective multicenter study. Am J Obstet Gynecol. 2016;214:349.e1–8.
44. Jorge JM, Wexner SD. Etiology and management of fecal incontinence. Dis Colon Rectum. 1993;36:77–97.
45. Sultan AH, Kamm MA, Hudson CN, et al. Anal-sphincter disruption during vaginal delivery. N Engl J Med. 1993;329:1905–11.
46. Steele SR, Lee P, Mullenix PS, et al. Is there a role for concomitant pelvic floor repair in patients with sphincter defects in the treatment of fecal incontinence? Int J Color Dis. 2006;21:508–14.
47. Fernando RJ, Sultan AH, Kettle C, Thakar R. Methods of repair for obstetric anal sphincter injury. Cochrane Database Syst Rev. 2013;(12):1–45. https://doi.org/10.1002/14651858.CD002866.pub3. PMID: 24318732.
48. Van Koughnett JAM, Wexner SD. Current management of fecal incontinence: choosing amongst treatment options to optimize outcomes. World J Gastroenterol. 2013;19(48):9216–30.
49. Glasgow SC, Lowry AC. Long-term outcomes of anal sphincter repair for fecal incontinence: a systematic review. Dis Colon Rectum. 2012;55(4):482–90.
50. D'Hoore A, Cadoni R, Penninckx F. Long-term outcome of laparoscopic ventral rectopexy for total rectal prolapse. Br J Surg. 2004;91(11):1500–5.
51. Broden B, Snellman B. Procidentia of the rectum studied with cineradiography. A contribution to the discussion of causative mechanism. Dis Colon Rectum. 1968;11:330–47.
52. Samaranayake CB, Luo C, Plank AW, Merrie AE, Plank LD, Bissett IP. Systematic review of ventral rectopexy for rectal prolapse and intussusception. Color Dis. 2010;12(6):504–12.
53. McLean R, Kipling M, Musgrave E, Mercer-Jones M. Short- and long-term clinical and patient-reported outcomes following laparoscopic ventral mesh rectopexy using biological mesh for pelvic organ prolapse: a prospective cohort study of 224 consecutive patients. Color Dis. 2018;20:424–36.
54. Mäkelä-Kaikkonen J, Rautio T, Kairaluoma M, Carpelan-Holmström M, Kössi J, Rautio A, Ohtonen P, Mäkelä J. Does ventral rectopexy improve pelvic floor function in the long term? Dis Colon Rectum. 2018;61:230–8.
55. Evans C, Stevenson AR, Sileri P, Mercer-Jones MA, Dixon AR, Cunningham C, Jones OM, Lindsey I. A multicenter collaboration to assess the safety of laparoscopic ventral rectopexy. Dis Colon Rectum. 2015;58:799–807.
56. Wexner SD, Baeten C, Bailey R, Bakka A, Belin B, Belliveau P, et al. Long-term efficacy of dynamic graciloplasty for fecal incontinence. Dis Colon Rectum. 2002;45(6):809–18.
57. Rongen MJ, Uludag O, El Naggar K, Geerdes BP, Konsten J, Baeten CG. Long-term follow-up of dynamic graciloplasty for fecal incontinence. Dis Colon Rectum. 2003;46(6):716–21.
58. Gohil AJ, Gupta AK, Jesudason MR, Nayak S. Graciloplasty for anal incontinence-is electrical stimulation necessary? Ann Plast Surg. 2019;82(6):671–8.
59. Sugrue J, Lehur PA, Madoff RD, et al. Long-term experience of magnetic anal sphincter augmentation in patients with fecal incontinence. Dis Colon Rectum. 2017;60:87–95.
60. Wong WD, Congliosi SM, Spencer MP, et al. The safety and efficacy of the artificial bowel sphincter for fecal incontinence: results from a multicenter cohort study. Dis Colon Rectum. 2002;45:1139–53.
61. Wong MT, Meurette G, Wyart V, Glemain P, Lehur PA. The artificial bowel sphincter: a single institution experience over a decade. Ann Surg. 2011;254(6):951–6.
62. Patel AS, Saratzis A, Arasaradnam R, Harmston C. Use of antegrade continence enema for the treatment of fecal incontinence and functional. Constipation in adults: a systematic review. Dis Colon Rectum. 2015;58:999–1013.

Low Anterior Resection Syndrome (LARS)

62

Liliana Bordeianou and Craig A. Messick

Key Concepts

- Significant alteration in bowel function altering a patient's quality of life commonly occurs after restorative proctectomy or low anterior bowel resection. This has been termed low anterior resection syndrome (LARS).
- Using a Delphi analysis, experts including patients with LARS have been able to describe the condition as eight symptoms and five consequences.
- No standardized tool exists that determines its severity. Careful questioning starting around 3 months after establishment of intestinal continuity is important to determine treatment options.
- It is important to determine if correctable problems that can mimic LARS are leading to these symptoms.
- Treatment starts with setting expectations, educating patients, and evaluating treatment outcomes. This involves a systematic incremental approach to treatment with precise written instructions and monitoring results.

Introduction

Current rectal cancer treatment involves a complex, multidisciplinary approach with individualized treatment tailored to disease location and its degree of local and systemic spread [1]. Following chemoradiotherapy and/or surgery, the subsequent injury to nerves altering pelvic floor function has become recognized and supported by a significant body of literature that describes their deleterious consequences [2, 3]. The collective bowel symptoms that develop have been grouped together under the eponym of low anterior resection syndrome (LARS). Though largely variable, patient-reported symptoms that develop within the first year include, but are not limited to, fecal incontinence (FI) (20–80%), urgency (30–90%), fragmentation (30–70%), painful defecation (20–50%), and clustering [4, 5]. How best to describe and approach patients who suffer from these symptoms has been generally lacking in the literature, largely due to no uniform LARS definition [3]. This has made meta-analyses and systematic research difficult or of low quality.

Despite lacking a consensus/definition, recent research has provided some insight into the frequency of LARS. LARS is defined as having bowel dysregulation causing a significant alteration in the patient's quality of life. As many as 58% of patients treated with a restorative proctectomy or low anterior resection (LAR), for a rectal cancer (or for benign etiologies), may report major symptoms of urgency, frequency, and clustering at 3 months. An astonishing 46% of patients continue to suffer from major symptoms of LARS at 12 months, and 41% continue to have symptoms at 54 months. This implies that for some, LARS may last a lifetime [6, 7].

Etiology

The etiology of LARS is poorly understood. It is speculated to be a combination of the loss of the rectal reservoir, autonomic denervation, an increase in colonic motility, damage to rectal mucosa from radiotherapy, a reduction of recto-anal sensitivity from pelvic dissection, and a decrease in the anal rest pressure. None of these theories have been properly studied or validated [8].

Definition

Low anterior resection syndrome has previously been pragmatically defined as "disordered bowel function after rectal resection, leading to a detriment in quality of life." Given the

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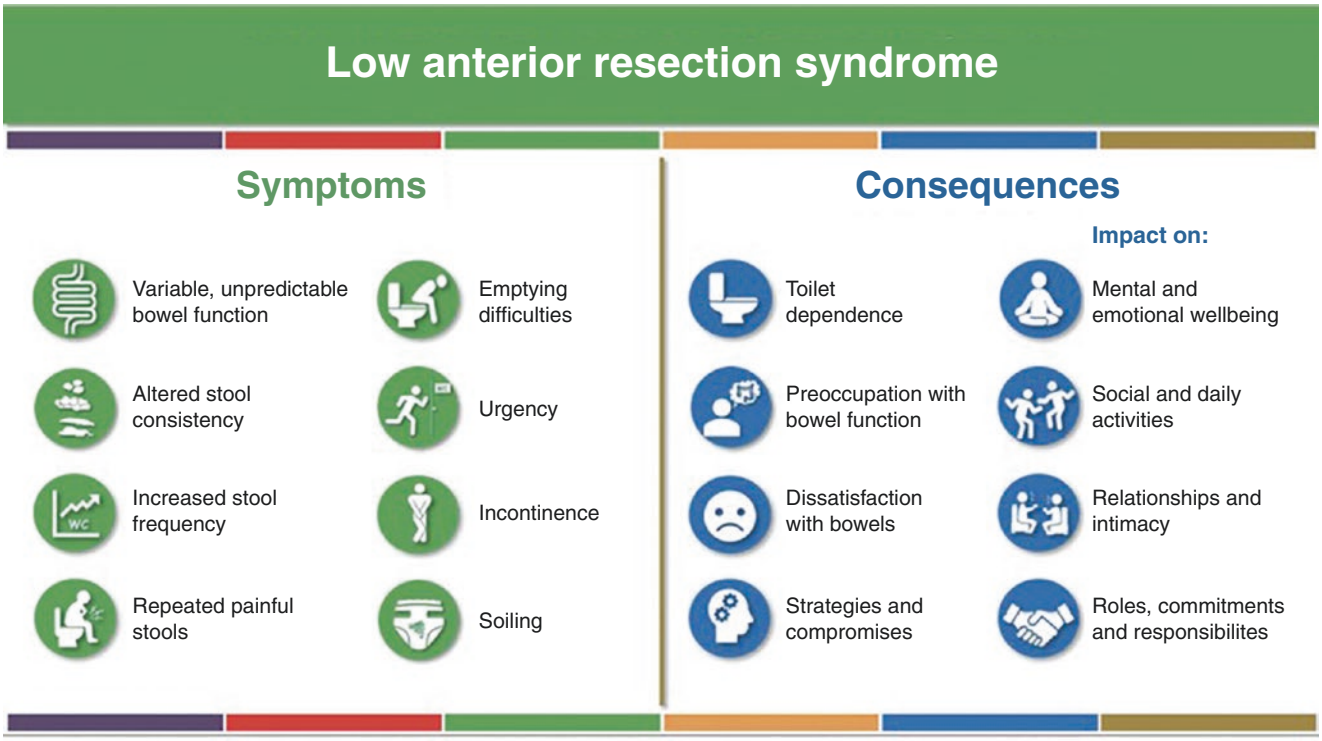

Fig. 62.1 Priorities identified in each phase of the study. (Reused with permission © Wolters Kluwer 2020 [11])

major and long-lasting impact of LARS on rectal cancer survivors, modern efforts are underway to improve its recognition, diagnosis, and treatment [9]. The first step was determining a definition. A recent Delphi analysis consensus effort involving 325 experts (including 156 patients with LARS) successfully distilled the condition of LARS to eight symptoms and five consequences, which together encompass the important aspects of the syndrome and serve as its definition [10].

For a LARS diagnosis, any patient who underwent LAR would have at least one symptom and at least one of the listed consequences (Fig. 62.1). Once LARS is recognized, the next step would be to assess the severity with a validated tool [11]. Unfortunately, none of the existing tools cover all eight LARS symptoms, again highlighting the current difficulties in the accurate measurement of LARS [12]. LARS is the type of entity that we all feel we know when we see it – the measurement of its severity requires in-depth patient conversations at each visit, patience to understand which aspect of the syndrome may be getting better or worse with intervention, and a bowel diary.

LARS: Scope of the Problem

The precise number of clinically affected patients who experience LARS is highly variable as previously mentioned [3]. Laurberg and colleagues originally described LARS from expert physician opinion and developed an online clinical scoring instrument, validated in many countries (see Fig. 62.2) [13]. Though intended to provide a clinical assessment about the severity of recognized LARS symptoms, it does not provide an accurate appraisal of all patients who experience LARS. It is still the mainstay for clinical assessment for patients with LARS symptoms.

Risk Factors for LARS

Patients with LARS must have had some portion of their rectum removed. This is important as other patients may develop similar symptoms but have a preserved rectum. One group are those that undergo definitive chemoradiotherapy for other pelvic cancers as similar posttreatment bowel dysfunction symptoms have been reported from this group. This has mostly been described in women who have undergone chemoradiotherapy for cervical or anal squamous cell carcinoma. Though the number affected remains largely unclear, major bowel symptoms affecting their quality of life have been reported in 50% of treated patients [14, 15].

For patients who have undergone LAR, additional risk factors have been reported. Age, gender (female > male), tumor location from the anal verge, extent of mesorectal dissection, use of neo(adjuvant) pelvic radiation therapy, and having fecal diversion (loop ileostomy) have all been implicated [4, 7, 16, 17]. Acceptable fecal continence does not

APPENDIX 2. LARS Score: Scoring Instructions

Add the scores from each 5 answers to one final score.

Do you ever have occasions when you cannot control your flatus (wind)?

☐ No, never	0
☐ Yes, less than once per week	4
☐ Yes, at least once per week	7

Do you ever have any accidental leakage of liquid stool?

☐ No, never	0
☐ Yes, less than once per week	3
☐ Yes, at least once per week	3

How often do you open your bowels?

☐ More than 7 times per day (24 hours)	4
☐ 4-7 times per day (24 hours)	2
☐ 1-3 times per day (24 hours)	0
☐ Less than once per day (24 hours)	5

Do you ever have to open your bowels again within one hour of the last bowel opening?

☐ No, never	0
☐ Yes, less than once per week	9
☐ Yes, at least once per week	11

Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?

☐ No, never	0
☐ Yes, less than once per week	11
☐ Yes, at least once per week	16

Total Score:

Interpretation:

0-20:	**No LARS**
21-29:	**Minor LARS**
30-42:	**Major LARS**

Fig. 62.2 Low anterior resection syndrome (LARS) scoring system. (Reused with permission © Wolters Kluwer 2020 [13])

protect against developing LARS. Eighty-five percent of patients who have most or all of the rectum removed maintain continence; however 42% of patients still experience LARS [18]. Additionally, inflammation due to an anastomotic leak has been shown to cause irreparable damage to the pelvic floor muscles adding to the severity of chronic bowel dysfunction [19].

Prediction of LARS for Patient Counseling and Surgical Planning

Considering the potential impact of both radiation and surgery for rectal or other pelvic cancers, a discussion of possible outcomes including postoperative bowel dysfunction and LARS is critical in preoperative counseling. Informed consent should not only discuss perioperative complications, but projected alteration in bowel dysfunction. The online Pre-Operative LARS (POLARS) nomogram has emerged as an aid to predict the development of LARS following restorative proctectomy [16]. When patients are confronted with the true risk of fecal urgency and other bowel problems that may dominate their lives, they may opt for a colostomy after proctectomy. Thus, an honest discussion of all surgical options including an end colostomy should be carried out with all patients, not just those who have baseline bowel dysfunction and mobility restrictions or patients confined to a wheelchair.

Prevention of LARS

There are no substantial studies on the prevention of LARS. Having symptoms and a definition will be key going forward to study this issue. The role of pelvic radiation is one area under study. Future research has also started on the effects of chronic diversion with a loop ileostomy (even 3 months) and long-term implications. The use of a mechanical bowel preparation may have an effect in LARS development and is under study [20]. Alternative neo-rectal reservoirs have been considered as ways to prevent LARS and FI. While short-term improvement in bowel function with a colonic J pouch has been documented, by 18 months, the patient-reported outcomes (PROM) are not statistically different

compared to an end-end anastomotic configuration [21]. Overall, no definitive intervention has proven effective to prevent LARS.

Diagnosis

The clinician should start to question their patient about bowel function starting around 3 months after restoration of intestinal continuity. Once suspected, exclusion and treatment of correctable LARS-like conditions should occur. Some of these LARS-like conditions include pancreatic malabsorption, bacterial small bowel overgrowth, or 5-FU-induced lactose intolerance. In addition, patients with LARS-like symptoms could also be suffering from radiation enteritis or fat and bile salt malabsorption from radiation-induced mucosal injury. Thus, patients with LARS or LARS-like conditions may be prescribed a trial of cholestyramine in an attempt to reduce and regulate bowel frequency [22]. Surgical strictures, ischemic conduits, or tumor recurrence can also produce a LARS-like pattern and should be considered. Flexible sigmoidoscopy in patients with LARS-like symptoms during the first 5 years after surgery should always be a consideration. This is particularly important if the patient has not been receiving adequate surveillance or the patient reports sudden worsening of their bowel function. Endoscopic evaluation should be done with the idea to exclude recurrence, stricture, or any correctable anatomical problem. If an intervention occurs, bowel symptoms should be reassessed post treatment.

Treatment Options

There is limited data to guide caregivers regarding the treatment of LARS. Most data are derived from small, nonrandomized trials with varied interventions and post-intervention assessments. Most of these studies did not employ the LARS score or any other validated tool, with most assessing FI only. Surgeons and caregivers should set realistic expectations for their patients. Treatment of LARS requires an individualized treatment plan that will not encompass one intervention, but likely multiple combined modalities in an effort to improve their symptoms. LARS should be viewed as a chronic disease, similar to diabetes or hypertension, and several interventions, adjustments, and modifications may be required over time to maintain and improve their quality of life. Some interventions may require other experts including gastroenterologists, primary care providers (PCPs), and mental health experts.

Despite these major limitations and difficulties, it is reassuring to know that with systematic care, patients with LARS can have meaningful improvements to their quality of life. In a recent study, simple implementation of a postoperative protocol to treat LARS systematically led to a drop in the LARS score from 31 (major LARS) to 18 (moderate LARS), with the rates of major LARS dropping from 51.9% to 26.3% [23].

Another randomized control trial (RCT) compared algorithmic care to routine ad hoc care and showed that algorithmic care demonstrated improved symptomatology and functional status in LARS patients [24]. This care can be administered by surgeons, gastroenterologists, PCPs, or advanced care practitioners. This requires patient education, patience, and a careful empathetic open dialogue between the patient and provider.

Regardless of who delivers care, it should be noted that a significant amount of information may be discussed or recommended per visit. Thus, it is extremely helpful to give precise written instructions for skin care and bowel altering medications so the patient does not rely on memory. Conversely, the provider should document data reported by the patient in a well-maintained bowel diary in an effort to monitor results over time. This will allow a systematic, incremental approach toward treatment.

Nonsurgical Interventions

Medical Therapy

Initial interventions for LARS should begin with dietary fiber and water to improve stool consistency, followed by fiber supplementation (bulking agents) and then anti-diarrheal/motility medications. Many patients remain reliant on these agents over the long term. Thus, patients should be reassured that long-term use of these medications is not detrimental.

Intraluminal bulking agents, such as dietary fiber supplementation and psyllium, are recommended with the idea of improving stool consistency, while simultaneously reducing fragmentation and clustering. If diet and fiber fail to provide adequate relief, antimotility agents like loperamide (non-opiate) and opiates such as atropine/diphenoxylate or tincture of opium may be added to the patient's medical regimen, typically along with continuing fiber and dietary modifications. Opioids function to reduce gastrointestinal propulsion. Loperamide effects only the intestinal muscle, whereas others have the potential for central nervous system alterations and are controlled substances that require longitudinal monitoring. Some patients with a clustering LARS phenotype have reported a deterioration in their LARS symptoms with opioids. When these interventions fail, a trial of amitriptyline is recommended (dose of 10–25 mg at night, as tolerated). Amitriptyline (tricyclic antidepressant) was evaluated in an open-label FI study and shown to decrease FI scores in 85% of patients [25].

Development of new medical therapies for LARS remains limited. This has resulted in clinicians extrapolating and trialing medications normally used to address symptoms of FI or urgency. Serotonin receptor agonists have been described as potentially useful in FI and eventually trialed in patients with LARS with modest effects [26]. Probiotics are postulated to improve GI symptoms by modifying the immunologic, digestive, or nutritional functions of gut bacteria. Treatment with probiotics in multiple formulations has been studied for a variety of GI disorders and is advocated by some authors for LARS patients. However, there is limited convincing data on the impact of probiotics on LARS symptoms. A small RCT study utilizing VSL#3 (probiotic) administration after loop ileostomy closure did not appear to have any effect on LARS symptoms [27].

Topical Treatments

Many patients with LARS report secondary symptoms of anal pain and skin irritation from skin breakdown caused by diarrhea and FI. Thus, counseling about skin care is an important component of LARS management. Barrier creams that contain zinc (such as Calmoseptine, Calmoseptine, Inc., Huntington Beach, California) and lanolin (if not allergic to wool) should be copiously applied up to the dentate line. When fungal superinfection is suspected, antifungal medication can be applied sparingly with a cotton ball, which dusts the powder over the anus. Another dry cotton ball could then be left near anus to wick away the moisture, which would otherwise collect between the buttocks even if the patient has a sanitary pad in their underclothes. Patients should be advised to avoid chemical wipes, abrasive toilet paper, and soaps that would dry out the skin and lead to chemical irritation. Instead, a gentle washcloth or use of wet toilet paper after defecation or a perineal wash using a bidet water sprayer may be advised. Finally, when pain is severe, temporary application of local anesthetic cream (Lidocaine 2%) on top of the barrier cream can be considered, until the anoderm re-epithelializes.

Biofeedback

Pelvic floor muscle retraining (biofeedback) may provide additional benefit to reduce LARS symptoms and should be considered in parallel with medical therapy and other interventions. However, data to support this is sparse. A recent systematic review of various low-quality studies looked at the effects of biofeedback on LARS. These researchers ultimately identified five trials that cumulatively involved 321 patients utilizing biofeedback for LARS, all conducted internationally [28]. Roughly 286 patients followed through with the recommended regimens. Only two of these trials were prospective, and the pelvic floor retraining protocols varied widely. Despite these limitations, 4/5 trials appeared to show an improvement in patients' bowel function. A recent open-label RCT suggested that most improvement appears to be for the symptoms of FI, with other aspects of the LARS remaining unchanged and no overall improvements in LARS score [29]. Clearly, better data on biofeedback and its efficacy in LARS is still needed, but in the interim, biofeedback remains a reasonable option in motivated patients, especially in those whose main symptom is FI. For patients whose main difficulties are incomplete emptying, clustering, or fragmentation, after six to eight biofeedback sessions, if no improvement is noted, stopping this therapy is reasonable.

Retrograde Colonic Irrigation (RCI)

Rectal irrigation is a frequently utilized treatment option for patients with LARS, regardless of their predominant symptom (fragmentation, clustering, diarrhea, or FI). Importantly this is not a simple rectal enema. Appropriate RCI involves retrograde, transrectal infusion of a high volume (500–1000 ml) of tepid water to fill the entire left side of the colon, followed by its evacuation. The treatment lasts approximatively 30 minutes and usually is performed in the evening or early morning based on patient preference. The key principle is similar to the concept used for colostomy irrigation. It is intended to condition the bowel to evacuate at the same time daily and aid in emptying the large bowel contents. This in turn decreases the need for another bowel movement for the rest of the day. The enema can be administered via a simple 28 Fr Foley catheter which is gently inserted into the neorectum. The catheter is then connected to a bag (typically a tube-feeding bag), which is hung high enough to provide hydrostatic pressure for the water to flow into the rectum and colon. The system has a regulator to allow gentle increase in colonic filling. This setup can be assembled from routine supplies found in any surgical clinic or purchased as a kit (e.g., Peristeen by Coloplast).

RCI has been shown to be effective in most cases of FI and is a frequent tool in the arsenal for LARS (see Chap. 61 on fecal incontinence). The data on RCI for LARS is derived from smaller studies, which appear to support its use in this particular group of patients. A RCT of 37 patients (18 treated with RCI, others with peripheral tibial nerve stimulation [PTNS]) found that patients using RCI reported a decrease in the maximum number of stool episodes per day and per night, as well as improvement in their LARS scores and Wexner FI scores [30].

In another two-group, parallel, open-label RCT of 27 patients with LARS patients treated with RCI, a statistically significant improvement in their LARS scores from 35

(major) to 12 (mild) was reported [31]. Martelucci et al. described 27 patients with LARS (19 early LARS and 8 chronic LARS) who reported a decrease in the number of median daily bowel movements and a decrease in their median LARS score while using RCI. Upon discontinuation of RCI, their symptoms returned [32]. Ultimately, 85% of patients who tried RCI asked to resume RCI after the study ended [32].

Initially patients receive education on RCI and are able to perform successful instillations. It is recommended a minimum trial of 6 months after they can successfully instill RCI, before considering escalation to a more aggressive treatment or to surgery. This also allows time to optimize and adjust their medical regimen, complete biofeedback, and allow the body to adapt to their new anatomy. Most patients may then decide that they are satisfied with the newly reached equilibrium and will not be interested in further escalation of treatment. Those who are still struggling, however, should be considered for surgical interventions.

Surgical Interventions

Sacral Nerve Neuromodulation (SNM)

Sacral nerve neuromodulation (also known as sacral nerve stimulation [SNS]) has emerged as an effective treatment for FI and has become a first-line therapy for FI which is not optimized with medical therapy. Although the mechanism by which SNM works remains unclear, it is postulated that its effects are probably mediated in the brain. The advantage with SNM is that it is minimally invasive and has a test phase before permanent device insertion (see Chap. 61 for details on insertion of SNM). There has been encouraging literature on the use of SNM in patients with LARS from small studies. A recent systematic review of SNM in patients with LARS identified ten studies, with variable endpoints [33]. Seven studies measured improvement in FI, while three looked at an improvement in the LARS score. Cumulatively, 94 patients were screened with PNE or tined lead implantation to demonstrate the effectiveness of SNM prior to permanent implantation of the stimulator. Seventy-five patients (79.8%) proceeded with permanent SNM implantation. Overall median improvement in LARS symptoms was 67.0% after SNM implantation. This is lower than success rates reported in the patients with benign etiologies of FI treated with SNM, but still meaningful considering the lack of treatment for this condition.

Given the minimally invasive nature of this intervention and the lack of other modalities before proceeding to stoma, a trial of SNM can be considered in all patients with LARS who have failed other options. Like all other treatments for LARS, SNM should be viewed as an intervention that is performed not as a replacement of prior therapy but rather as an additive to previously instituted treatments and bowel regimens.

Research is underway on other forms of neuromodulation to treat LARS, some of them nonsurgical. For example, there is emerging data on PTNS in either the office or at home [34]. The data on this intervention remains intriguing, but this option is not currently available in the USA to treat any form of bowel dysfunction. It is speculated that the FDA has not approved this for bowel issues due to contradictions in the data on its efficacy and discouraging results after a RCT showed no difference between PTNS stimulation and sham stimulation for patients with FI [35].

Antegrade Continence Enemas (ACE)

Historical data on use of antegrade enemas via an appendicostomy tube, Chait or Malone antegrade continence enema (MACE) tube, or cecostomy tube have been limited to the pediatric population. However, a 2016 meta-analysis of antegrade continence enemas in adults with FI (and constipation) offered initial insight into its potential role for adults with FI and patients with LARS. In their review of 17 observational studies (426 patients, 165 patients had FI), the pooled success rate (defined as continued use at follow-up or successful resolution of symptoms) for patients with FI was 83.6% (95% CI 75.0–92.1) at a median follow-up of 39 months [36]. The authors concluded that following failure of all other options, antegrade enemas should be considered in motivated patients before creation of a permanent colostomy [36]. A systematic review by Patel et al. published in 2015 produced similar outcomes and shared the same conclusions. Though these studies did not report which type of stoma was used to insert the antegrade enema, 1 study from France with 19 patients suffering from FI and an additional 10 patients who had undergone restorative proctectomy had a percutaneous endoscopic cecostomy (PEC) tube for access [35–37]. Antegrade enemas via PEC tubes were reported by the baseline FI and proctectomy patients as successful in 73% and 90%, respectively, with corresponding improvement in baseline CCIS from 14.3 (baseline) to 2.7 (post-PEC) at 6 months. However, by 2 years the scores up trended to 10.4. Other types of tubes such as the MACE tube have much more limited data and at this point are considered investigational as a treatment for LARS.

Fecal Diversion

Fecal diversion is a last resort therapy after all previous treatment options have failed to improve symptoms. Typically, when patients resort to a stoma, they are overwrought with symptoms. Whether a loop or end, small bowel (ileostomy) or colon (colostomy), stoma, fecal diversion undoubtedly offers patients a means to reestablish an acceptable quality of life. Though daunting to consider up front, the discussion of fecal diversion, preferably a colostomy (being cognizant

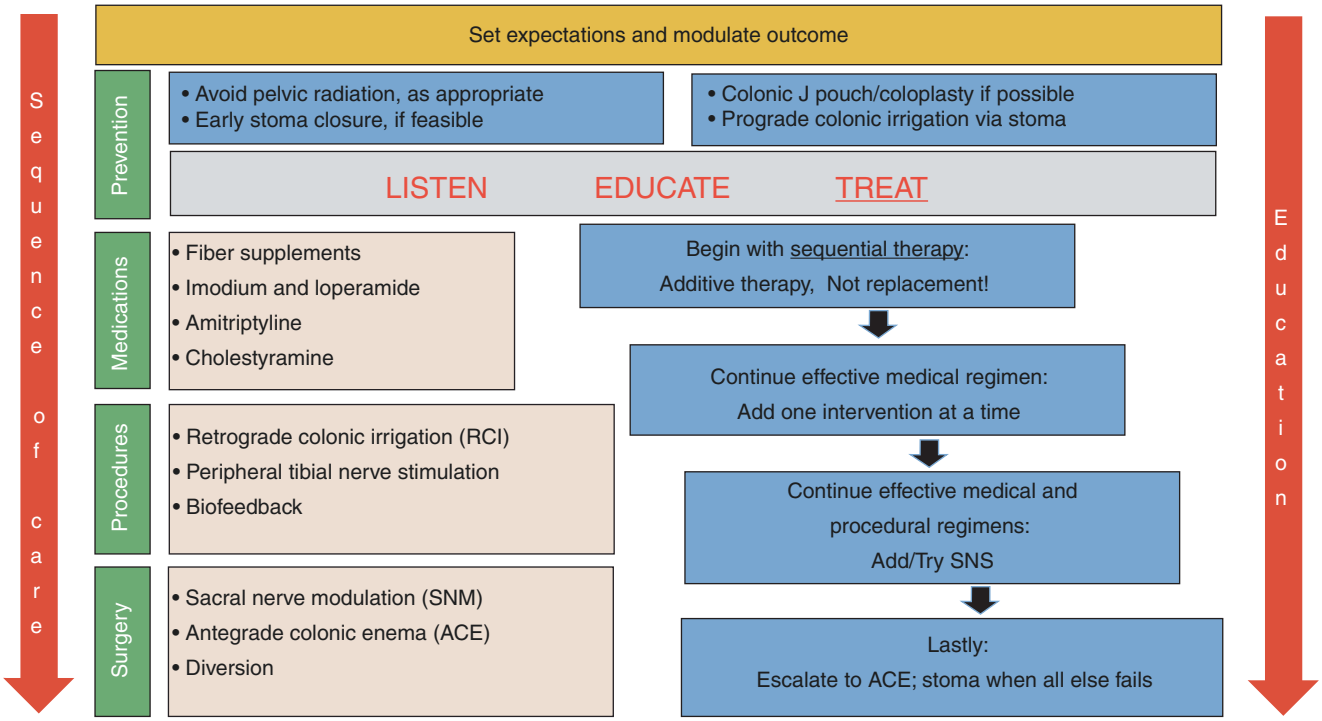

Fig. 62.3 Summary of the treatment algorithm

when constructing of the blood flow disarrangement due to the sigmoid and rectal resection), should be brought up as an option for those with severe bowel dysfunction and/or severe FI. It is imperative for the surgeon to perform the very best stoma possible as the goal is to improve the quality of life, not exchange it for a poorly constructed and functioned stoma. Figure 62.3 summarizes the algorithm for treatment.

Conclusion

Low anterior resection syndrome (LARS) is common. Recognition of this syndrome is increasing. However, treatments for LARS are still rather limited. Further research is underway to guide our understanding and treatment of this condition. In the interim, a real, clinician-patient-informed discussion, rooted in high-quality data and compassionate advice, is required from the very start of our decision-making when it comes to the surgical and medical approaches offered to treat rectal cancer. At the start of this journey, the goal of this discussion – which should include our multidisciplinary team – should calibrate the quest for cure and the quest for organ preservation surgery against the expected functional outcomes, to provide our patients advice and help them make decisions. Careful, consistent, and compassionate patient management will improve patient experience and quality of life. Treatment of these patients is a long-term commitment.

References

1. Engstrom PF, et al. NCCN clinical practice guidelines in oncology: rectal cancer. J Natl Compr Cancer Netw. 2009;7(8):838–81.
2. Chapman SJ, et al. A cross-sectional review of reporting variation in postoperative bowel dysfunction after rectal cancer surgery. Dis Colon Rectum. 2017;60(2):240–7.
3. Keane C, et al. Defining low anterior resection syndrome: a systematic review of the literature. Color Dis. 2017;19(8):713–22.
4. Jimenez-Gomez LM, et al. Factors associated with low anterior resection syndrome after surgical treatment of rectal cancer. Color Dis. 2017. E.pup PMID28963744
5. Pucciani F. A review on functional results of sphincter-saving surgery for rectal cancer: the anterior resection syndrome. Updat Surg. 2013;65(4):257–63.
6. Chen TY, et al. Bowel function 14 years after preoperative short-course radiotherapy and total mesorectal excision for rectal cancer: report of a multicenter randomized trial. Clin Colorectal Cancer. 2015;14(2):106–14.
7. Emmertsen KJ, Laurberg S. Impact of bowel dysfunction on quality of life after sphincter-preserving resection for rectal cancer. Br J Surg. 2013;100(10):1377–87.
8. Buzatti K, Petroianu A. Pathophysiological aspects of the low anterior resection syndrome for treatment of rectal cancer. Rev Col Bras Cir. 2017;44(4):397–402.
9. Bryant CL, et al. Anterior resection syndrome. Lancet Oncol. 2012;13(9):e403–8.
10. Keane C, et al. International consensus definition of low anterior resection syndrome. Dis Colon Rectum. 2020;63(3):274–84.
11. Keane C, et al. International consensus definition of low anterior resection syndrome. Color Dis. 2020;22(3):331–41.
12. Al-Saidi A, et al. How should the low anterior resection syndrome score be interpreted? Dis Colon Rectum. 2020;63:520.

13. Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. Ann Surg. 2012;255(5):922–8.
14. Haas S, et al. Anal sphincter dysfunction in patients treated with primary radiotherapy for anal cancer: a study with the functional lumen imaging probe. Acta Oncol. 2018;57(4):465–72.
15. Haas S, et al. Abnormal neuronal response to rectal and anal stimuli in patients treated with primary radiotherapy for anal cancer. Radiother Oncol. 2018;128(2):369–74.
16. Battersby NJ, et al. Development and external validation of a nomogram and online tool to predict bowel dysfunction following restorative rectal cancer resection: the POLARS score. Gut. 2018;67(4):688–96.
17. Hoerske C, et al. Long-term outcomes and quality of life after rectal carcinoma surgery. Br J Surg. 2010;97(8):1295–303.
18. Luca F, et al. Functional results of robotic total intersphincteric resection with hand-sewn coloanal anastomosis. Eur J Surg Oncol. 2016;42(6):841–7.
19. Kverneng Hultberg D, et al. The impact of anastomotic leakage on long-term function after anterior resection for rectal cancer. Dis Colon Rectum. 2020;63:619.
20. Nowakowski MM, et al. Defunctioning ileostomy and mechanical bowel preparation may contribute to development of low anterior resection syndrome. Wideochir Inne Tech Maloinwazyjne. 2018;13(3):306–14.
21. Brown CJ, Fenech D, McLeod RS. Reconstructive techniques after rectal resection for rectal cancer. Cochrane Database Syst Rev. 2008;(2):CD006040.
22. Muls AC, et al. Managing gastrointestinal symptoms after cancer treatment: a practical approach for gastroenterologists. Frontline Gastroenterol. 2013;4(1):57–68.
23. van der Heijden JAG, et al. Implementation of a postoperative screening and treatment guidance for the low anterior resection syndrome: preliminary results. Dis Colon Rectum. 2019;62(9):1033–42.
24. Andreyev HJ, et al. Algorithm-based management of patients with gastrointestinal symptoms in patients after pelvic radiation treatment (ORBIT): a randomised controlled trial. Lancet. 2013;382(9910):2084–92.
25. Santoro GA, et al. Open study of low-dose amitriptyline in the treatment of patients with idiopathic fecal incontinence. Dis Colon Rectum. 2000;43(12):1676–81; discussion 1681–2.
26. Itagaki R, et al. Serotonin (5-HT3) receptor antagonists for the reduction of symptoms of low anterior resection syndrome. Clin Exp Gastroenterol. 2014;7:47–52.
27. Stephens JH, Hewett PJ. Clinical trial assessing VSL#3 for the treatment of anterior resection syndrome. ANZ J Surg. 2012;82(6):420–7.
28. Visser WS, et al. Pelvic floor rehabilitation to improve functional outcome after a low anterior resection: a systematic review. Ann Coloproctol. 2014;30(3):109–14.
29. Lee KH, Kim JS, Kim JY. Efficacy of biofeedback therapy for objective improvement of pelvic function in low anterior resection syndrome. Ann Surg Treat Res. 2019;97(4):194–201.
30. Rosen HR, et al. Randomized clinical trial of prophylactic transanal irrigation versus supportive therapy to prevent symptoms of low anterior resection syndrome after rectal resection. BJS Open. 2019;3(4):461–5.
31. Enriquez-Navascues JM, et al. A randomized trial comparing transanal irrigation and percutaneous tibial nerve stimulation in the management of low anterior resection syndrome. Color Dis. 2020;22(3):303–9.
32. Martellucci J, et al. Role of transanal irrigation in the treatment of anterior resection syndrome. Tech Coloproctol. 2018;22(7):519–27.
33. Huang Y, Koh CE. Sacral nerve stimulation for bowel dysfunction following low anterior resection: a systematic review and meta-analysis. Color Dis. 2019;21(11):1240–8.
34. Altomare DF, et al. Short-term outcome of percutaneous tibial nerve stimulation for low anterior resection syndrome: results of a pilot study. Color Dis. 2017;19(9):851–6.
35. Horrocks EJ, et al. Double-blind randomised controlled trial of percutaneous tibial nerve stimulation versus sham electrical stimulation in the treatment of faecal incontinence: CONtrol of Faecal Incontinence using Distal NeuromodulaTion (the CONFIDeNT trial). Health Technol Assess. 2015;19(77):1–164.
36. Chan DS, Delicata RJ. Meta-analysis of antegrade continence enema in adults with faecal incontinence and constipation. Br J Surg. 2016;103(4):322–7.
37. Patel AS, et al. Use of antegrade continence enema for the treatment of fecal incontinence and functional constipation in adults: a systematic review. Dis Colon Rectum. 2015;58(10):999–1013.

Sexual Function After Colorectal Surgery in Women

63

Deborah S. Keller and Jenny Alex Ky-Miyasaka

Key Concepts

- When considering pelvic cancer in women, the focus has traditionally been on curing the cancer. As therapy has improved and there are more long-term survivors, sexual function and its impact on quality of life has become a key concern of these women.
- Pelvic surgical dissection in women for benign conditions like inflammatory bowel disease can also severely affect postoperative sexual function and affect quality of life.
- Measuring female sexual function can be challenging. The Pelvic Floor Disorders Consortium (PFDC) Working Group (which includes many members from the American Society of Colorectal Surgeons) is a cross-disciplinary collaboration that has evaluated these questionnaires and published recommendations on their use.
- Depending on individual patient's needs, a multidisciplinary approach to improving quality of life for this group of patients is recommended. The team may include the colorectal surgeon; psychologist, psychiatrist, or appropriate counselor; sex therapist; pelvic floor physical therapist; oncologist; radiation oncologist; geriatrician; nutritionist; and exercise physiotherapist.

Background

In the United States, colorectal cancer (CRC) is the third most common and second most deadly cancer in women [1]. However, advances in colorectal cancer awareness and screening, adjuvant therapy, and surgical technique have resulted in improved survival from colorectal cancer [2]. Traditional outcome measures after surgery for colorectal cancer were survival and local recurrence. However, with the increasing rates of survivorship, a new focus must be placed on functional outcomes and quality of life after surgery for survivors. Sexuality is not considered a medical concern compared with the priority of treating colorectal cancer or cancer-related symptoms. However, sexual function has proved to be one of the most common and important quality of life concerns in long-term survivors [3, 4]. In a survey on the importance of discussing sexual issues, over 80% the woman stated it to be important [4].

Accordingly, sexual dysfunction is one of the most common long-term effects after colorectal cancer treatment [3, 5]. Yet studies show the issue is rarely and inadequately discussed among patients and providers and, thus, often untreated [3, 5]. Sexual dysfunction can occur after any colorectal surgery. Study has shown no differences between female patients who had abdominal procedures and those who underwent pelvic dissection in regard to sexual function, self-esteem, body image, and health-related quality of life [4]. Issues can arise after surgery for benign disease as well as cancer, so providers should anticipate and be prepared to address issues. When sexual issues are not addressed, it can have a significant negative impact on the quality of life of patients [6].

There is a need to understand the etiology and scope of the problem and develop standards for how we discuss, measure, and treat sexual dysfunction after surgery and treatment for colorectal cancer. To truly be effective, providers need to have excellent communication skills, an open and nonjudgmental approach, and knowledge of the potential ramifications of disease and treatment of sexuality problems [6]. The stigma needs to be removed from discussing this very private issue to remove the negative influences on the social well-being of colorectal surgery patients. While studies on sexual function after colorectal cancer treatment have been performed, most to date focused on males with a limited number of female patients, are limited by retrospective design, or

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have failed to use validated instruments to measure outcomes [7]. As we work toward developing standards, there is also an increasing awareness of the importance of patient-reported outcomes (PROs), the patient's assessment of their own physical, social, psychological, and sexual functioning, for the most valid information on the effects of cancer treatment.

The Scope of the Problem

Sexual Dysfunction After Surgery for Colorectal Cancer

Colorectal cancer survivors often report that their overall quality of life is good. But when asked properly, women report significant problems with sexual functioning and relationships with their partners following treatment [8–10]. In fact, female sex itself is independently associated with lower sexual function and enjoyment after colorectal cancer [11]. Given the anatomical proximity of the genital area to the treatment site, female sexual functioning is often negatively affected [3]. This posttreatment sexual dysfunction is significant, with studies reporting the prevalence rates between 19% and 62% [12]. Furthermore, symptoms of sexual dysfunction can be exacerbated by anxiety, depression, and fatigue which are common after colorectal surgery and in colorectal cancer survivors [13, 14].

The 2019 prospective QoLiRECT study (Quality of Life in RECTal cancer) measured health-related quality of life in Scandinavian rectal cancer patients at diagnosis and 1 year, showing lower rates of pretreatment sexual activity in women than men (29% and 41%, respectively); these rates were further reduced at the 1-year point (25% and 34%) [15]. The extent of the resection and presence of a stoma can also impact sexual function [13, 16–18]. For example, women who had abdominoperineal resection compared to anterior resection for rectal cancer were less sexually active, had sexual intercourse less frequently, and were less likely to achieve arousal or orgasm [17]. While anterior resection patients had better quality of life scores than abdominoperineal resection patients, high-anterior resection patients had significantly better quality of life (QOL) scores and function than low-anterior resection patients [19]. While stoma patients are reported to have significantly worse QOL and greater sexual dysfunction than non-stoma patients, QOL improved greatly for patients whose stoma was reversed [18, 19].

Sexual Dysfunction After Surgery for Benign Colorectal Disease

The issue of sexual dysfunction is not isolated to malignant disease. Surgical treatment for pelvic floor disorders may be "curative" by repairing incontinence but may also have undesired effects on sensation, blood flow, and anatomy that can affect sexual arousal and orgasm or cause dyspareunia [20]. There is particular interest in sexual dysfunction after restorative proctocolectomy with an ileal pouch anal anastomosis (IPAA) or pelvic pouch surgery for inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), and polyposis syndromes. IBD has an increasing worldwide prevalence [21], and sexual function is often impaired in female patients, with reported rates of sexual dysfunction of 40–60% [22]. Females with UC who are managed nonoperatively have normal fertility, which suggests that ulcerative colitis and medical therapy do not decrease female reproductive ability, but pelvic pouch surgery has a significant impact on sexual function [23]. Surgery for IBD is aimed to improve QOL, but sexual dysfunction is a frequent complication after the proctectomy, as pelvic dissection may result in injury to the autonomic nerves [24].

Etiology of Sexual Dysfunction

The etiology of sexual dysfunction after colorectal surgery is a multifaceted issue, with both physical and psychological causes, and different causes may concurrently have a role. Recent literature reviews reported that 30 to 40% of female patients who were sexually active prior to treatment became sexually inactive posttreatment. More than half of women experience changes in body image after colorectal cancer treatment, and rates of sexual dysfunction can be even higher from the physiological changes that can result from radiation, chemotherapy, and surgery [14]. Women specifically experienced reduced lubrication, more dyspareunia, reduced vaginal size, and less sexual enjoyment after surgery compared with the time of diagnosis, making intercourse less appealing [11, 15, 25]. Surgery, chemotherapy, radiotherapy, and medication commonly given for symptomatic treatment, as well as the psychological sequelae of the diagnosis and disease itself, can affect sexual function [6]. Table 63.1 shows the common sexual dysfunction caused by radiation, chemotherapy, and surgery.

It is important to acknowledge there are substantial differences in the risks related to treatment for colon compared to rectal or pelvic disease, especially for cancers. Colonic surgery generally does not involve other major organs and is usually a one-stage procedure with an anastomosis after excision of the pathology, while pelvic or rectal surgery involves other organs, such as the vagina and bladder, as well as the pelvic nerves that are very close to the pathology; these structures may therefore be affected by the surgery in a restricted space [26]. Furthermore, rectal cancer treatment may involve a two-stage procedure with the creation and subsequent closure of a stoma. Preoperative chemoradiother-

apy is also an important part of the multimodality treatment of locally advanced rectal cancer, reducing local recurrence [27, 28], and has their own impact on sexual function.

Radiation

Radiation is a key component in the treatment algorithm of locally advanced rectal cancer, reducing the frequency of local recurrence after total mesorectal excision (TME) compared to surgery alone [27, 29]. Radiotherapy plays a role in female sexual dysfunction by damaging the pelvic autonomic nerves, microvasculature, and soft tissue, creating acute edema and inflammation [30–32]. The rapid cell turnover of the vagina and vulva make them very sensitive to radiation effects. Acute effects include erythema, desquamation, and mucositis. The mucosa may demonstrate severe congestion and hyperemia [33]. These effects usually resolve within 3 months after radiotherapy, but in some patients, the radiation effects are progressive and may become symptomatic even after a latent period [32]. There is progressive vascular compromise and tissue hypoxia that may result in epithelial sloughing, ulcer formation, and continuous progression from ulceration and necrosis to eventual fibrosis [32, 33]. With this are the physical symptoms of vaginal wall thinning, atrophy, adhesions, and fibrosis, which can lead to decreased vaginal elasticity, narrowing, shortening, and ultimately vaginal stenosis [34–36]. Radiation-induced endarteritis obliterans can create ischemia, leading in a hemorrhagic, fragile, friable vagina and vaginal entrance, with similar effects possible in the bladder and rectum [33, 35, 37, 38]. As a result, radiation injury can induce ovarian failure in premenopausal women and create the inability for arousal, dyspareunia, inability to achieve orgasm, and even permanent menopause [34, 39]. The degree of vaginal changes and ovarian failure depends on the primary diagnosis, treatment field, and total dose delivered to the vagina and pelvis [40]. Modern radiotherapy modalities are evolving with the aim to decrease the late effects after rectal cancer treatment, as the limiting factor for the total dose delivery of radiation is normal tissue tolerance [33].

There is little controlled data examining the effect of radiotherapy on sexual dysfunction centered on women, and most published work suffers from retrospective design, small sample size, or lack of validated scoring instruments. However, all demonstrate a severe negative effect on sexual functioning in women following radiotherapy, especially for rectal cancer. The landmark Dutch TME trial reported that preoperative short-term radiotherapy (5Gy × 5) had a negative impact on sexual activity and sexual function [16, 41]. Marijnen et al.

Table 63.1 Female sexual dysfunction from radiotherapy, chemotherapy, and colorectal surgery

Physiologic changes	Radiation therapy	Chemotherapy	Surgery
Vaginal vault changes	Shortening of the vagina; decreased lubrication; dyspareunia; risk of vaginal stenosis	Decreased lubrication; dyspareunia; increased risk of vaginal infection from tears; mucositis of the vaginal cavity	Postoperative adhesions from pelvic surgery can cause dyspareunia
Sexual pattern	Decreased lubrication with the need to use artificial lubricant to avoid tears and infection; diarrhea can create apprehension, fear of fecal incontinence	Nausea/vomiting can decrease desire; decreased lubrication with the need to use artificial lubricant to avoid tears and infection	If stoma present, can reduce the spontaneity of sexual activity and cause discomfort and embarrassment during intercourse; loss of rectal sexual pleasuring if proctectomy performed
Skin changes	Texture/color changes can affect body image; tattoos can remind patient of diagnosis	Skin sensitivity can cause an extreme reaction to cold; neuropathy and hand/foot syndrome can affect ability and enjoyment of touch	Surgical scars can affect body image and confidence
Vascular, sensory, and continence	Vascular scarring—decreased genital blood flow, decreased vaginal lubrication	Change in senses—increased sensitivity to smell; peripheral neuropathy impacting touch	Urinary/fecal incontinence risk
Nerve damage	Decreased skin sensitivity and vaginal lubrication	Decreased skin sensitivity and vaginal lubrication	Decreased skin sensitivity and vaginal lubrication
Hair pattern	Alopecia—affects body image; daily reminder of treatment/diagnosis	Alopecia—affects body image; daily reminder of treatment/diagnosis	NA
Delayed complications	Risk of fecal or urinary incontinence due to fibrosis	Peripheral neuropathy may be permanent, can affect sensations/enjoyment	Pelvic pain during intercourse from adhesions; nerve damage can affect sensation
Fertility impact	Premature ovarian failure	Type/dose affect risk	Adhesions can increaserisk of female infertility posttreatment
Fatigue	Affects social interaction, libido	Affects social interaction, libido	Affects social interaction, libido

followed female rectal cancer patients randomly assigned to neoadjuvant radiotherapy and then total mesorectal excision (TME) or surgery only for 24 months after treatment, finding radiation had a significant negative impact on sexual interest, pleasure, and satisfaction, and radiated patients were significantly less sexually active after treatment compared to before treatment [41]. Lange et al. aimed to identify risk factors for sexual dysfunction following this cohort of female rectal cancer patients randomly assigned to neoadjuvant radiotherapy and then total mesorectal excision (TME) or surgery alone preoperatively and at 3, 6, 12, 18, and 24 months postoperatively [16]. The authors found sexual activity levels continued to decline from over 50% before surgery to 18.4% at 2 years posttreatment [16]. Nearly two-thirds of the sexually active women reported newly developed sexual dysfunction after treatment, with neoadjuvant radiotherapy as the only significant risk factor for dysfunction [16]. In investigating the long-term quality of life 14 years after treatment in these cohorts from the Dutch TME trial, irradiated females reported significant sexual dysfunction from more vaginal dryness and dyspareunia compared with the general population [42]. A cross-sectional study by Bregendahl et al. of sexual dysfunction in all women who underwent abdominoperineal resection or low-anterior resection for rectal cancer in Denmark between 2001 and 2007 found a significant association between neoadjuvant radiotherapy and reduced vaginal dimensions, dyspareunia, lack of desire, and sexual inactivity [43]. The authors also found bowel dysfunction in patients that received preoperative radiotherapy, which was associated with lack of sexual desire, sexual inactivity, and sexual dissatisfaction [43]. In a US-based study, Tekkis et al. reported female rectal cancer patients treated with radiotherapy had a fourfold increase in dyspareunia compared to surgery-only patients [17]. Bruheim et al. used the validated Sexual function and Vaginal Changes Questionnaire (SVQ) to assess the impact of radiotherapy on sexual function in 172 female patients from the Norwegian Rectal Cancer Registry [25]. Patients were assessed at a median of 4.5 years posttreatment, finding women treated with radiotherapy reported more vaginal problems in terms of vaginal dryness, dyspareunia, and reduced vaginal dimension, but sexual interest and worries about their sex life were not significantly impaired compared to women treated without radiotherapy [25]. Thyo et al. performed a long-term follow-up study with the validated Sexual function and Vaginal Changes Questionnaire on female colorectal cancer patients between 2001 and 2014 who were sexually active at the time of diagnosis ($n = 2402$), as a basis for comparison [44]. They found in rectal cancer patients, radiotherapy exposure increased the odds for overall sexual dysfunction [OR 1.80 (95% CI 1.02–3.16)] and was associated with dyspareunia [OR 1.72 (95% CI 0.95–3.12)] [44]. Rodrigues et al. compared physical and psychological morbidity, sexual functioning, and relationship satisfaction among women with uterine, rectal, or anal cancers treated with pelvic radiotherapy and comparable controls, finding pelvic irradiation patients reported significantly higher rates of fatigue, weakness, diarrhea, vaginal discharge, and stress, with lower scores of satisfaction with sexual function (all $p < 0.005$). Adams et al. highlighted the late and persistent effect of pelvic radiotherapy in a survey of patients receiving radiation as a primary or adjuvant treatment ($n = 418$, 57.1% response rate) [45]. Twenty-four percent of women stated that the radiation treatment adversely affected their ability to have a sexual relationship. The treatment-related symptoms were as frequent in people 6–11 years after radiotherapy as those within 1–5 years after treatment, showing the late effects are common and continue to reduce quality of life [45].

Chemotherapy

The effects of chemotherapy on sexual dysfunction are less described, as chemotherapy is often grouped with radiation when administered for rectal cancer (neoadjuvant chemoradiation). However, chemotherapy alone is associated with a loss of desire and decreased frequency of intercourse for women. The common side effects of chemotherapy such as nausea, vomiting, diarrhea, or gain and loss of hair can create poor self-esteem, affect an individual's sexual self-image, and decrease sexual interest [46]. For women, chemotherapy may cause a loss of estrogen production from the ovaries, leading to decreased dimension, thinning, dryness, and loss of elasticity of the vagina, as well as dyspareunia and orgasmic dysfunction. A population-based study from the Netherlands assessed the impact of chemotherapy on colon cancer survivors up to 10 years post-diagnosis using the validated SF-36 and the EORTC colorectal module (EORTC-QLQ-CR38) [47]. Though not specific for females, among the sexually active respondents, survivors reported sex to be significantly less enjoyable than the normative population [47].

Surgery

For surgical treatment, knowledge of the anatomy and areas prone to nerve damage that can impact sexual function after surgery is critical. Colonic surgery generally does not impinge on other major organs and is usually a one-stage procedure with end-to-end anastomosis of the bowel after excision of the tumor. However, in pelvic surgery, other organs as well as the pelvic nerves are very close to the pathology and therefore may be affected by both the surgical and radiotherapy treatments.

An extensive autonomic nervous system of sympathetic and parasympathetic fibers supplies the rectum and genitourinary tract, affecting sexual function (Fig. 63.1). The sympathetic autonomic plexus arises from the T12–L2 lumbar sympathetic nerves, passing anterior to the aorta to form

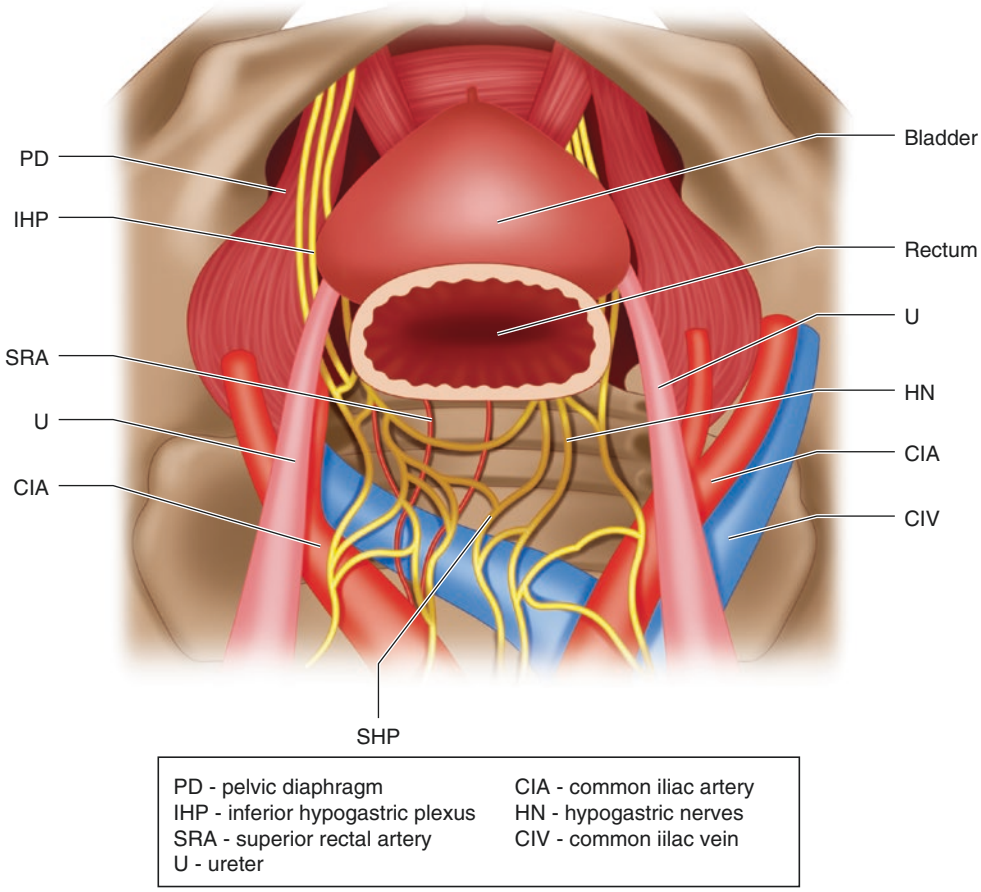

Fig. 63.1 Common sites of nerve injury in colorectal surgery

the superior hypogastric plexus by the origin of the inferior mesenteric artery. It branches into the superior hypogastric plexus as the nerves enter the pelvis, dividing into the left and right hypogastric nerves at the sacral promontory. Damage to the superior hypogastric plexus and hypogastric nerves causes urinary urgency and incontinence in females [30]. The hypogastric nerves course posterolateral to the mesorectum and join parasympathetic nerves running medially along the mesorectal fascia to form the inferior hypogastric plexus. These nerves are responsible for detrusor contractility, vaginal lubrication, and genital swelling during sexual arousal. Damage to these nerves causes decreased blood flow to the vagina and vulva, which can reduce vaginal lubrication [48]. The inferior hypogastric plexus is a network with the paired sympathetic hypogastric nerves and parasympathetic pelvic splanchnic nerves on the pelvic sidewall, with the neurovascular bundle extending anterolaterally to the rectum, passing laterally to the distal ureters, cervix, vaginal fornix, base of the urinary bladder, and lower lateral wall of the vagina [49]. As the inferior hypogastric plexus contains both sympathetic and parasympathetic efferent fibers, damage to this plexus can cause issues in urogenital and sexual function; erection and ejaculation are known issues in men, while the specific disturbance in women is not clearly defined.

Major improvements in recurrence, survival, and quality of life have resulted from the standardization and widespread implementation of total mesorectal excision (TME) for rectal cancer surgery. A TME is a highly precise and sharp dissection along the avascular, areolar tissue plane between the mesorectal fascia and the parietal pelvic fascia under direct vision (Fig. 63.2) [50]. By definition, a TME involves a nerve-preserving dissection which helps to avoid urinary and sexual dysfunction [51]. With a TME, the problem of accidental bladder denervation was reduced from 50% to 60% to less than 20% [52]; the impact on sexual function in women is less described. The surgical approach to the TME may also help reduce nerve injury and subsequent sexual dysfunction. There is no clear evidence of any differences in quality of life regarding bladder and sexual function between laparoscopic and open TME [53]. The robotic approach has been reported to have lower impairment of urinary and sexual function, but the majority of studies have centered on males, and further research is required [54, 55].

Sexual Dysfunction After Surgery for Benign Colorectal Disease

The issue of sexual dysfunction is not isolated to malignant disease. Surgical treatment for pelvic floor disorders may be

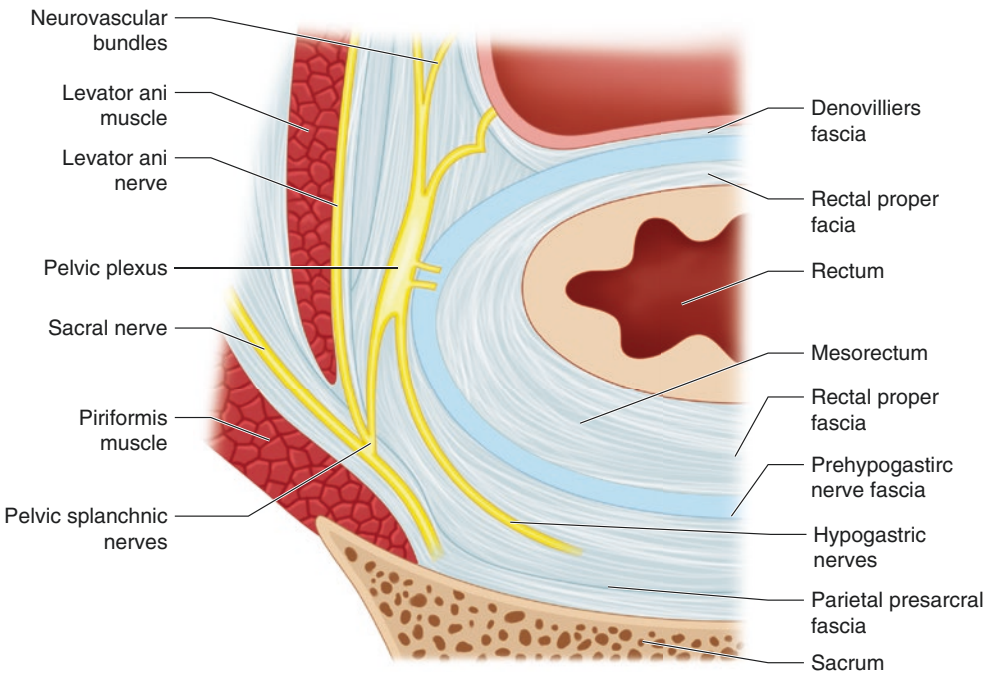

Fig. 63.2 The planes for total mesorectal excision and pelvic surgery

"curative" by repairing incontinence but may also have undesired effects on sensation, blood flow, and anatomy that can affect sexual arousal and orgasm or cause dyspareunia [20]. There is particular interest in sexual dysfunction after restorative proctocolectomy or pelvic pouch surgery for inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD). IBD has an increasing worldwide prevalence [21], and sexual function is often impaired in female patients, with reported rates of sexual dysfunction of 40–60% [22]. Females with UC who are managed nonoperatively have normal fertility, which suggests that ulcerative colitis and medical therapy do not decrease female reproductive ability, but pelvic pouch surgery has a significant impact on sexual function [23]. Pouch surgery is aimed to improve QOL, but SD is a frequent complication after the proctectomy, as pelvic dissection may result in injury to the autonomic nerves [24]. There are reported reduced fecundity, dyspareunia, and controversy on need for cesarean section post-IPAA to prevent anal sphincter injury [56].

The Impact of Sexual Dysfunction on Fertility

In addition to sexual dysfunction, there is reported reduced fecundity among women who undergo colorectal surgery. Surgical resection for colon cancer likely has no effect on female fertility, but resection below the peritoneal reflection for rectal cancer may adversely affect fertility by damaging the autonomic nerves; this is similar to the risk of decreased fertility after pelvic surgery for conditions such as inflammatory bowel disease (IBD) and polyposis syndromes [57]. In IBD and polyposis syndromes, such as Lynch, a colectomy with ileal pouch anal anastomosis (IPAA) has reductions in fertility rates reported between 44% and 82% [23, 58]. Research has found that the laparoscopic approach results in improved fertility rates when compared to open surgery, likely due to reduced scarring of the fallopian tubes [59, 60]. IBD surgery also appears to have a negative impact on pregnancy-related outcomes, including risks of miscarriage, need for assisted reproductive technology, delivery via caesarean section, and occurrences of stillbirth and preterm births, but there are conflicting results and poor-quality evidence [61]. Specifically, there is controversy on the need for cesarean section post-IPAA to prevent anal sphincter injury [56].

Chemotherapy with 5-fluorouracil is reported to have little influence on fertility, but the impact of agents such as oxaliplatin and irinotecan on gonadal failure is unclear [62]. Guidelines recommend that oncologists discuss the possibility of infertility with their patients, while acknowledging there are insufficient data available to accurately assess this risk in colorectal cancer [63]. The use of radiation in either the adjuvant or neoadjuvant setting may cause premature ovarian failure using current dosing schedules [64]. Methods for fertility preservation include ovarian transposition and embryo cryopreservation, while ovarian tissue cryopreservation and ovarian suppression and the use of apoptotic inhibitors remain investigational with promising results [57, 65]. In general, the effect of pregnancy and female hormones on the incidence, progression, and recurrence of CRC remains unclear, and further research is needed [65].

Defining the Problem for Effective Treatment

The normal female sexual response has four phases, desire, excitement, orgasm, and resolution, whereas sexual dysfunction involves desire, arousal, orgasmic, and sexual pain disorders [66]. The most common sexual issues reported by women include loss of desire for sexual activity, loss of sensation and numbness, a change in genital sensation from pain, and delayed ability to orgasm, often due to medications and/or anxiety. Patients may report emotional or motivational changes, physical concerns including vaginal dryness, inability to climax, and dyspareunia often due to radiation and pelvic surgery, which relate to the desire, excitement, orgasmic, and pain categories, respectively. Sexual pain specifically is reported by as many as one in five women who have pelvic radiotherapy [67]; these patients report continued desire for intercourse, emphasizing the need for better awareness and treatment options. Unlike other side effects after surgery or colorectal cancer treatment, sexual dysfunction may not resolve within the first year or two after treatment and can interfere with the patient's return to a normal function and quality of life. When discussing issues, it is important for the provider to ask appropriate questions to identify the specific issue or issues and best guide treatment with the multidisciplinary team. Treatment interventions by issue or phase of dysfunction are listed in Table 63.2.

Desire

Where low desire is present, it can adversely affect sexual arousal, with the lack of vaginal lubrication and subsequent relationship difficulties [40, 68]. If there is clear treatment-induced menopause or hypogonadism, use of hormone replacement therapy with estrogen and/or testosterone can be effective, assuming there are no oncological contraindications to use [40]. Where the desire loss is due to emotional adjustment difficulties or the side effects of their medical management, a psychological or psychosexual management approach may be most effective. Use of psychological or psychosexual counseling, cognitive behavioral therapy, or mindfulness training alone or in combination with pharmacological or sexual device interventions can help improve sexual functioning from lack of desire for individuals or couples [40, 69, 70].

Arousal and Orgasm

Many women have limited awareness of the objective vaginal changes that accompany sexual arousal. The majority of studies are focused on men, with erectile dysfunction as the primary metric used to gauge improvement. Thus, in females, treatments for arousal and orgasmic difficulties are often grouped with desire, and hinge on hormone replacement for desire, with psychological, psychosexual, and cognitive behavioral therapy recommended for both [40].

Sexual Pain

Despite the prevalence, proactive management of vaginal changes to reduce subsequent sexual pain after pelvic radiotherapy and treatment-induced menopause are not part of routine care after colorectal surgery [71]. This has been explicitly demonstrated in women having neoadjuvant chemoradiotherapy for rectal cancer, where starting post-radiotherapy vaginal dilation is disrupted by surgery, with frequent failure to coordinate the management of multimodal late effects after surgery [72]. In superficial dyspareunia from treatment-induced menopause, the most effective management is hormone replacement therapy and, where feasible, vaginal estrogens [73]. In women already in menopause or when estrogen therapy is contraindicated, nonhormonal vaginal moisturizers can be used to restore vaginal pH and improve moisture content of the vaginal and vulval mucosa [71]. Adding an intimate lubricant to decrease friction during sexual intercourse or vulvar contact can additionally reduce pain. Graduated vaginal dilation and penetration within a framework of sensate focus can help break the cycle of dyspareunia, distress, anticipation of dyspareunia, and sexual avoidance [40, 74]. For women with deep dyspareunia, vaginal adhesions, fibrosis, stenosis, or shortening, vaginal dilation is recommended, though the evidence base and patient compliance are poor [75, 76]. There is an increasing awareness of chronic pelvic floor myofascial pain occurring as sequelae of colorectal surgery or adjuvant treatment [76]; this can be exacerbated during intercourse.

Table 63.2 Female sexual difficulties by phase of dysfunction

Desire	Arousal	Orgasm	Sexual Pain
Hormone replacement therapy ± testosterone supplementation—psychosexual therapy Psychological therapy (mindfulness, cognitive behavioral therapy) Psychosexual therapy Couple therapy	Topical estrogen Psychosexual therapy (sensate focus) Psychological therapy (mindfulness) Guided fantasy/ masturbation	Psychosexual therapy (sensate focus) Psychological therapy (mindfulness) Couple therapy Vibrator therapy Guided fantasy/ masturbation	Vaginal moisturizers Vaginal lubricants Vaginal dilation Topical estrogen

A standardized physical exam and treatment from an interdisciplinary team, including myofascial trigger point release, biofeedback, and electrical stimulation, can aid in diagnosing and successfully treating myofascial pelvic pain [77].

Measuring Sexual Dysfunction

Most studies of sexual dysfunction treatment use validated questionnaire scores as an outcome measure. Validated instruments that reliably measure patient-reported functional status help ensure clear communication between providers, patients, and researchers [78]. This is especially true in treating pelvic floor disorders, which relies heavily on patient-reported symptoms to measure outcomes. In 2020, the Pelvic Floor Disorders Consortium (PFDC) Working Group on Patient Reported Outcomes, a cross-disciplinary collaboration, published recommendations for all practitioners in treatment of female sexual dysfunction [78]. An intensive review of several key instruments with evidence of validity and reliability was performed by the Sexual Function in Women workgroup [79–90]. The consensus selected two instruments for best practice—the Female Sexual Function Index Short Version (FSFI-9), a 9-item questionnaire for women to assess sexual desire, arousal, lubrication, orgasm, satisfaction, and pain domains, and the Pelvic Organ Prolapse/Incontinence Sexual Questionnaire International Urogynecological Association (IUGA)-Revised (PISQ-IR), a 20-item condition-specific validated questionnaire (12 questions in 4 domains if not sexually active) that specifically targets women with pelvic floor disorders (https://static-content.springer.com/esm/art%3A10.1007%2Fs00192-012-2020-8/MediaObjects/192_2012_2020_MOESM1_ESM.pdf) (Table 63.3) [79, 80]. The FSFI-9 has been tested in peri- and postmenopausal women and is best applied where sexual function is a secondary end point and brevity is a priority [78, 79]. The PDFC recommends the PISQ-IR for providers treating women with known pelvic floor disorders and the FSFI-9 for providers seeking to measure and monitor female sexual function outside of patients with pelvic floor disorders [78].

Table 63.3 Items in the Female Sexual Function Index (FSFI) 9 item questionnaire

Number	Item (domain)
1	Level of sexual desire or interest (desire)
2	Level of sexual arousal (arousal)
3	How often maintain lubrication (lubrication)
4	Difficulty becoming lubricated (lubrication)
5	How often reach orgasm
6	Difficulty reaching orgasm (orgasm)
7	Satisfaction with amount of emotional closeness with partner (satisfaction)
8	Level of discomfort/pain during or following vaginal penetration (pain)
9	Satisfaction with overall sex life (satisfaction)

Moving Forward

Given the prevalence and impact of colorectal surgery on sexual function in women, further work is needed to address sexual dysfunction and help incorporate screening for symptoms as standard procedure. Despite clear benefits for patients, providers, and researchers, widespread implementation of patient-reported outcomes and patient-reported outcome measures (PROMs) for recording sexual dysfunction have not yet been achieved [91]. Interviews with colorectal surgery patients and literature reviews were conducted to help define needs for the initial research initiatives and next steps to address sexual dysfunction in women. From this work, the following foundation steps were selected.

Initiating the Conversation

In a survey of cancer patients using the Patient-Reported Outcomes Measurement Information System (PROMIS(®)) Sexual Function measure, nearly 80% reported it was important to discuss how surgery and cancer may impact sexual functioning. However, only 29% asked about sexual dysfunction, and less than half received any information about sexual dysfunction from their provider [92]. The principal reason for the persistent low profile of sexual dysfunction discussions remains the reluctance among patients and health professionals to talk about treatment-induced sexual difficulties [40, 92, 93]. Patients report reluctance to ask questions about sexual dysfunction during appointments. They mention feeling embarrassed or ashamed, as well as unsure on how exactly to broach the subject or describe sexual issues for the first time. Patients also reported that the provider seemed busy and they did not think the subject of sexual dysfunction was important [in comparison to the discussion on surgical or cancer outcomes]. A lack of clinical time to sexual dysfunction has previously been identified as an obstacle by providers, with the argument that follow-up clinics are not a suitable environment for the detailed discussion of treatment-induced sexual dysfunction due to time constraints, the need to prioritize surveillance in cancer cases, lack of privacy, and the absence of clear management and referral pathways [40, 93]. Providers may also be reluctant to discuss sexual dysfunction due to lack of knowledge regarding how to start the conversation, treatment for sexual problems, or concerns about the appropriateness of discussing sexual function. Tools must be used to overcome the reluctance and initiate the conversation on sexual dysfunction, as patients consistently state they feel more comfortable

if providers bring up the topic [92]. Using a combination of physical examination, clinical interview, and validated questionnaires may help to engage patients and initiate the difficult conversation [94].

Developing Options for Diverse Patients

Cultural factors such as age, ethnicity, sexual orientation, and relational status can significantly influence sexuality but are often not taken into consideration in research and clinical practice [95]. Assumptions can also be incorrectly made that sexual dysfunction is "irrelevant" for certain patients due to these cultural factors [5, 13]. Regardless of age, sexual orientation, or partner status, sexual function is an important aspect of QOL. In patient interviews, it was stated that providers assume elderly patients as having less need for sexual function. Assuring that providers appreciate that elderly patients still had the desire for sexual function was stressed. Using a native speaker/translator to facilitate answering questions and involving the sexual partner in the discussions only after asking patient permission was suggested to help overcome cultural barriers. Sensitivity and understanding of the unique challenges to sexual function in women who fall under the lesbian, gay, bisexual, transgender, and questioning (LGBTQ) category or transitioning women should also be considered.

Creating Multidisciplinary Treatment Teams

Providers report that lack of knowledge about treatment options and treating sexual dysfunction within their scope of practice may limit the ability to fully discuss and treat sexual dysfunction with patients [5]. Recognizing the depth and contributions from different members of a diverse multidisciplinary treatment team is key for sexual dysfunction patients. Depending on the individual patient's needs team members can include the colorectal surgeon; psychologist, psychiatristor appropriate counselor; sex therapist; pelvic floor physical therapist; oncologist; radiation oncologist; geriatrician; nutritionist; and exercise physiotherapist.

Conclusions

Sexual dysfunction is common in women after colorectal surgery and has a substantial impact on quality of life. The effects can be long-lasting, especially when chemoradiotherapy is part of the treatment plan. Changes in sexual function can occur after diagnosis and throughout the continuum of care. However, the issue is rarely and inadequately discussed and, thus, often untreated. By understanding the common causes, symptoms, and tools to grade the effects of sexual dysfunction in women, larger-scale controlled trials can be carried out to help providers better understand the needs and best practices for treatment of female sexual dysfunction.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7–34. [30620402]. https://doi.org/10.3322/caac.21551.
2. Siegel RL, Ward EM, Jemal A. Trends in colorectal cancer incidence rates in the United States by tumor location and stage, 1992–2008. Cancer Epidemiol Biomarkers Prev. 2012;21:411–6. [22219318]. https://doi.org/10.1158/1055-9965.EPI-11-1020.
3. Hendren SK, O'Connor BI, Liu M, Asano T, Cohen Z, Swallow CJ, Macrae HM, Gryfe R, McLeod RS. Prevalence of male and female sexual dysfunction is high following surgery for rectal cancer. Ann Surg. 2005;42:212–23. [16041212]. https://doi.org/10.1097/01.sla.0000171299.43954.ce.
4. da Silva GM, Hull T, Roberts PL, Ruiz DE, Wexner SD, Weiss EG, Nogueras JJ, Daniel N, Bast J, Hammel J, Sands D. The effect of colorectal surgery in female sexual function, body image, self-esteem and general health: a prospective study. Ann Surg. 2008;248:266–72. [18650637]. https://doi.org/10.1097/SLA.0b013e3181820cf4.
5. Traa MJ, De Vries J, Roukema JA, Rutten HJ, Den Oudsten BL. The sexual health care needs after colorectal cancer: the view of patients, partners, and health care professionals. Support Care Cancer. 2014;22:763–72. [24240645]. https://doi.org/10.1007/s00520-013-2032-z.
6. Mercadante S, Vitrano V, Catania V. Sexual issues in early and late stage cancer: a review. Support Care Cancer. 2010;18:659–65. [20237806]. https://doi.org/10.1007/s00520-010-0814-0.
7. Stephens RJ, Thompson LC, Quirke P, Steele R, Grieve R, Couture J, Griffiths GO, Sebag-Montefiore D. Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: data from the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 randomized clinical trial. J Clin Oncol. 2010;28:4233–9. [20585099]. https://doi.org/10.1200/JCO.2009.26.5264.
8. Kasparek MS, Hassan I, Cima RR, Larson DR, Gullerud RE, Wolff BG. Long-term quality of life and sexual and urinary function after abdominoperineal resection for distal rectal cancer. Dis Colon Rectum. 2012;55:147–54. [22228157]. https://doi.org/10.1097/DCR.0b013e31823d2606.
9. Temple LK. Erectile dysfunction after treatment for colorectal cancer. BMJ. 2011;343:d6366. [22010129]. https://doi.org/10.1136/bmj.d6366.
10. Traa MJ, De Vries J, Roukema JA, Den Oudsten BL. Sexual (dys) function and the quality of sexual life in patients with colorectal cancer: a systematic review. Ann Oncol. 2012;23:19–27. [21508174]. https://doi.org/10.1093/annonc/mdr133.
11. Den Oudsten BL, Traa MJ, Thong MS, Martijn H, De Hingh IH, Bosscha K, van de Poll-Franse LV. Higher prevalence of sexual dysfunction in colon and rectal cancer survivors compared with the normative population: a population-based study. Eur J Cancer. 2012;48:3161–70. [22608772]. https://doi.org/10.1016/j.ejca.2012.04.004.
12. Ho VP, Lee Y, Stein SL, Temple LK. Sexual function after treatment for rectal cancer: a review. Dis Colon Rectum. 2011;54:113–25. [21160322]. https://doi.org/10.1007/DCR.0b013e3181fb7b82.
13. Averyt JC, Nishimoto PW. Addressing sexual dysfunction in colorectal cancer survivorship care. J Gastrointest Oncol. 2014;5:388–94. [25276411]. https://doi.org/10.3978/j.issn.2078-6891.2014.059.

14. Zebrack BJ, Foley S, Wittmann D, Leonard M. Sexual functioning in young adult survivors of childhood cancer. Psychooncology. 2010;19:814–22. [19862693]. https://doi.org/10.1002/pon.1641.
15. Sörensson M, Asplund D, Matthiessen P, Rosenberg J, Hallgren T, Rosander C, González E, Bock D, Angenete E. Self-reported sexual dysfunction in patients with rectal cancer. Colorectal Dis. 2019. [31713295]. https://doi.org/10.1111/codi.14907.
16. Lange MM, Marijnen CA, Maas CP, Putter H, Rutten HJ, Stiggelbout AM, Meershoek-Klein Kranenbarg E, van de Velde CJ, Cooperative CIOTD. Risk factors for sexual dysfunction after rectal cancer treatment. Eur J Cancer. 2009;45:1578–88. [19147343]. https://doi.org/10.1016/j.ejca.2008.12.014.
17. Tekkis PP, Cornish JA, Remzi FH, Tilney HS, Strong SA, Church JM, Lavery IC, Fazio VW. Measuring sexual and urinary outcomes in women after rectal cancer excision. Dis Colon Rectum. 2009;52:46–54. [19273955]. https://doi.org/10.1007/DCR.0b013e318197551e.
18. Sun V, Grant M, Wendel CS, McMullen CK, Bulkley JE, Herrinton LJ, Hornbrook MC, Krouse RS. Sexual function and health-related quality of life in long-term rectal cancer survivors. J Sex Med. 2016;13:1071–9. [27318020]. https://doi.org/10.1016/j.jsxm.2016.05.005.
19. Engel J, Kerr J, Schlesinger-Raab A, Eckel R, Sauer H, Holzel D. Quality of life in rectal cancer patients: a four-year prospective study. Ann Surg. 2003;238:203–13. [12894013]. https://doi.org/10.1097/01.sla.0000080823.38569.b0.
20. Pauls RN, Berman JR. Impact of pelvic floor disorders and prolapse on female sexual function and response. Urol Clin North Am. 2002;29:677–83. [12476530]. https://doi.org/10.1016/s0094-0143(02)00056-3.
21. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, Panaccione R, Ghosh S, Wu JCY, Chan FKL, Sung JJY, Kaplan GG. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2018;390:2769–78. [29050646]. https://doi.org/10.1016/S0140-6736(17)32448-0.
22. Sanders JN, Gawron LM, Friedman S. Sexual satisfaction and inflammatory bowel diseases: an interdisciplinary clinical challenge. Am J Obstet Gynecol. 2016;215:58–62. [26849974]. https://doi.org/10.1016/j.ajog.2016.01.188.
23. Johnson P, Richard C, Ravid A, Spencer L, Pinto E, Hanna M, Cohen Z, McLeod R. Female infertility after ileal pouch-anal anastomosis for ulcerative colitis. Dis Colon Rectum. 2004;47:1119–26. [15164254]. https://doi.org/10.1007/s10350-004-0570-7.
24. Bleier JI, Maykel JA. Outcomes following proctectomy. Surg Clin North Am. 2013;93:89–106. [23177067]. https://doi.org/10.1016/j.suc.2012.09.012.
25. Bruheim K, Tveit KM, Skovlund E, Balteskard L, Carlsen E, Fosså SD, Guren MG. Sexual function in females after radiotherapy for rectal cancer. Acta Oncol. 2010;49:826–32. [20615170]. https://doi.org/10.3109/0284186X.2010.486411.
26. Panjari M, Bell RJ, Burney S, Bell S, McMurrick PJ, Davis SR. Sexual function, incontinence, and wellbeing in women after rectal cancer–a review of the evidence. J Sex Med. 2012;9:2749–58. [22905761]. https://doi.org/10.1111/j.1743-6109.2012.02894.x.
27. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351:1731–40. [15496622]. https://doi.org/10.1056/NEJMoa040694.
28. McCarthy K, Pearson K, Fulton R, Hewitt J. Pre-operative chemoradiation for non-metastatic locally advanced rectal cancer. Cochrane Database Syst Rev. 2012;12:CD008368. [23235660]. https://doi.org/10.1002/14651858.CD008368.pub2.
29. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, Quirke P, Couture J, de Metz C, Myint AS, Bessell E, Griffiths G, Thompson LC, Parmar M. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet. 2009;373:811–20. [19269519]. https://doi.org/10.1016/S0140-6736(09)60484-0.
30. Maas CP, Moriya Y, Steup WH, Kiebert GM, Kranenbarg WM, van de Velde CJ. Radical and nerve-preserving surgery for rectal cancer in The Netherlands: a prospective study on morbidity and functional outcome. Br J Surg. 1998;85:92–7. [9462393]. https://doi.org/10.1046/j.1365-2168.1998.00530.x.
31. Havenga K, Maas CP, DeRuiter MC, Welvaart K, Trimbos JB. Avoiding long-term disturbance to bladder and sexual function in pelvic surgery, particularly with rectal cancer. Semin Surg Oncol. 2000;18:235–43. [10757889]. https://doi.org/10.1002/(sici)1098-2388(200004/05)18:3<235::aid-ssu7>3.0.co;2-7.
32. Rodrigues AC, Teixeira R, Teixeira T, Conde S, Soares P, Torgal I. Impact of pelvic radiotherapy on female sexuality. Arch Gynecol Obstet. 2012;285:505–14. [21769555]. https://doi.org/10.1007/s00404-011-1988-5.
33. Jensen PT, Froeding LP. Pelvic radiotherapy and sexual function in women. Transl Androl Urol. 2015;4:186–205. [26816824]. https://doi.org/10.3978/j.issn.2223-4683.2015.04.06.
34. Grigsby PW, Russell A, Bruner D, Eifel P, Koh WJ, Spanos W, Stetz J, Stitt JA, Sullivan J. Late injury of cancer therapy on the female reproductive tract. Int J Radiat Oncol Biol Phys. 1995;31:1281–99. [7713788]. https://doi.org/10.1016/0360-3016(94)00426-L.
35. Jensen PT, Groenvold M, Klee MC, Thranov I, Petersen MA, Machin D. Longitudinal study of sexual function and vaginal changes after radiotherapy for cervical cancer. Int J Radiat Oncol Biol Phys. 2003;56:937–49. [12829128]. https://doi.org/10.1016/s0360-3016(03)00362-6.
36. Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. N Engl J Med. 1999;340:1383–9. [10228188]. https://doi.org/10.1056/NEJM199905063401802.
37. Andreyev HJ. Gastrointestinal problems after pelvic radiotherapy: the past, the present and the future. Clin Oncol (R Coll Radiol). 2007;19:790–9. [17904338]. https://doi.org/10.1016/j.clon.2007.08.011.
38. Birgisson H, Påhlman L, Gunnarsson U, Glimelius B. Late adverse effects of radiation therapy for rectal cancer – a systematic overview. Acta Oncol. 2007;46:504–16. [17497318]. https://doi.org/10.1080/02841860701348670.
39. Donovan KA, Thompson LM, Hoffe SE. Sexual function in colorectal cancer survivors. Cancer Control. 2010;17:44–51. [20010518]. https://doi.org/10.1177/107327481001700106.
40. White ID. Sexual difficulties after pelvic radiotherapy: improving clinical management. Clin Oncol (R Coll Radiol). 2015;27:647–55. [26170122]. https://doi.org/10.1016/j.clon.2015.06.018.
41. Marijnen CA, van de Velde CJ, Putter H, van den Brink M, Maas CP, Martijn H, Rutten HJ, Wiggers T, Kranenbarg EK, Leer JW, Stiggelbout AM. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol. 2005;23:1847–58. [15774778]. https://doi.org/10.1200/JCO.2005.05.256.
42. Wiltink LM, Chen TY, Nout RA, Kranenbarg EM, Fiocco M, Laurberg S, van de Velde CJ, Marijnen CA. Health-related quality of life 14 years after preoperative short-term radiotherapy and total mesorectal excision for rectal cancer: report of a multicenter randomised trial. Eur J Cancer. 2014;50:2390–8. [25060825]. https://doi.org/10.1016/j.ejca.2014.06.020.
43. Bregendahl S, Emmertsen KJ, Lindegaard JC, Laurberg S. Urinary and sexual dysfunction in women after resection with and without preoperative radiotherapy for rectal cancer: a population-based cross-sectional study. Colorectal Dis. 2015;17:26–37. [25156386]. https://doi.org/10.1111/codi.12758.

44. Thyø A, Elfeki H, Laurberg S, Emmertsen KJ. Female sexual problems after treatment for colorectal cancer – a population-based study. Colorectal Dis. 2019;21:1130–9. [31095852]. https://doi.org/10.1111/codi.14710.
45. Adams E, Boulton MG, Horne A, Rose PW, Durrant L, Collingwood M, Oskrochi R, Davidson SE, Watson EK. The effects of pelvic radiotherapy on cancer survivors: symptom profile, psychological morbidity and quality of life. Clin Oncol (R Coll Radiol). 2014;26:10–7. [23992740]. https://doi.org/10.1016/j.clon.2013.08.003.
46. Ganz PA, Desmond KA, Leedham B, Rowland JH, Meyerowitz BE, Belin TR. Quality of life in long-term, disease-free survivors of breast cancer: a follow-up study. J Natl Cancer Inst. 2002;94:39–49. [11773281]. https://doi.org/10.1093/jnci/94.1.39.
47. Thong MS, Mols F, Lemmens VE, Creemers GJ, Slooter GD, van de Poll-Franse LV. Impact of chemotherapy on health status and symptom burden of colon cancer survivors: a population-based study. Eur J Cancer. 2011;47:1798–807. [21454071]. https://doi.org/10.1016/j.ejca.2011.02.006.
48. Daniels IR, Woodward S, Taylor FG, Raja A, Toomey P. Female urogenital dysfunction following total mesorectal excision for rectal cancer. World J Surg Oncol. 2006;4:6. [16448559]. https://doi.org/10.1186/1477-7819-4-6.
49. Carmichael JCMS. Anatomy and embryology of the colon, rectum, and anus. In: Steele SR, Hull TL, Read TE, Saclarides TJ, Senagore AJ, Whitlow CB, editors. The ASCRS textbook of colon and rectal surgery. 3rd ed. New York: Springer; 2016. p. 17.
50. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery–the clue to pelvic recurrence? Br J Surg. 1982;69:613–6. [6751457].
51. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. Lancet. 1993;341:457–60. [8094488].
52. Maurer CA. Urinary and sexual function after total mesorectal excision. Rec Results Cancer Res. 2005;165:196–204. [15865034]. https://doi.org/10.1007/3-540-27449-9_21.
53. Vennix S, Pelzers L, Bouvy N, Beets GL, Pierie JP, Wiggers T, Breukink S. Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database Syst Rev. 2014:CD005200. [24737031]. https://doi.org/10.1002/14651858.CD005200.pub3.
54. Kim HJ, Choi GS, Park JS, Park SY, Yang CS, Lee HJ. The impact of robotic surgery on quality of life, urinary and sexual function following total mesorectal excision for rectal cancer: a propensity score-matched analysis with laparoscopic surgery. Colorectal Dis. 2018;20:O103–13. [29460997]. https://doi.org/10.1111/codi.14051.
55. Rouanet P, Bertrand MM, Jarlier M, Mourregot A, Traore D, Taoum C, de Forges H, Colombo PE. Robotic versus laparoscopic total mesorectal excision for sphincter-saving surgery: results of a single-center series of 400 consecutive patients and perspectives. Ann Surg Oncol. 2018;25:3572–9. [30171509]. https://doi.org/10.1245/s10434-018-6738-5.
56. Gklavas A, Kyprianou C, Exarchos G, Metaxa L, Dellis A, Papaconstantinou I. Sexual function after proctectomy in patients with inflammatory bowel disease: a prospective study. Turk J Gastroenterol. 2019;30:943–50. [31767548]. https://doi.org/10.5152/tjg.2019.18676.
57. Spanos CP, Mamopoulos A, Tsapas A, Syrakos T, Kiskinis D. Female fertility and colorectal cancer. Int J Colorectal Dis. 2008;23:735–43. [18458919]. https://doi.org/10.1007/s00384-008-0483-3.
58. Rajaratnam SG, Eglinton TW, Hider P, Fearnhead NS. Impact of ileal pouch-anal anastomosis on female fertility: meta-analysis and systematic review. Int J Colorectal Dis. 2011;26:1365–74. [21766164]. https://doi.org/10.1007/s00384-011-1274-9.
59. Bartels SA, D'Hoore A, Cuesta MA, Bensdorp AJ, Lucas C, Bemelman WA. Significantly increased pregnancy rates after laparoscopic restorative proctocolectomy: a cross-sectional study. Ann Surg. 2012;256:1045–8. [22609840]. https://doi.org/10.1097/SLA.0b013e318250caa9.
60. Beyer-Berjot L, Maggiori L, Birnbaum D, Lefevre JH, Berdah S, Panis Y. A total laparoscopic approach reduces the infertility rate after ileal pouch-anal anastomosis: a 2-center study. Ann Surg. 2013;258:275–82. [23360923]. https://doi.org/10.1097/SLA.0b013e3182813741.
61. Lee S, Crowe M, Seow CH, Kotze PG, Kaplan GG, Metcalfe A, Ricciuto A, Benchimol EI, Kuenzig ME. The impact of surgical therapies for inflammatory bowel disease on female fertility. Cochrane Database Syst Rev. 2019;(7):CD012711. [31334846]. https://doi.org/10.1002/14651858.CD012711.pub2.
62. Zbuk K, Sidebotham EL, Bleyer A, La Quaglia MP. Colorectal cancer in young adults. Semin Oncol. 2009;36:439–50. [19835739]. https://doi.org/10.1053/j.seminoncol.2009.07.008.
63. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, Beck LN, Brennan LV, Oktay K, American SOCO. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol. 2006;24:2917–31. [16651642]. https://doi.org/10.1200/JCO.2006.06.5888.
64. Wallace WH, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys. 2005;62:738–44. [15936554]. https://doi.org/10.1016/j.ijrobp.2004.11.038.
65. Kumar A, Merali A, Pond GR, Zbuk K. Fertility risk discussions in young patients diagnosed with colorectal cancer. Curr Oncol. 2012;19:155–9. [22670094]. https://doi.org/10.3747/co.19.942.
66. Basson R, Berman J, Burnett A, Derogatis L, Ferguson D, Fourcroy J, Goldstein I, Graziottin A, Heiman J, Laan E, Leiblum S, Padma-Nathan H, Rosen R, Segraves K, Segraves RT, Shabsigh R, Sipski M, Wagner G, Whipple B. Report of the international consensus development conference on female sexual dysfunction: definitions and classifications. J Urol. 2000;163:888–93. [10688001].
67. Stinesen Kollberg K, Waldenström AC, Bergmark K, Dunberger G, Rossander A, Wilderäng U, Åvall-Lundqvist E, Steineck G. Reduced vaginal elasticity, reduced lubrication, and deep and superficial dyspareunia in irradiated gynecological cancer survivors. Acta Oncol. 2015;54:772–9. [25761090]. https://doi.org/10.3109/0284186X.2014.1001036.
68. Traa MJ, Roukema JA, De Vries J, Rutten HJ, Langenhoff B, Jansen W, Den Oudsten BL. Biopsychosocial predictors of sexual function and quality of sexual life: a study among patients with colorectal cancer. Transl Androl Urol. 2015;4:206–17. [26816825]. https://doi.org/10.3978/j.issn.2223-4683.2015.03.01.
69. Brotto LA, Yule M, Breckon E. Psychological interventions for the sexual sequelae of cancer: a review of the literature. J Cancer Surviv. 2010;4:346–60. [20602188]. https://doi.org/10.1007/s11764-010-0132-z.
70. Brotto LA, Erskine Y, Carey M, Ehlen T, Finlayson S, Heywood M, Kwon J, McAlpine J, Stuart G, Thomson S, Miller D. A brief mindfulness-based cognitive behavioral intervention improves sexual functioning versus wait-list control in women treated for gynecologic cancer. Gynecol Oncol. 2012;125:320–5. [22293042]. https://doi.org/10.1016/j.ygyno.2012.01.035.
71. Carter J, Goldfrank D, Schover LR. Simple strategies for vaginal health promotion in cancer survivors. J Sex Med. 2011;8:549–59. [20722792]. https://doi.org/10.1111/j.1743-6109.2010.01988.x.
72. Miles T, Johnson N. Vaginal dilator therapy for women receiving pelvic radiotherapy. Cochrane Database Syst Rev. 2014;CD007291. [25198150]. https://doi.org/10.1002/14651858.CD007291.pub3.
73. Fernandes T, Costa-Paiva LH, Pinto-Neto AM. Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on sexual function in postmenopausal women: a randomized controlled trial. J Sex Med. 2014;11:1262–70. [24612478]. https://doi.org/10.1111/jsm.12473.

74. Graziotton A. Sexual pain disorders: dyspareunia and vaginismus. In: Porst H, Buvat J, editors. Standard practice in sexual medicine. Oxford: Blackwell Publishing; 2006. p. 342–50.
75. Bakker RM, ter Kuile MM, Vermeer WM, Nout RA, Mens JW, van Doorn LC, de Kroon CD, Hompus WC, Braat C, Creutzberg CL. Sexual rehabilitation after pelvic radiotherapy and vaginal dilator use: consensus using the Delphi method. Int J Gynecol Cancer. 2014;24:1499–506. [25248115]. https://doi.org/10.1097/IGC.0000000000000253.
76. Johnson N, Miles TP, Cornes P. Dilating the vagina to prevent damage from radiotherapy: systematic review of the literature. BJOG. 2010;117:522–31. [20163407]. https://doi.org/10.1111/j.1471-0528.2010.02502.x.
77. Meister MR, Shivakumar N, Sutcliffe S, Spitznagle T, Lowder JL. Physical examination techniques for the assessment of pelvic floor myofascial pain: a systematic review. Am J Obstet Gynecol. 2018;219:497.e1–497.e13. [29959930]. https://doi.org/10.1016/j.ajog.2018.06.014.
78. Bordeianou LG, Anger JT, Boutros M, Birnbaum E, Carmichael JC, Connell KA, De EJB, Mellgren A, Staller K, Vogler SA, Weinstein MM, Yafi FA, Hull TL. Members of the Pelvic Floor Disorders Consortium Working Groups on Patient-Reported Outcomes. Measuring pelvic floor disorder symptoms using patient-reported instruments: proceedings of the consensus meeting of the pelvic floor consortium of the American Society of Colon and Rectal Surgeons, the International Continence Society, the American Urogynecologic Society, and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction. Dis Colon Rectum. 2020;63:6–23. [31804265]. https://doi.org/10.1097/DCR.0000000000001529.
79. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, Ferguson D, D'Agostino R. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000;26:191–208. [10782451]. https://doi.org/10.1080/009262300278597.
80. Rogers RG, Coates KW, Kammerer-Doak D, Khalsa S, Qualls C. A short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12). Int Urogynecol J Pelvic Floor Dysfunct. 2003;14:164–8; discussion 168. [12955337]. https://doi.org/10.1007/s00192-003-1063-2.
81. McGahuey CA, Gelenberg AJ, Laukes CA, Moreno FA, Delgado PL, McKnight KM, Manber R. The Arizona Sexual Experience Scale (ASEX): reliability and validity. J Sex Marital Ther. 2000;26:25–40. [10693114]. https://doi.org/10.1080/009262300278623.
82. Rust J, Golombok S. The GRISS: a psychometric instrument for the assessment of sexual dysfunction. Arch Sex Behav. 1986;15:157–65. [3718204]. https://doi.org/10.1007/bf01542223.
83. Rust J, Derogatis L, Rodenberg C, Koochaki P, Schmitt S, Golombok S. Development and validation of a new screening tool for hypoactive sexual desire disorder: the Brief Profile of Female Sexual Function (B-PFSF). Gynecol Endocrinol. 2007;23:638–44. [17926163]. https://doi.org/10.1080/09513590701592306.
84. Mazer NA, Leiblum SR, Rosen RC. The brief index of sexual functioning for women (BISF-W): a new scoring algorithm and comparison of normative and surgically menopausal populations. Menopause. 2000;7:350–63. [10993034]. https://doi.org/10.1097/00042192-200007050-00009.
85. Quirk FH, Heiman JR, Rosen RC, Laan E, Smith MD, Boolell M. Development of a sexual function questionnaire for clinical trials of female sexual dysfunction. J Womens Health Gend Based Med. 2002;11:277–89. [11988137]. https://doi.org/10.1089/152460902753668475.
86. Rogers RG, Rockwood TH, Constantine ML, Thakar R, Kammerer-Doak DN, Pauls RN, Parekh M, Ridgeway B, Jha S, Pitkin J, Reid F, Sutherland SE, Lukacz ES, Domoney C, Sand P, Davila GW, Espuna Pons ME. A new measure of sexual function in women with pelvic floor disorders (PFD): the Pelvic Organ Prolapse/Incontinence Sexual Questionnaire, IUGA-Revised (PISQ-IR). Int Urogynecol J. 2013;24:1091–103. [23632798]. https://doi.org/10.1007/s00192-012-2020-8.
87. Mitchell KR, Ploubidis GB, Datta J, Wellings K. The Natsal-SF: a validated measure of sexual function for use in community surveys. Eur J Epidemiol. 2012;27:409–18. [22711585]. https://doi.org/10.1007/s10654-012-9697-3.
88. Weinfurt KP, Lin L, Bruner DW, Cyranowski JM, Dombeck CB, Hahn EA, Jeffery DD, Luecht RM, Magasi S, Porter LS, Reese JB, Reeve BB, Shelby RA, Smith AW, Willse JT, Flynn KE. Development and Initial Validation of the PROMIS(®) sexual function and satisfaction measures version 2.0. J Sex Med. 2015;12:1961–74. [26346418]. https://doi.org/10.1111/jsm.12966.
89. Jensen PT, Klee MC, Thranov I, Groenvold M. Validation of a questionnaire for self-assessment of sexual function and vaginal changes after gynaecological cancer. Psychooncology. 2004;13:577–92. [15295778]. https://doi.org/10.1002/pon.757.
90. Carpenter JS, Jones SM, Studts CR, Heiman JR, Reed SD, Newton KM, Guthrie KA, Larson JC, Cohen LS, Freeman EW, Jane Lau R, Learman LA, Shifren JL. Female sexual function index short version: a MsFLASH item response analysis. Arch Sex Behav. 2016;45:1897–905. [27502350]. https://doi.org/10.1007/s10508-016-0804-5.
91. Gilbert A, Sebag-Montefiore D, Davidson S, Velikova G. Use of patient-reported outcomes to measure symptoms and health related quality of life in the clinic. Gynecol Oncol. 2015;136:429–39. [25448486]. https://doi.org/10.1016/j.ygyno.2014.11.071.
92. Flynn KE, Reese JB, Jeffery DD, Abernethy AP, Lin L, Shelby RA, Porter LS, Dombeck CB, Weinfurt KP. Patient experiences with communication about sex during and after treatment for cancer. Psychooncology. 2012;21:594–601. [21394821]. https://doi.org/10.1002/pon.1947.
93. White ID, Allan H, Faithfull S. Assessment of treatment-induced female sexual morbidity in oncology: is this a part of routine medical follow-up after radical pelvic radiotherapy. Br J Cancer. 2011;105:903–10. [21897386]. https://doi.org/10.1038/bjc.2011.339.
94. Althof SE, Parish SJ. Clinical interviewing techniques and sexuality questionnaires for male and female cancer patients. J Sex Med. 2013;10 Suppl 1:35–42. [23387910]. https://doi.org/10.1111/jsm.12035.
95. Bober SL, Varela VS. Sexuality in adult cancer survivors: challenges and intervention. J Clin Oncol. 2012;30:3712–9. [23008322]. https://doi.org/10.1200/JCO.2012.41.7915.

Male Genitourinary Dysfunction as a Consequence of Colorectal Surgery

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Key Concepts

- Male genitourinary function can be severely affected after pelvic surgery—even when performed for benign disease. Sympathetic and parasympathetic nerves instrumental to normally functioning neural pathways can be located in close proximity to left colon and rectal structures.
- Many questionnaires are available to measure male genitourinary function. None are perfect and choosing the best tool depends on the outcome being studied.
- Radiotherapy and to some degree chemotherapy both can have detrimental effects on male genitourinary function.
- Selecting interventions to improve quality of life depends on compassionate questioning and building a rapport with the patient. This ideally should begin before starting treatment.
- Sexual function and dysfunction after surgery in LGBTQ patients is often ignored by caregivers and poorly studied. This group of patients can experience unique quality of life problems after pelvic surgery, and awareness is the first step to studying and understanding their needs.

Introduction

Pelvic autonomic nerve dysfunction is a complication of many common colon and rectal procedures. The magnitude of the morbidity is dependent upon the affected nerves, extent of damage, and prior genitourinary function [1, 2]. While direct surgical damage to the nerves is a common etiology of impaired function, it can also be impaired by the adjunctive therapies employed such as pelvic radiotherapy or systemic chemotherapy. Additionally, long-term fecal diversion can impair function due to the psychological impact on body image and its impact on desire. The large and heretofore neglected LGBTQ population also has different but equally important sexual health concerns related to the performance of common colorectal surgical procedures.

Male genitourinary function is relatively easy to describe but has proven much more difficult to quantitatively measure as evidenced by the sheer number of urinary and sexual function metrics available for use. These are often narrowly written and specialty-specific metrics that do not lend themselves well to generalization to the entire patient population and various specialties providing pelvic surgical care. The Pelvic Floor Disorders Consortium is a group of sub-specialist pelvic practitioners (colorectal surgeons, urogynecologists, urologists, gynecologists, gastroenterologists, physical therapists) actively working to define best pelvic metrics and practices so that all practitioners can speak with one voice to enhance the care of these patients [3].

Intimate familiarity with pelvic neuroanatomy and physiology is critical for the practicing colorectal surgeon. Identification of relevant anatomy at specific points of pelvic dissection is important for preservation of functional autonomic anatomy. These neural pathways drive male genitourinary function, which is a major determinate of quality of life especially in younger patients. Injury to these structures can manifest as urinary retention or incontinence as well as erectile dysfunction and/or ejaculatory dysfunction. Studies have estimated the prevalence of male genitourinary dysfunction ranges from 20% to 80% following pelvic colon and rectal procedures [4–7]. Surgeons participating in pelvic procedures should be able to discuss genitourinary function comfortably, putting the patient at ease. Studies have shown that patients and providers alike have difficulty due to embarrassment participating in this discussion. Detailed knowledge of genitourinary function can alleviate these feelings in the provider and mitigate patient's discomfort [2].

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Neuroanatomy and Physiology of the Male Genitourinary Tract

Normal function of the male genitourinary system requires functionally and anatomically intact sympathetic and parasympathetic neural pathways. The proximity of these structures to the left colon and rectum makes male genitourinary dysfunction a common morbidity associated with a number of pelvic colon and rectal procedures. Knowledge of sympathetic and parasympathetic anatomic pathways can aid in avoidance of injury to these structures (Fig. 64.1). Additionally, knowledge of sympathetic and parasympathetic neurophysiology is critical to the discussion of potential side effects and consent process of many common pelvic procedures [9–13].

Sympathetic Pelvic Anatomy and Physiology

Sympathetic innervation of the pelvic viscera originates from T12-L2 spinal level manifesting as the superior hypogastric plexus. The superior hypogastric plexus manifests as a group of nerve fibers around the distal aorta to the aortic bifurcation (Fig. 64.2). These fibers coalesce into the bilateral hypogastric nerves at the level of the sacral promontory and course laterally around the rectum (Fig. 64.3) to join the nervi erigentes to form the inferior hypogastric plexus at level of the anterior peritoneal reflection. The inferior hypogastric plexus then courses anterior to Denonvilliers' fascia to supply the genitourinary system (Fig. 64.4).

Sympathetic inflow in males predominately regulates ejaculation and to a lesser degree penile erection. Ejaculation can be separated into two phases. The first, expulsion, is the sympathetically mediated movement of seminal fluid in the prostatic urethra. The second phase, emission, is the somatically mediated contraction of penile musculature resulting in delivery of seminal fluid out of the urethra. Damage to the sympathetic inflow to the pelvic viscera predominately results in retrograde ejaculation. Aberrant sympathetic innervation of the bladder results in bladder atonia with urinary retention and overflow incontinence.

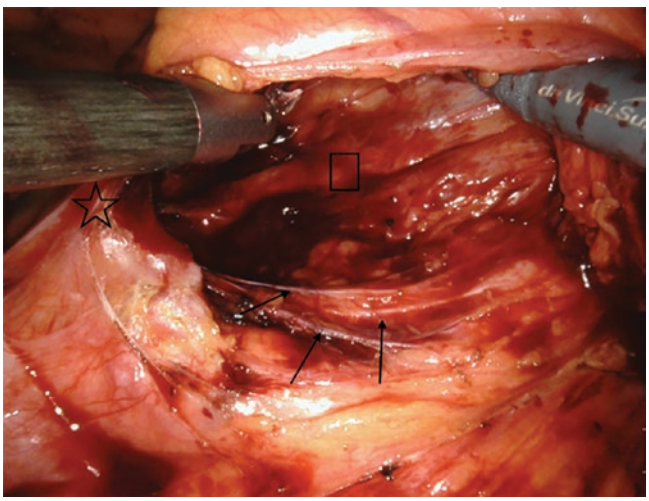

Fig. 64.2 Interoperative photo of superior hypogastric plexus, arrows are on hypogastric nerves, box is on the ureter, star is on the inferior mesenteric artery

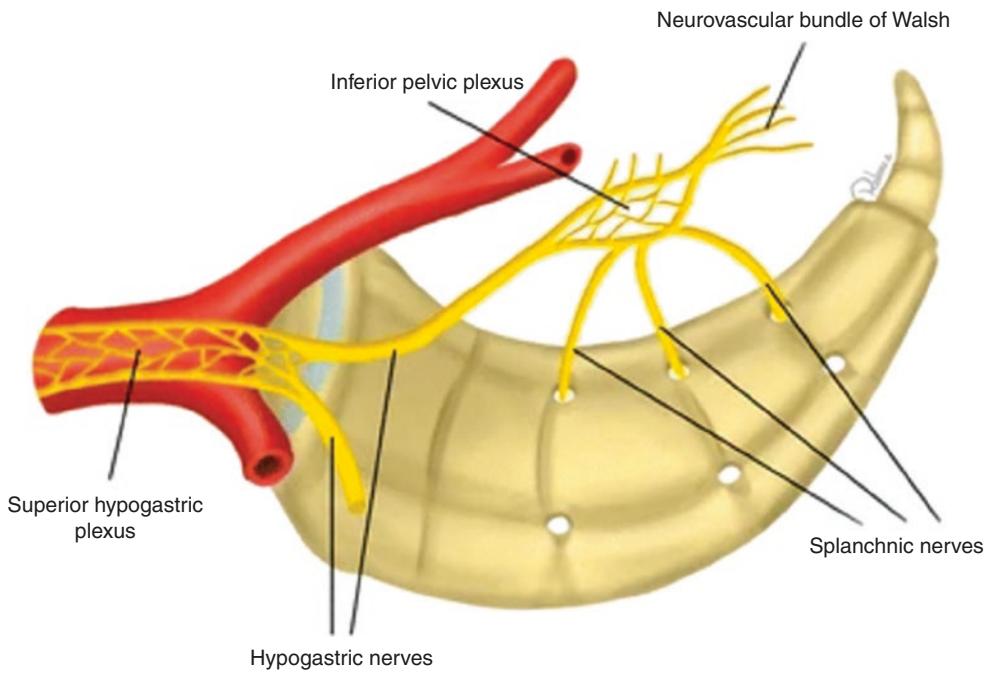

Fig. 64.1 Schematic representation of autonomic neuroanatomy. (Reused with permission from Runkel and Reiser [8]. Copyright © 2013 Springer Nature)

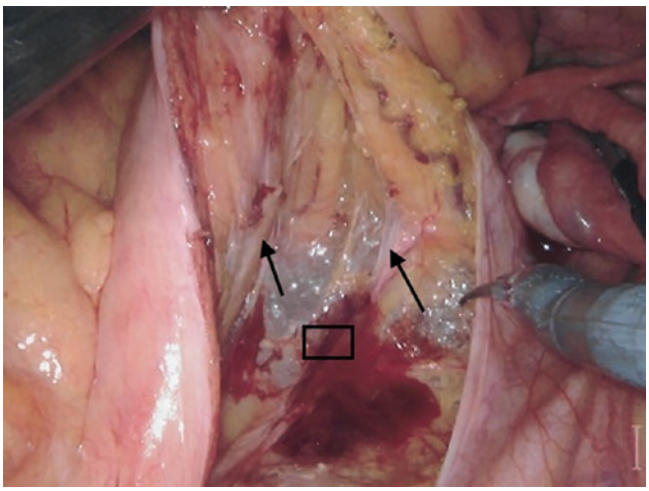

Fig. 64.3 Interoperative photo of superior hypogastric nerves, arrows are on the right and left hypogastric nerves, box is on the sacral promontory

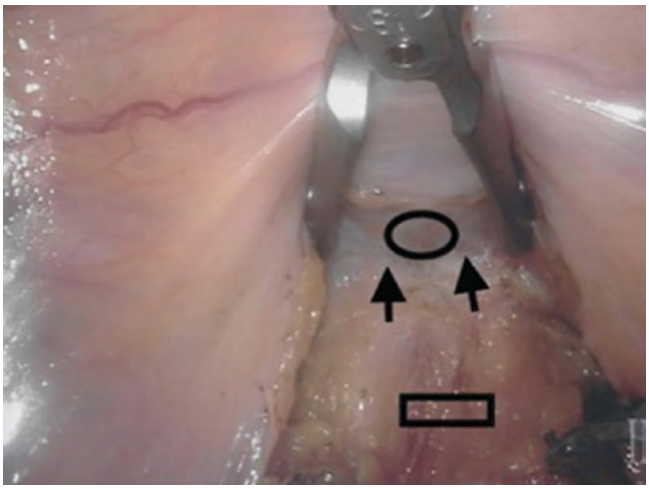

Fig. 64.4 Interoperative photo of Denonvilliers' fascia, arrows are on Denonvilliers' fascia, circle is on the prostate, rectangle is on the rectum

Parasympathetic Pelvic Anatomy and Physiology

Parasympathetic innervation of the pelvic viscera originates from the S2-S4 levels with predominance from the S3 level. These fibers coalesce into the pelvic splanchnic nerves or nervi erigentes that ascend bilaterally to the inferior hypogastric plexus that contains both parasympathetic and sympathetic fibers via the superior hypogastric plexus. The inferior hypogastric plexus courses along the pelvic sidewall and at the level of the prostate courses deep to Denonvilliers' fascia to supply the seminal vesicles/prostate and posterior bladder (Fig. 64.4).

Parasympathetic innervation regulates male erectile function by precipitating vasodilation and engorgement of the penile vascular sinuses. Injury to the nervi erigentes or inferior hypogastric plexus predominantly results in male impotence. Injury to the inferior hypogastric plexus due to its inclusion of sympathetic fibers can also result in retrograde ejaculation. The "micturition center" is felt to lie within the S2-S4 levels and is highly regulated at the central nervous system level. Damage to parasympathetic bladder pathways results in detrusor sphincter dyssynergia and functional bladder outlet obstruction.

Male Genitourinary Functional Metrics

In order to describe a phenomenon, one must be able to reproducibly and objectively measure it. In men due to anatomic and physiologic reasons, genitourinary dysfunction is easily described and manifests as erectile dysfunction, orgasmic and/or ejaculatory dysfunction, and urinary retention. As with many metrics measuring clinical outcomes, generalizable systems of objective measurement for male genitourinary dysfunction have proved elusive. Many metrics are narrowly written to derive specialty-specific outcomes and are not applicable to the entire pelvic health population. Others are so broad as to prove unwieldy and not usable in the busy clinical practice. The Pelvic Floor Disorders Consortium in a multispecialty effort has worked to standardize pelvic care [3]. Its first task has been to sort through the myriad of pelvic health metrics to standardize measurements such that a description of male sexual or urinary dysfunction has the same meaning to the broad group of practitioners providing care to these patients.

Male Sexual Dysfunction Metrics

The International Index of Erectile Function (IIEF-15)

The consortium recommends the use of the International Index of Erectile Function (IIEF-15). This is the most cited instrument for assessing sexual function in men. One of the major advantages of the IIEF is that it includes five separately validated domains: erectile function (six questions), orgasmic/ejaculatory function (two questions), sexual desire (two questions), intercourse satisfaction (three questions), and overall satisfaction (two questions). It is also validated in ten different languages [14–16].

Sexual Health Inventory for Men (SHIM or IIEF-5)

The IIEF-5 or SHIM (Sexual Health Inventory for Men) is brief, practical, and highly cited in the scientific literature. The questionnaire includes five questions from the more comprehensive IIEF. Like the longer IIEF, the IIEF-5 was validated in male patients with erectile dysfunction due to a variety of causes. The IIEF-5 consists of question from the erectile function domain (items 2, 4, 5, and 15) and the intercourse satisfaction domain (item 7). The other remaining three domains (orgasmic/ejaculatory function, sexual desire, and overall satisfaction) are not represented in the IIEF-5. The erectile function domain was shown to have independent validity in the assessment of male sexual function.

Expanded Prostate Cancer Index Composite (EPIC)

EPIC is a comprehensive 50-question instrument that assesses health-related quality of life in 4 separately validated domains including urinary function (12 questions), bowel function (14 questions), sexual function (13 questions), and hormonal function (11 questions) each of which can be scored independently. The strength of this questionnaire is also its weakness in that it is through but impractical to use in clinical practice. It has also only been validated in men with prostate cancer.

Male Urinary Dysfunction Metrics

The Pelvic Floor Consortium has also examined metrics describing male urinary function. This is summarized in a 2004 review article by Naughton et al. that weighted the various metrics according to the strength of evidentiary support. The following were the highest ranked [17].

Urogenital Distress Inventory/Urogenital Distress Inventory-6

The UDI examines 19 lower urinary tract symptoms and the degree to which those are distressing. It is validated only in women but is used also in the male population. The UDI-6 is an abbreviated form of the UDI and has been validated in both men and women. It is useful only for English-speaking populations.

King's Health Questionnaire

The King's health questionnaire has been validated in men and women. It examines ten factors related to urinary symptoms and their impact on quality of life. It is useful in multiple different languages.

Danish Prostatic Symptom Score

The Danish Prostatic Symptom Score is a metric assessing the degree to which men are distressed by their urinary function. It includes 12 symptoms assessing both frequency and distress to result in a composite score that is valid and reliable in the general population.

International Continence Society Male/ International Continence Society Male Short-Form Questionnaires

The ICS male questionnaire assesses 20 urinary symptoms and the severity of distress each of the symptoms causes. An abbreviated form of the ICS is available. The questionnaire was reduced to two major sections: the ICS male voiding subscore, which contains five questions, and the ICS male incontinence subscore, which contains six questions. The two sections are totaled equaling the final score.

Colorectal Procedures Resulting in Genitourinary Dysfunction

Anterior Resection vs Low Anterior Resection vs Complete Proctectomy

Patients undergoing procedures involving the left colon and rectum are at the highest risk for development of genitourinary dysfunction postoperatively. The risk of genitourinary dysfunction increases as procedures go lower into the confined spaces of the pelvis. Genitourinary dysfunction tends to be greater after oncologic than non-oncologic surgery—although some literature is contradictory.

The superior hypogastric plexus and right and left hypogastric nerves are at highest risk when mobilizing the sigmoid and upper mesorectum away from the retroperitoneum and isolating the origin of the inferior mesenteric artery. These structures are typically readily apparent and easy to preserve at this level when dissecting. Therefore, genitourinary dysfunction after anterior resection is quite limited.

As dissection progresses to the mid- and upper rectum, the risk of injury to the inferior hypogastric plexus and nervi erigentes increases as the anatomy is less apparent and the narrow workspace impairs exposure. The nervi erigentes course along the pelvic sidewall and at the level of the seminal vesicles and prostate course anteriorly deep to Denonvilliers' fascia. Adherence to proper techniques and dissection planes specifically staying superficial to Denonvilliers' fascia when mobilizing the anterolateral rectum will minimize, but not eliminate, the genitourinary dysfunction seen after proctectomy. The highest risk of dysfunction appears after abdominoperineal resection and is multifactorial involving damage to autonomic nerves, disruption of normal pelvic floor anatomy and function, and the psychological impact of a significant change in body image [18–24].

Minimally Invasive vs Open Techniques

The information regarding sexual function following minimally invasive total mesorectal excision (TME) is limited and controversial. The magnified view available with minimally invasive proctectomy enables excellent exposure of the pelvic cavity and facilitates sharp dissection of the lateral, anterior, and presacral spaces, all being autonomic nerve locations. Despite this advantage, studies have shown a variable impact on male sexual dysfunction after minimally invasive compared to open proctectomy. The studies can all be criticized as small, single center, and with a retrospective design. Comparison of robotic and laparoscopic proctectomy is equally problematic and fraught with poor-quality studies giving variable results in regard to postoperative male sexual function [25, 26].

Genitourinary Dysfunction Related to Pelvic Radiotherapy

Pelvic radiotherapy is an adjunct in the management algorithm of many pelvic malignancies. Pelvic radiotherapy results in cellular death, which is obviously beneficial for cancer treatment but can for years and decades manifest as adverse toxicity of the treated organ and adjacent organs. Erectile dysfunction and infertility are common long-term complications of pelvic radiotherapy for male patients, and the causes are felt to be multifactorial. Urinary dysfunction is also a common complication of pelvic radiotherapy and includes urinary urgency and incontinence, radiation cystitis, ureteral and urethral stricture, and fistula. Systemic chemotherapy also can have a detrimental effect on genitourinary dysfunction but not to the same degree as radiotherapy or surgical treatments. With cancer patients having increased long-term survival, management of these therapy-related complications will be recognized more frequently as an important factor for quality of life in cancer survivorship [27–32].

Psychological Impact and Counseling

The first step in providing care to men with sexual dysfunction following pelvic surgery is to develop a rapport with the patient preoperatively that allows for frank discussion of intimate matters. In patients undergoing surgery that could potentially affect genitourinary function postoperatively, a thorough history of preoperative function is key to predicting the risk of aberrant postoperative function. The informed consent process should also have a detailed discussion of the potential for genitourinary dysfunction and specifically what types of dysfunction might be experienced.

Patients returning after pelvic surgery or radiotherapy should be actively questioned and encouraged to discuss symptoms of genitourinary dysfunction. Acknowledgment by the surgeon that a problem exists and support and encouragement that function typically improves with time can be extremely beneficial to the distressed patient. Early discussion of potential treatment pathways can allay patient anxiety. Cultivation of a relationship with a urologic colleague with an interest in male genitourinary dysfunction can also provide an early avenue to rehabilitation and long-term treatment [33, 34].

Management of Male Genitourinary Dysfunction

Vacuum Constriction Device (VCD)

The oldest and most widely used device for erectile dysfunction as well as the least expensive is the vacuum constriction device or the so-called penis pump. A cylindrical reservoir is applied to the shaft of the penis, and negative pressure is applied resulting in engorgement of the corpora. An elastic band is then slid off the base of the cylinder constricting the penile base. The sexual act is completed and the constricting band is removed resulting in disgorgement of the penis.

This modality has minimal associated risk, predominantly bruising at the penile base. Patient satisfaction with this modality ranges from 50% to 80%. The most common complaint is interruption of intimacy to use the device, an unnatural feeling erection, blocked ejaculation, and anorgasmia [35].

Intracorporeal (IC) Injections

Until the introduction of oral therapy, intracorporeal injection of vasoactive drugs into the corporal tissue of the penis

was a mainstay in the treatment of erectile dysfunction and remains an effective management option for patients with neurogenic erectile dysfunction after pelvic surgery.

Most commonly alprostadil is used as a single agent. It requires patient education in the office and then dose titration at home to optimize the erection quality. Other injectable treatments which are a combination of medication include Bimix (papaverine/phentolamine) or Trimix (alprostadil/phentolamine/papaverine). While these are more effective, the complication rate is higher than single-agent alprostadil.

The predominant complications associated with intracavernosal injection are pain at the injection site, penile hematoma, penile fibrosis, and priapism. Despite this, successful erection is achieved in 90% of patients, and patient satisfaction with this modality consistently approaches 80%. Interestingly, 30–70% of patients will cease use of this modality over time [36–38].

Intraurethral Alprostadil

Introduction of vasoactive drugs via the urethra or as a cream applied to the penile shaft obviates the need for penile shaft injections. The success rate with these modalities is lower than injection therapy (60%), but this method of therapy has a wider acceptance among patients combined with a lower complication rate (versus injection therapy). The primary complaint is penile pain and mild urethral bleeding [37].

Oral Medications

Due to direct to patient marketing, the oral phosphodiesterase inhibitors used to treat erectile dysfunction are well recognized among patients and the general public. These drugs result in a systemic increase in the nitric oxide concentration such that when the penis receives appropriate neurologic impulses, vasodilation is increased resulting in penile erection. These drugs require appropriate neurologic impulses; hence they are less successful in neurogenic impotence that is encountered after pelvic surgery [39].

Penile Prosthesis

For patients who have failed medical options for erectile dysfunction, there are several surgically implanted devices that can achieve a degree of penile rigidity sufficient for penetrative intercourse.

The implantable devices come in two varieties, the inflatable prosthesis and the semirigid rod. The inflatable prosthesis gives the most natural erection and allows for penile deflation. The device is however more complicated leading to higher rates of device malfunction requiring revisional surgery. Patients also require a certain degree of manual and mental dexterity to operate the device. The semirigid rod while easy to operate leaves the penis in a permanent semi-rigid state, which can be difficult to conceal. As with any implantable device, both modalities are at risk of infection and erosion requiring device explantation. Additionally, penile fibrosis and scarring may impair penile length and efficacy of the device [40–42].

Retrograde Ejaculation/Anejaculation

Retrograde also termed a dry orgasm results from an inability of the urethral sphincter to close during orgasm resulting in all or part of the ejaculate entering the bladder. The condition is not harmful and the sense of orgasm is preserved. It does however result in male infertility. Patients with this condition related to pelvic surgery do not typically respond to medical therapy such as pseudoephedrine. Most unless seeking to father children do not seek treatment. If trying to father children, then the assistance of a fertility specialist is required. Semen can be harvested from the urine and washed, and then assisted fertilization techniques can result in a successful pregnancy [43].

Chronic Intermittent Catheterization vs Indwelling Urinary Catheter

Long-term urinary dysfunction as a result of pelvic surgery is unusual and manifests as urinary retention with or without overflow incontinence. In the short term, bladder decompression with an indwelling catheter and treatment with alpha-blockade usually results in relief of urinary retention. Patients with urinary retention that persists despite these measures are typically offered chronic intermittent catheterization. Chronic intermittent catheterization is the scheduled decompression of the bladder usually performed by the patient after office-based instruction. Long-term indwelling catheters or a suprapubic catheter may be offered to patients with non-recoverable bladder function or who cannot participate in chronic intermittent catheterization [44].

LGBTQ Populations

Sexual function in LGBTQ populations is regrettably unexplored and poorly understood. Most available data is found in the urology field, documenting functional results and psychological impact after prostatectomy. Despite the rising amount of research in gay and bisexual men (GBM), it seems that surgeons are disregarding the fact that the anorectum can serve as a sexual organ and that more than 30% of the general population sees the anus and rectum as sexual organs [45–52]. Increasing awareness of the sexual health needs of

the LGBTQ community has precipitated a rising interest toward understating how changes in sexual function after pelvic surgery can affect sexual roles, satisfaction, relationships, quality of life, and identity in GBM.

Many GBM show sex-specific situational anxiety upon learning about diagnoses whose treatment might imply dramatic anatomical and functional genitourinary changes, such as prostate cancer management. Experiencing a decline in sexual function elicits the same confidence issues in GBM as it does with heterosexual men. Patients experience identity problems with decreased sense of masculinity and loss of sexual self-esteem. Profound impacts on relationships are documented when one partner undergoes treatment affecting genitourinary function.

Data focused on mental health and behavioral aspects as a consequence of pelvic surgery in GBM shows greater mental health challenges and less emotional support post-treatment when compared with heterosexual men. LGBTQ patients experience more mood and anxiety disorders, more depression, and an elevated risk for suicidal ideation and attempts compared with heterosexual adults. These problems are highly associated with discrimination by the general population along with less familial and social support and less partner involvement in treatment compared to the male heterosexual population. GBM experiencing erectile dysfunction and urinary incontinence suffer from decreased intimacy resulting from loss of spontaneity and sexual self-esteem, lack of confidence in their own sexual functioning (performance anxiety), and fear of dribbling during sex. As a result of functional changes related to pelvic surgery, gay couples may need to adjust their sexual practice by changing the role from insertive to receptive intercourse [53]. These changes are not only related to the position during sex but also to the role concerning initiation of the sexual act, the type of affection related to the relationship, and sexual identity. It has been assumed that gay couples or bisexual men can easily change their role in a sexual relationship, but this has much deeper implications than previously considered. Anodyspareunia or the experience of pain with receptive anal intercourse is a recognized consequence of anorectal and pelvic surgery. A metric validated in GBM has established a clinical diagnostic criterion of anodyspareunia. Patients who met the criteria for anodyspareunia reported having avoided anal sex for periods of time (82%), and some restricted their role in the relationship to insertive anal sex only (49%). About one-third (31%) reported disruption of their sexual relationship, and 15% conveyed inability to have new sexual partners. For all these reasons, gay or bisexual men engaging in anal intercourse and undergoing pelvic surgery have an increased risk of social isolation, depression, and suicide due to the detrimental effect of abnormal sexual function. Some will describe their conditions as impending relationship breakers and consider that doctors underestimate the value of sex in gay relations [46, 54].

Male Sexual Dysfunction Metrics in the Gay Population

Gay Sexual Functioning Inventory

In 2019, Rosser et al. develop an innovative and comprehensive tool to assess common sexual behaviors between men, including both insertive and receptive anal sex, "The Sexual Functioning of Gay and Bisexual Men Following Prostate Cancer Treatment: Results from the Restore Study." This instrument incorporated 37 items developed after 39 in-depth interviews, including 19 with GBM treated with radical prostatectomy, 6 with radiation, and 6 with a combination or advanced treatment. Also included were three male partners and six caregivers. Items were scored using a 5-item Likert-type scale. This is the first report in the literature quantifying the incidence of sexual and urinary problems in GBM treated for prostate cancer and describing the consequences on their health-related quality of life [55].

Genitourinary Dysfunction Related to Fecal Diversion

An unfortunate reality for many patients with colon and rectal disorders is loss of gastrointestinal continuity. While a functional and productive life continues, the psychological impact for many patients with a permanent stoma cannot be underestimated. Validated quality of life metrics for ostomates exist and have shown nearly universal alterations in body image, lifestyle changes related to the ostomy (80%), and impaired sexuality (40%). In general, studies comparing patient's quality of life in ostomates versus non-ostomates show improved quality of life independent of bowel function for non-ostomates. Studies have also documented an increased risk of suicide in ostomates [56–58].

Conclusions

In treating pelvic malignancies, long-term cure is the primary goal. Significant issues involving gastrointestinal and genitourinary dysfunction plague patients who undergo pelvic surgery. It is incumbent upon the treating surgeon to understand the complications of therapy and the factors that may minimize them. These treatment-related side effects can have a profound negative impact on quality of life in our can-

cer survivors. Knowledge of treatment options related to these adverse aspects of treatment can have a significant positive impact on patient quality of life.

References

1. Bober SL, Varela VS. Sexuality in adult cancer survivors: challenges and intervention. J Clin Oncol. 2012;30:3712–9.
2. Park ER, Norris RL, Bober SL. Sexual health communication during cancer care: barriers and recommendations. Cancer J. 2009;15:74–7.
3. Bordeianou LG, Anger JT, Boutros M, Birnbaum E, Carmichael JC, et al. Measuring pelvic floor disorder symptoms using patient-reported instruments. Proceedings of the consensus meeting of the pelvic floor consortium of the American Society of Colon and Rectal Surgeons, the International Continence Society, the American Urogynecologic Society, and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction. Dis Colon Rectum. 2020;63:6–23.
4. Havenga K, Enker WE, McDermott K, et al. Male and female sexual and urinary function after total mesorectal excision with autonomic nerve preservation for carcinoma of the rectum. J Am Coll Surg. 1996;182:495–502.
5. Balslev I, Harling H. Sexual dysfunction following operation for carcinoma of the rectum. Dis Colon Rectum. 1983;26:785–8.
6. Hojo K. Extended wide lymphadenectomy and preservation of pelvic autonomic nerves in the rectal cancer surgery. G Chir. 1989;10:149–53.
7. Towe M, Huynh LM, El-Khatib F, Gonzalez J, Jenkins LC, Yafi FA. A review of male and female sexual function following colorectal surgery. Sex Med Rev. 2019;7(3):422–9.
8. Runkel N, Reiser H. Nerve-oriented mesorectal excision (NOME): autonomic nerves as landmarks for laparoscopic rectal resection. Int J Colorectal Dis. 2013;28(10):1367–75.
9. Kim NK, Kim YW, Cho MS. Total mesorectal excision for rectal cancer with emphasis on pelvic autonomic nerve preservation: expert technical tips for robotic surgery. Surg Oncol. 2015;24(3):172–80.
10. Vodusek DB. Anatomy and neurocontrol of the pelvic floor. Digestion. 2004;69:87–92.
11. Chew M-H, Yeh Y-T, et al. Pelvic autonomic nerve preservation in radical rectal cancer surgery: changes in the past 3 decades. Gastroenterol Rep. 2016;4(3):173–85.
12. Haroun HSW. Clinical anatomy of the splanchnic nerves. MOJ Anat Physiol. 2018;5(2):87–90.
13. Robertson S, Ariyasinghe C, et al. Parasympathetic pelvic splanchnic nerves, Radiopaeda.org.
14. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology. 1997;49:822–30.
15. Rosen RC, Cappeleri JC, Smith MD, Lipsky J, Pena BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res. 1999;11:319–26.
16. Rosen RC, Catania J, Pollack L, Althof S, O'Leary M, Seftel AD. Male Sexual Health Questionnaire (MSHQ): scale development and psychometric validation. Urology. 2004;64:777–82.
17. Naughton MJ, Donovan J, Badia X, et al. Symptom severity and QOL scales for urinary incontinence. Gastroenterology. 2004;126:S114–23.
18. Costa P, Cardoso JM, Louro H, et al. Impact on sexual function of surgical treatment in rectal cancer. Int Brazil J Urol. 2018;44(1):141–9.
19. Keating JP. Sexual function after rectal excision. ANZ J Surg. 2004;74(4):248–59.
20. Haglind E. Self reported experience of sexual function and quality after abdominoperineal excision in a prospective cohort. Int J Surg. 2014;12(11):1221–7.
21. Ball M, Nelson CJ, Shuk E, et al. Men's experience with sexual dysfunction post rectal cancer treatment: a qualitative study. J Cancer Educ. 2013;28(3):494–502.
22. Chew MH, Yeh YT, Lim E, Seow-Choen F. Pelvic autonomic nerve preservation in radical rectal cancer surgery: changes in the past 3 decades. Gastroenterol Rep. 2016;4(3):173–85.
23. Attaallah W, Ertekin SC, Yegen C. Prospective study of sexual dysfunction after proctectomy for rectal cancer. Asian J Surg. 2018;41(5):454–61.
24. Attaallah W, Ertekin SC, Tinay I, Cumhur Y. High rate of sexual dysfunction following surgery for rectal cancer. Ann Coloproctol. 2014;30(5):210–5.
25. Chen JH, Ayscue JM, Bayasi M, et al. Quality of life after minimally invasive surgery for rectal cancer. Mini-invasive Surg. 2018;2:42.
26. Chan DKH, Chong CS, Lieske B, Tan KK. Laparoscopic resection for rectal cancer: what is the evidence? BioMed Res Int. 2014;2014:347810.
27. Incrocci L, Jensen PT. Pelvic radiotherapy and sexual function in men and women. J Sex Med. 2013;10(S1):53.
28. Krouwel EM, Elzevier HW, van der Wielen GJ, et al. Sexual concerns after (pelvic) radiotherapy: is there any role for the radiation oncologist? J Sex Med. 2015;12(9):1927–39.
29. Olsson C, Alsadius D, Pettersson N, et al. Patient-reports sexual toxicity after radiation therapy in long-term prostate cancer survivors. Br J Cancer. 2015;113:802–8.
30. Vomvas D, Iconomou G, Soubasi E, et al. Assessment of sexual function in patients with cancer undergoing radiotherapy – a single centre prospective study. Int J Cancer Res Treat. 2012;32(2):657–64.
31. Schover LR, van der Kaaij M, van Dorst E, et al. Sexual dysfunction and infertility as late effects of cancer treatment. EJC Suppl. 2014;12(1):41–53.
32. Allameh F, Azghandi S, Fallah KM. Is chemotherapy related with erectile dysfunction in non-urologic cancer patients? Int J Cancer Manag. 2018;11(9):e82529.
33. Schover LR. Counseling cancer patients about changes in sexual function. Oncology. 1999;13(11):1585.
34. Avasthi A, Grover S Sathyanarayana Rao TS. Clinical practice guidelines for management of sexual dysfunction. Indian J Psychiatry. 2017;59(suppl1):s91–S115.
35. Aghamir MK, Hosseini R, Alizadeh F. A vacuum device for penile elongation: fact or fiction? BJU Int. 2006;97(4):777–8.
36. Bearelly P, Phillips EA, Pan S, et al. Long-term intracavernosal injection therapy: treatment efficacy and patient satisfaction. Int J Impot Res. 2019;32:345.
37. Guay AT, Perez JB, et al. Clinical experience with intraurethral alprostadil (MUSE) in the treatment of men with erectile dysfunction. A retrospective study. Medicated urethral system for erection. Eur Urol. 2000;38(6):671–6.
38. Krzastek SC, Bopp J, et al. Recent advances in the understanding and management of erectile dysfunction. Version1, F1000Res 2019; 8:F1000 Faculty Rev-102 Published Onlines 2019 Jan 25.
39. Broderick GA. Oral pharmacotherapy and the contemporary evaluation and management of erectile dysfunction. Rev Urol. 2003;5(Suppl 7):S9–S20.
40. Dick B, Tsambarlis P, et al. An update on: long-term outcomes of penile prostheses for the treatment of erectile dysfunction. Expert Rev Med Devices. 2019;16(4):281–6.
41. Levine LA, Becher EF, Bella AJ, et al. Penile prosthesis surgery: current recommendations from the international consultation on sexual medicine. J Sex Med. 2016;13(4):489–158.

42. Moncada I, Martinez-Salamanca JI, et al. Current role of penile implants for erectile dysfunction. Curr Opin Urol. 2004;14(6):375–80.
43. Jefferys A, Siassakos D, Wardle P. The management of retrograde ejaculation: a systemic review and update. Fertil Steril. 2012;97(2):306–12.
44. Fitzpatrick JM, Kirby RS. Management of acute urinary retention. BJU Int. 2006;97(Suppl 2):16–22.
45. Herbenick D, Bowling J, Fu T-C, Dodge B, Guerra-Reyes L, Sanders S. Sexual diversity in the United States: results from a nationally representative probability sample of adult women and men. PLoS One. 2017;12(7):e0181198. https://doi.org/10.1371/journal.pone.0181198.
46. Simon Rosser BR, Capistrant B, Torres B, et al. The effects of radical prostatectomy on gay and bisexual men's mental health, sexual identity and relationships: qualitative results from the restore study. Sex Relation Ther. 2016;31(4):446–61.
47. Blank TO, Bellizzi K, Murphy K, Ryan K. How do men "make sense" of their prostate cancer?: age and treatment factors. The Gerontologist. 2003;43(1):342–3.
48. Eton DT, Lepore SJ. Prostate cancer and health-related quality of life: a review of the literature. Psycho-Oncology. 2002;11(4):307–26.
49. Gotay CC, Holup JL, Muraoka MY. Challenges of prostate cancer: a major men's health issue. Int J Mens Health. 2002;1:59–66.
50. Gray RE, Fitch MI, Fergus KD, Mykhalovskiy E. Hegemonic masculinity and the experience of prostate cancer: a narrative approach. J Aging Identity. 2002;7:43–62.
51. Chapple A, Zieband S. Prostate cancer: embodied experience and perceptions of masculinity. Soc Health Illness. 2002;24:820–41.
52. Fergus KD, Gray RE, Fitch MI. Sexual dysfunction and the preservation of manhood: experiences of men with prostate cancer. J Health Psychol. 2002;7(3):303–16.
53. Hartman ME, Irvine J, Currie KL, Ritvo P, Trachtenberg L, Louis A, Matthew AG. Exploring gay couples' experience with sexual dysfunction after radical prostatectomy: a qualitative study. J Sex Marital Ther. 2014;40(3):233–53.
54. Damon W, Simon Rosser BR. Anodyspareunia in men who have sex with men: prevalence, predictors, consequences and the development of DSM diagnostic criteria. J Sex Marital Ther. 2005;31(2):129–41.
55. Simon Rosser BR, Kohli N, Polter EJ, et al. The sexual functioning of gay and bisexual men following prostate cancer treatment: results from the restore study. Arch Sex Behav. 2019;49:1589.
56. Baxter N, Novotny P, Young-Fadok T. A stoma quality of life scale. Dis Colon Rectum. 2006;49:205–12.
57. Nugent K, Daniels P, Johnson C. Quality of life in stoma patients. Dis Colon Rectum. 1999;42:1569–74.
58. Sprangers MA, et al. Quality of life in colorectal cancer. Stoma vs nonstoma patients. Dis Colon Rectum. 1995;38:361.

Middle and Anterior Pelvic Compartment: Issues for the Colorectal Surgeon

65

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Key Concepts

- When considering pelvic organ prolapse, the pelvis is divided into anterior, middle, and posterior compartments. The anterior and middle compartments are typically more susceptible to pelvic organ prolapse.
- When considering surgical intervention, looking at the pelvis as a whole and considering all compartments is desired. Therefore a multidisciplinary approach offers the chance to coordinate testing and plan treatment.
- Urogynecologists use a designation called the Pelvic Organ Prolapse Quantification (POP-Q) exam to objectively describe and stage middle compartment prolapse.
- From the gynecology, urogynecology, or urology standpoint, addressing the middle and anterior compartments can be performed via transvaginal route when indicated. For posterior compartment surgeons, this may be combined with a perineal approach to rectal prolapse.
- An abdominal approach, either open, laparoscopic, or robotic, can combine surgeons with technical expertise from all three compartments and allow addressing all prolapse issues at the same operation.

Definition, Etiology, and Epidemiology

Female pelvic organs are classically described in three compartments: anterior, middle, and posterior. The anterior compartment contains the bladder and urethra, the middle compartment contains the uterus and vagina, and the posterior compartment contains the rectum and anus. Pelvic organ prolapse (POP) is an anatomical alteration in the pelvic support structures which results in the downward descent of any of the pelvic organs through the muscular pelvic floor [1]. Patients with POP describe their symptoms as a feeling of vaginal or perineal bulging or pressure most commonly experienced with standing, exercising, and straining which resolves when the activity is discontinued [1]. It is best understood by patients as the development of a pelvic floor hernia through which her pelvic organs are slipping. Since prolapse of the uterus and vagina is twice as common as other organs, the focus of POP is often on these structures [2]. It is important for the colorectal surgeon to recognize the proximity of the pelvic organs and the likelihood that more than one compartment can be affected in patients with POP.

The etiology of POP is multifactorial. It is likely that a combination of anatomic, physiologic, and lifestyle factors contributes over time to the development of POP. Established risk factors for primary POP exist and are listed in Table 65.1. Observational studies have found that increasing number of vaginal births (vaginal parity) was the strongest predictor for POP in women <60 years of age [3]. When compared to nulliparous women, women who delivered two children vaginally had an 8.4 relative risk for POP, and women who had delivered four or more children vaginally had a 10.9 relative risk for POP [4].

Table 65.1 Established risk factors for primary and recurrence pelvic organ prolapse

Primary POP	Recurrent POP
Vaginal parity	Age younger than 60 years at time or primary vaginal repair
Advancing age	Obesity
Obesity	Stage III or IV prolapse at initial presentation

Primary POP is defined as symptomatic POP with clinical evidence of prolapse beyond the introitus. Recurrent POP is defined as the need for surgery following primary repair

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Advancing age increases the risk for POP. Studies have suggested that the prevalence of POP increases by 40% with each decade of life with a peak age of 71–73 years [5]. A higher body mass index (BMI > 25 in most studies) was associated with a higher risk for POP [6]. It is not clear if having a hysterectomy for non-POP conditions increases the risk for POP. One cohort study suggested that undergoing a hysterectomy increased your cumulative risk for developing POP by 5% [7].

The published prevalence of POP in the USA varies from 3% to 50% depending upon the definition utilized [8]. However, it is commonly accepted that POP is a disorder seen more frequently in the older adult between the ages of 70 and 79 years. The lifetime risk of surgery in the USA for POP by the age of 80 years is 12.6% [9]. Given the aging US population, there may be a dramatic increase in health services required for POP. Wu et al. [9] predicted that by the year 2050, the number of women in the USA suffering from symptomatic POP will increase by a minimum of 46%. Others believe this is an overestimate because it does not take into account decreasing parity and increasing elective Cesarean section rates [8]. Already in the USA, POP surgery accounts for more than 300,000 surgical procedures per year, and ambulatory costs for visits for POP have increased by 40% from 1996 to 2005 [10]. The risk of recurrence following repair of POP is significant. Earlier studies prior to the year 2000 suggested that following a primary repair, women have a 30–50% risk of needing a second repair [4]. However, more recent studies suggest the risk of failure of primary repair requiring a second repair is lower, 6–30% [11, 12]. The improvement in outcomes may be the result of better surgical technique or the redefining of POP recurrence. In general, primary repairs are performed without mesh unless a sacrocolpopexy is performed so there is limited data on the use of mesh to lower the risk of recurrence. However, suspension of the vaginal apex, as is accomplished with a sacrocolpopexy, is associated with a decreased reoperation rate [13]. Established risk factors for recurrent prolapse requiring repeat repair are listed in Table 65.1 and include age younger than 60 years for those patients with a previous vaginal repair of POP, obesity, and undergoing a prior repair for higher-stage POP (III, IV; see below for staging). Other risk factors for primary or recurrent POP that have not been studied as well include chronic constipation, connective tissue disorder, menopause, smoking, hormone replacement therapy, physical activity, family history, ethnicity, pulmonary disease, diabetes, education, and pelvic floor defects imaged on ultrasound or MRI [14].

Evaluation of the Anterior and Middle Compartments

Evaluation of the patient with POP is driven by the presenting symptoms. The most common symptom that patients complain of is a bulging or pressure feeling within the vagina. Other common symptoms are listed in Table 65.2. Urinary symptoms are often associated with POP. These can include urinary frequency, urgency, and incontinence with activities such as coughing, laughing, or sneezing (stress incontinence). Patients may also have a feeling of incomplete emptying or find it more difficult to initiate voiding and describe pushing on the bladder *splinting* to aid in voiding. Bowel function should be assessed as well since patients may have a history of straining, splinting to complete defecation, or experience fecal incontinence. Finally, it is important to address issues of sexual dysfunction including dyspareunia. There are many validated tools available to examine these symptoms and their impact on quality of life. Some of the common assessment tools used by urogynecologists include Pelvic Floor Distress Inventory (PFDI), Pelvic Floor Impact Questionnaire (PFIQ), and Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ). The PFDI is a 20-question validated questionnaire that addresses prolapse and anal and urinary distress symptoms [15]. The PFIQ is a 7-question validated survey that assesses life impact in women with pelvic floor disorders [15]. The PISQ is a 12-question validated survey which has been shown to measure sexual function in women with pelvic floor disorders [16].

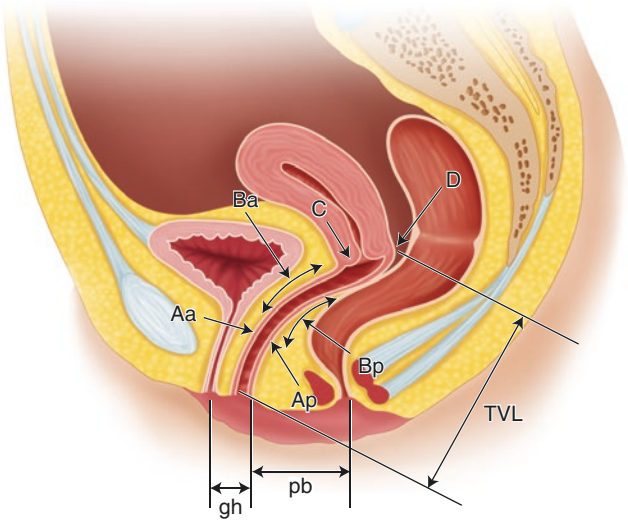
The examination of the pelvic floor can be performed in either the left lateral, standing, or lithotomy position. Findings are more consistent if the bladder and rectum are empty. If a patient has a pessary or a tampon in, these should be removed. A routine pelvic exam as well as a rectal exam should be performed at rest and with strain. To assess for defects within the muscular floor of the pelvis, the levators can be palpated through the rectum or vagina. If the full

Table 65.2 Symptoms associated with pelvic organ prolapse

Pelvic organ function	Symptoms
Sexual function	Bulging, heaviness, pressure, pain, decreased pleasure, decreased body image
Urination	Leaking, urgency, frequency, weak stream, feeling of incomplete emptying, splinting, positional voiding, pain
Defecation	Stool or flatus leakage, feeling of incomplete evacuation, straining, urgency, splinting or digitizing to evacuate, pain

extent of the prolapse is not seen on exam in lithotomy, it can be repeated in standing position with Valsalva. For the best demonstration of POP, give time for the prolapse to protrude, and consider repositioning the patient and asking the patient if they believe the maximum extent of the prolapse is felt or seen.

Urogynecologists use the Pelvic Organ Prolapse Quantification (POP-Q) exam to objectively describe and stage POP (Fig. 65.1). The POP-Q exam measures the opening of the vagina (genital hiatus, GH), the perineal body (PB), the total vaginal length (TVL), and each compartment of the vagina (anterior, apical, posterior). It is important to note that all measurements are all taken during Valsalva, except for the total vaginal length. The anterior and posterior walls and uterus (or vaginal cuff if prior hysterectomy) are measured in relation to the hymenal ring. Point A is located 3 centimeters proximal from the hymenal ring on the anterior and posterior vaginal wall. On the anterior wall, this location correlates to the bladder neck (Aa). Point B is the most distal point of the anterior and posterior vaginal wall with Valsalva between the A point and the vaginal apex. The A and B points can be negative (if inside the hymen) or positive (if outside the hymen). The C point represents the cervix (or vaginal cuff if prior hysterectomy), and the D point is the posterior vaginal fornix (only present if a cervix is present). Each compartment of the vagina is then given a stage based on the measurement. An overall stage is also assigned correlating to the highest degree of prolapse from any compartment. The stages are as follows: Stage 0 (Aa, Ba, Ap, Bp all = −3 and C or D ≤ (TVL-2)), Stage 1 (Stage 0 criteria not met and leading edge <−1), Stage 2 (leading edge ≥ −1 but ≤ +1), Stage 3 (leading edge > +1 but < (TVL −2)), and Stage 4 (leading edge ≥ + (TVL-2)) (Fig. 65.2). The American Urogynecologic Society website provides a free interactive and downloadable app that can be used to educate patients about exam findings [17].



Anterior wall Aa	Anterior wall Ba	Cervix or cuff C
Genital hiatus gh	Perineal body pb	Total vaginal length TVL
Posterior wall Ap	Posterior wall Bp	Posterior fornix D

Fig. 65.1 The POP-Q examination with staging

In general, a complete history and physical exam is sufficient to determine an operative plan for anterior and middle compartment prolapse. Other investigations can be performed if the findings on physical exam do not concur with the patient's symptoms and include ultrasound imaging of the pelvic floor, dynamic magnetic resonance imaging (MRI), or cinedefecography. The most common indication for further work-up is a patient's history of urinary symptoms. Patients are referred for urodynamics should they have symptoms or urinary leakage, frequency, or difficulty with voiding. Urodynamics is a functional study of the lower urinary tract and is performed with a comfortably full bladder to determine uroflowmetry and post-voiding residuals. Common findings during urodynamics are seen in Table 65.3. Office-based ultrasound imaging is commonly performed at the time of urodynamics to confirm post-void residual volumes and evaluate levator ani function. Finally, MRI and cinedefecography images the rectum during evacuation and can assess for the presence of intussusception, rectocele, and enterocele. MRI defecography allows for detection of ligamentous and muscular pelvic floor structures as well as providing a good assessment of the anterior compartment and confirmation of POP-Q findings.

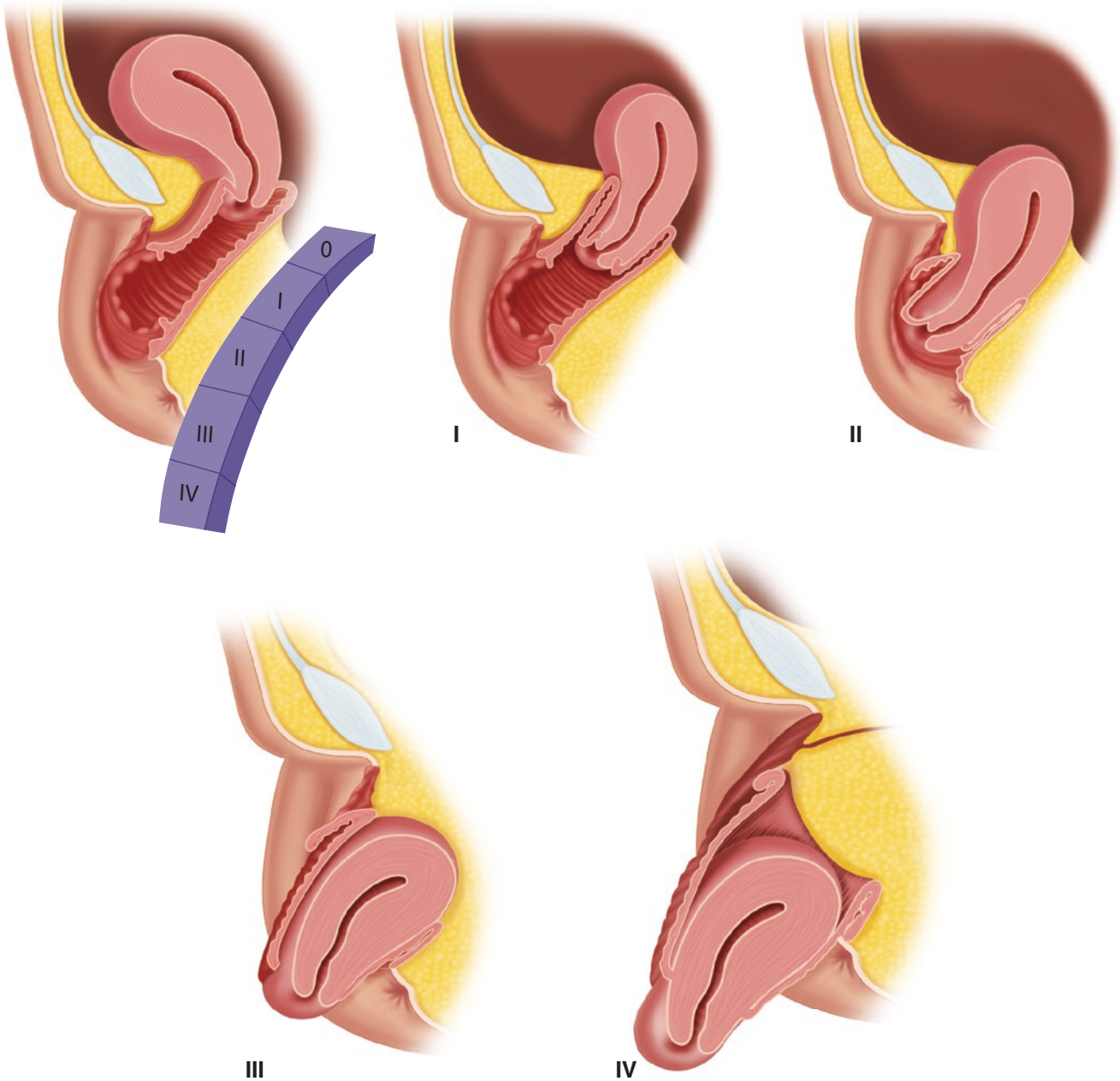


Fig. 65.2 Pelvic organ prolapse staging

Indications and Outcomes for Common Nonoperative and Operative Approaches for Anterior and Middle Compartment Prolapse

Asymptomatic patients with POP should be educated about symptoms associated with POP and be reassured about treatment options. Nonoperative options for symptomatic patients are limited. However, many symptoms related to POP can be managed initially with lifestyle modifications. The sensation of bulging may improve, or the progression of prolapse slowed by performing pelvic floor strengthening exercise either alone or with a trained professional therapist. However, pelvic floor retraining has not been shown to prevent the need for corrective surgery in patients with symptomatic POP [18]. There is limited evidence to suggest that local or systemic estrogens may also help prevent progression of POP [19]. Finally, a pessary can be offered

as an alternative to a surgical repair. A pessary can be fitted well into the vagina and is an effective, short-term, low-risk option for up to 90% of women [20]. A pessary is generally used for Stage II through IV prolapse; however, it is less successful in Stages III and IV [20]. It is best if patients can maintain their own pessary hygiene by removing, cleaning, and replacing the pessary every 3 months. Up to 9% of patients can experience a mild ulceration of the vaginal wall secondary to the pessary [20]. Resolution of the tissue injury occurs with local estrogen therapy.

Table 65.3 Common findings on urodynamics with uroflowmetry and assessment of post-void residual

Diagnosis	Findings on urodynamics
Incomplete bladder emptying	Large post-void residual
Stress incontinence	Involuntary leakage of urine with increased intra-abdominal pressure and no detrusor contraction
Increased bladder sensation	Increased perceived bladder filling with an early desire to void at a low volume with no abnormal increase in detrusor pressure
Detrusor overactivity	Involuntary detrusor contractions during bladder filing
Detrusor underactivity	Poor detrusor contractions during voiding

Operative interventions for POP are reserved for Stage II–IV symptomatic patients. It is imperative that the patient's symptoms match their clinical findings if an operation is to be performed. The goal of any operation related to POP is to restore normal anatomy. Operative indications, techniques, and outcomes are listed in Table 65.4. There is a lack of consensus which approach is best for identified anatomical defects, and the risks and benefits of each approach should be considered carefully with the patient. The first decision that must be made is whether an obliterative or reconstructive approach should be taken. In older women who are no longer sexually active, an obliterative surgery (colpocleisis) can be successfully performed. In the presence of a uterus, a Le Fort partial colpocleisis can be performed by denuding a strip of epithelium from the anterior and posterior vaginal walls and suturing them together. This approach allows for the drainage of secretions from the cervix. A pap smear should be performed and found to be normal prior to this procedure. In the absence of a uterus, a colpectomy or tight

Table 65.4 Operative indications, techniques, and outcomes for anterior and middle compartment pelvic organ prolapse surgery

Indication	Surgical technique	Outcomes
Apical uterine prolapse (Grades II–IV)		
1. Shortened vaginal length, intra-abdominal pathology, high risk for recurrence, young age	1. Supracervical or total hysterectomy + abdominal sacral colpopexy	1. Recurrence rates of 7% (synthetic mesh) vs. 38% (cadaveric fascia) at 5 years [51]
2. Poorer surgical candidate, does not want mesh in prolapse repair	2. Vaginal hysterectomy + uterosacral ligament suspension	2. 35% recurrence rate at 2 years [48]
3. Poorer surgical candidate, does not want mesh in prolapse repair	3. Vaginal hysterectomy + sacrospinous fixation	3. 36% recurrence rate at 2 years [48]
4. Desire uterine preservation	4. Abdominal sacro-hysteropexy	4. No benefit of uterine preservation with prolapse repair [49]
5. Elderly, poorer surgical candidate, not sexually active	5. Le Fort colpocleisis +/− midurethral sling	5. High patient satisfaction, low recurrence rate [50]
Apical vaginal prolapse (Grades II–IV)		
1. Shortened vaginal length, intra-abdominal pathology, high risk for recurrence	1. Abdominal sacral colpopexy	1. Recurrence rates of 7% (synthetic mesh) vs. 38% (cadaveric fascia) at 5 years [51]
2. Poorer surgical candidate, does not want mesh in prolapse repair	2. Uterosacral ligament suspension	2. 35% recurrence rate at 2 years [48]
3. Poorer surgical candidate, does not want mesh in prolapse repair	3. Sacrospinous fixation	3. 36% recurrence rate at 2 years [48]
4. Elderly, poorer surgical candidate, not sexually active	4. Colpocleisis +/− midurethral sling	4. High patient satisfaction, low recurrence rate [21]
Anterior vaginal wall prolapse (cystocele)	Anterior colporrhaphy with native tissue vs. mesh	40–60% success in RCT, improved durability with mesh but 10% erosion rate [52]
Posterior vaginal wall prolapse (rectocele)	Posterior colporrhaphy and perineorrhaphy	80–95% success rate, no improvement with mesh repair [53]
POP and stress urinary incontinence	Sacrocolpopexy and retropubic midurethral sling Midurethral sling +/− anterior colporrhaphy	50% reduction in the risk of postoperative stress urinary incontinence [54] 80% mid- and long-term success rates [23]

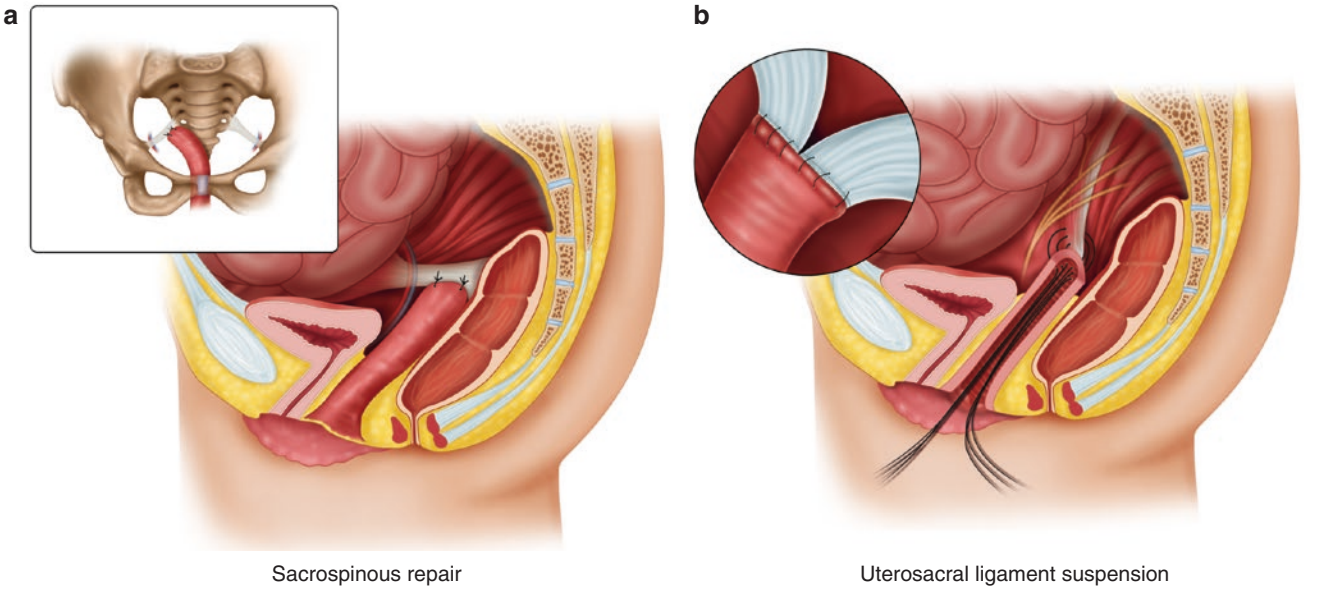


Fig. 65.3 Sacrospinous ligament fixation (**a**) and uterosacral ligament suspension (**b**)

anterior and posterior colporrhaphy can be performed. The operation is performed by completely excising the vaginal mucosa from the urethrovesical junction to the vaginal apex. The prolapse is then reduced with sequential interrupted sutures until the prolapse is above the levator plate. A wide perineorrhaphy is then performed to incorporate the levator muscles and reduce the genital hiatus to 1–2 cm in size. It may be necessary to address urinary symptoms at the time of colpocleisis as this is a common cause for poor quality of life postoperatively [21].

If reconstructive surgery is planned, the second decision which must be made is whether a transvaginal or transabdominal approach is best. Most urogynecologists approach women who are ≥80 years with a transvaginal approach as studies have shown that this approach is associated with a low incidence of serious postoperative adverse events [22]. The most common postoperative complication following the vaginal approach is a urinary tract infection. The third decision that must be made is what defects should be repaired concurrently. Anterior vaginal wall prolapse is often associated with apical prolapse and stress urinary incontinence, and concomitant repair should be considered as this may improve outcomes for findings of more severe prolapse.

Transvaginal reconstruction of POP includes apical vaginal suspensions with either sacrospinous ligament fixation (SSLF) or uterosacral ligament suspension (USLS), anterior colporrhaphy, and posterior colporrhaphy (Fig. 65.3). Vaginal vault apical suspension can be performed either at the time of vaginal hysterectomy or in patients with post-hysterectomy vault prolapse. SSLF and USLS can be performed only if there is adequate vaginal length. The sacrospinous ligament can be palpated through the wall of the vagina tracking from the ischial spine posteriorly, as a thick cord, toward the sacrum (Fig. 65.3a). To begin, the vagina is everted and opened, and any enterocele, the bladder, and the rectum are mobilized to prevent injury. The sacrospinous ligament is identified on one side and attached to the full thickness of the fibromuscular layer of the undersurface of the vaginal apex. The peritoneum is not entered in a sacrospinous ligament fixation so this procedure may be preferred in women with suspected pelvic adhesions. A USLS is performed in a similar fashion; however, instead the vagina is attached to the uterosacral ligaments intraperitoneally (Fig. 65.3b). These ligaments can be found posterior and medial to the ischial spine. The uterosacral ligaments can be joined in the midline to increase the strength of the repair. A USLS is most commonly performed in conjunction with a vaginal hysterectomy, although the hysterectomy can also be performed laparoscopically.

The objective of an anterior colporrhaphy is to plicate the layers of the muscular wall of the vagina and the paravaginal tissue to reduce the protrusion of the bladder into the vagina. While grasping the vagina with well-placed Allis clamps, a transverse incision is made from the urethrovesical junction to the apex of the vagina. The bladder is mobilized, and then plication sutures are placed to reduce the cystocele. Excess vaginal epithelium is then trimmed and the vaginal incision is closed. During a posterior colporrhaphy to treat a rectocele, the posterior vaginal wall is incised in the midline, and the perirectal fascia is mobilized laterally as far as possible. Small defects in the rectovaginal fascia are repaired with vertical mattress sutures. For larger defects, the puborectalis muscles are plicated. Care must be taken to not plicate too much tissue or the vaginal lumen may be narrowed.

Stress urinary incontinence (SUI) is commonly associated with anterior vaginal wall prolapse and should be initially managed with conservative therapies. These therapies include pelvic floor physical therapy directed at returning strength and muscle tone to the pelvic floor. Another nonsurgical option for SUI is an incontinence pessary. If patients have overactive bladder associated with SUI, physical therapy and behavior modifications are the first-line treatment. Antimuscarinic therapy can be tried if these conservative measures fail. The most effective surgical approach to stress urinary incontinence is midurethral slings. These procedures were first introduced in the 1990s. The slings have been made of autologous tissue or polypropylene mesh. The repair is associated with a very low risk of mesh infection (2%) and mesh repair has a lower rate of failure [23]. The two most current techniques are placement of mesh through a retropubic or trans-obturator approach. In the retropubic approach, mesh is passed through a small vaginal incision and through the retropubic space hugging the pubic bone and exits the abdominal wall in the suprapubic location. In the trans-obturator approach, mesh is passed through a small vaginal incision into the obturator foramen to exit lateral to the labia majora. Both repairs have good long-term subjective and objective success rates that approach 80% [23].

The most common abdominal approach to POP is the sacrocolpopexy (Fig. 65.4). Women who are best candidates for this procedure include those with a shortened vaginal length, intra-abdominal pathology, or risk factors for recurrent POP (age < 60 years, Stage III–IV prolapse, and BMI > 26 kg/m^2) [24–26]. This procedure can be performed laparoscopically or robotically safely and effectively [27, 28]. If a sacrocolpopexy is to be performed, hysterectomy is usually recommended if the uterus is still present. Alternatively, a hysteropexy can be performed in a similar fashion as sacrocolpopexy. Supracervical hysterectomy is generally performed because securing the mesh to the cervical tissue provides a more durable hold and avoids a vaginal incision. A vaginal incision increases the risk of postoperative mesh exposure in the vagina. Once the hysterectomy is complete, the bladder and rectum are dissected off of the vaginal apex, and the mesh is sutured to both the anterior and posterior cervix and vaginal wall. This mesh is then attached to the longitudinal ligament of the sacrum just below the sacral promontory. The best results have been achieved by using synthetic polypropylene mesh [11].

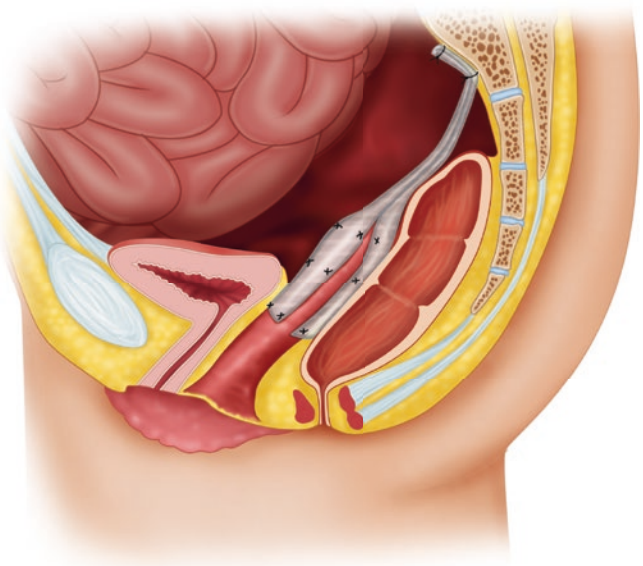


Fig. 65.4 Placement of mesh for sacrocolpopexy

The use of mesh for POP has greatly declined. After the FDA issued a warning in 2008 and in 2011, mesh is no longer placed vaginally during an anterior or posterior repair. However, mesh is used routinely for apical support only during a sacrocolpopexy or hysteropexy. The Colpopexy and Urinary Reduction Efforts (CARE) trial demonstrated that the use of mesh in intra-abdominal procedures was associated with an overall mesh erosion rate of 10.5% [11]. As a result of this finding, it is recommended that large-pore polypropylene mesh be used for performing a sacrocolpopexy as this mesh has the lowest rate of mesh infection among the participants in the CARE trial [11]. In addition, Chughtai et al. demonstrated that placing vaginal mesh for both a sacrocolpopexy and for a midurethral sling had the highest rate for mesh infection (OR 2.13, 95%CI: 1.76–2.56) [29]. The authors suggested a dose-response relationship with the use of mesh. However, D'Hoore et al. demonstrated similar findings of increased rate of mesh infection when a ventral rectopexy with mesh was performed with a posterior colporrhaphy using mesh. He attributed this increased rate of infection to the creation of a vaginal wound resulting in mesh exposure [30].

Multidisciplinary Approach to Pelvic Floor Prolapse

While surgery is indicated for patients with Stage II POP or greater who are symptomatic and who have failed conservative therapy, there is no consensus about which surgical approach is superior. Anatomic failure rate can be as high as 25% [11]. Of those that undergo surgery, 13% will require a repeat operation in 5 years, and 30% may need repeat surgery for POP in their lifetime [31, 32]. Large-scale, community-based research regarding POP failures is lacking, and the follow-up in many trials is only 1–2 years. Failure rates for vaginal and native tissue repairs are higher than those for mesh sacrocolpopexy, and many recurrences are attributed to the posterior compartment. A recent study showed an 82% symptomatic improvement after laparo-

scopic sacrocolpopexy [33]. Of those patients not improved, two thirds had mid vaginal recurrent prolapse, and one third had urinary and bowel dysfunction. Of the patients that were physically examined, 28% had posterior anatomic failure. In a randomized study comparing three different rectocele repairs, 21–51% of patients continued to have symptoms of straining, incomplete evacuation, or defecatory dysfunction despite overall symptom improvement [34].

It is important to review the anatomical relationships of organs in the posterior pelvis to understand how best to manage POP in a multidisciplinary approach. The most distal support of the vaginal wall is provided by the perineum, the lower rectovaginal septum, and the levator ani. The mid vagina is supported laterally to the fascia of the levator ani muscles. The upper vagina is supported by the cardinal-uterosacral ligament complex [35]. The rectum is a retroperitoneal structure which has a short mesorectum and begins at the sacral promontory. The mesorectum allows the rectum to pull away from the sacrum during defecation and notably is elongated in patients with significant intussusception and prolapse. The lateral ligaments are located on the posterior lateral sides of the rectum close to the coccyx. These lateral ligaments are connective tissue structures containing nerves and the middle rectal artery and support the lower rectum above the levator ani. The most distal support of the rectum is provided by the levator ani, the internal and external anal sphincters, and the perineum. The anterior low rectal wall and the mid vaginal wall are typically fused, and continued excessive pressure from the rectal side can cause bulging of the rectal wall into the mid vagina creating a rectocele. There is an interdependence of load-bearing structures of pelvic support (levator ani muscles, connective tissue, nerves) which can affect all of the pelvic compartments to varying degrees.

Addressing symptoms of posterior vaginal wall prolapse with a more thorough initial evaluation and management of constipation and obstructive defecation may help to improve outcomes after surgical management of pelvic organ prolapse. Bulging, pelvic pressure, vaginal splinting, obstructive defecation syndrome, dyssynergic defecation, tenesmus, and rectal bleeding are common patient complaints and have all been described to occur with posterior compartment defects. Other than splinting and stool trapping, many of these symptoms do not correlate with physical findings or the POP-Q exam. A wide genital hiatus and/or perineal defect is often found in patients with posterior vaginal prolapse and can occur with rectal intussusception, posterior enteroceles, and sigmoidoceles. Symptoms from intussusception and enteroceles are nonspecific and cannot be explained by physical examination alone. Internal rectal prolapse (intussusception) may simulate rectocele or enterocele and result in obstructive defecation [36]. These entities can also occur in isolation or in conjunction with each other. Dynamic studies (dynamic MR or cinedefecography) should be obtained when the patient complaints do not agree with the findings on physical examination. Defecography (dynamic MR or cinedefecography) may identify occult pelvic floor issues (e.g., significant rectal intussusception) which can progress after a single-compartment approach. Currently, there are no studies that address how intussusception and enteroceles coexist and how their presence impacts surgical outcome.

The condition of posterior prolapse (rectocele, internal intussusception, and full rectal prolapse) has historically been treated as a separate entity from middle and anterior prolapse despite similar etiological factors. This type of compartmentalization may lead to suboptimal outcomes, worsening of prolapse in the other compartment, and defecatory dysfunction. Whether significant symptomatic rectoceles occur in isolation is a matter of debate and requires further studies. Barium trapping and rectocele size have not been shown to reliably correlate with patient symptoms and should not be used as criterion for surgery in patients with constipation and rectoceles [37, 38]. There is also no correlation between posterior vaginal wall prolapse, constipation, and measurements of anorectal function [39]. Rectoceles may be the result of obstructive defecation rather than the cause [40]. Initial management of rectoceles and ODS with biofeedback prior to surgery can show a 71% response rate [41]. Correcting the rectocele bulge does little to relieve symptoms of constipation and intussusception. If straining at stool is allowed to continue in the postoperative period, pressure on the anatomic repair may result in recurrence of prolapse.

A multidisciplinary approach with urogynecologists working with colorectal surgeons allows for evaluation of all three compartments and a more thorough preoperative assessment. Several reports have suggested that a multidisciplinary surgical approach may improve surgical outcomes for patients with POP [28, 42]. The sutured rectopexy and mesh rectopexy help to elevate the mid and low rectum out of the deep pelvis treating the internal rectal prolapse that is frequently found in conjunction with rectoceles and help to eliminate symptoms of obstructive defecation. A combined sacrocolpopexy and rectopexy for mid and posterior prolapse has been reported to be safe with a low risk of recurrence improving bowel function (constipation and fecal incontinence) and quality of life for most women with pelvic organ prolapse and rectal prolapse [43]. Early reports suggested that combined surgery would improve patient satisfaction and be cost saving by utilizing a single surgery for management of a complex problem [44]. The addition of a rectopexy (sutured or ventral mesh rectopexy) does not add significant morbidity or mortality or time to the sacrocolpopexy [28, 42].

The approach to combined operations can be open, laparoscopic, or robotic and is based upon the surgeon's preference. The order of the procedures depends on the surgeons' choice and experience. If a uterus is still present, a supracervical hysterectomy is generally performed first. The urogynecologist will typically do the hysterectomy, perform the anterior vesicovaginal dissection, and begin the posterior dissection along the cervix and posterior vagina. The sacral dissection starts with the identification of the sacral promontory, the common iliac artery/vein, and the right ureter. The middle sacral artery originates from the aorta and is a midline structure seen on top of the anterior longitudinal ligament. The colorectal surgeon opens and dissects the rectovaginal space down toward the pelvic floor. The lateral stalks to the rectum are preserved to minimize postoperative constipation symptoms. A ventral rectopexy is performed with polypropylene mesh sutured to the anterior rectum or the perineum. Some authors have advocated the use of biologic mesh to avoid the risk of mesh erosion [45]. This mesh is then sutured to the sacral promontory along with the sacrocolpopexy mesh. A sutured rectopexy may be as effective as a mesh rectopexy in this situation and is done with permanent suture placed through the lateral ligaments of the rectum and sutured below the sacral promontory stitches [46]. The mesh is covered by the peritoneum at the end of the case, and cystoscopy is frequently performed to ensure that there has not been injury to either ureter during dissection and closure. Evaluation of the anterior and posterior vaginal prolapse is done by the urogynecologist, and the decision for a posterior repair or perineorrhaphy is made at the end of the case. Oftentimes, there is no need for a formal posterior repair once the upper vagina and the mid and low rectum are supported. Although not commonly done, resection rectopexy combined with sacrocolpopexy is reported to be safe, but some have reported a higher complication rate [47]. Avoidance of constipation and straining in the postoperative period is recommended, and the use of stool softeners and laxatives is encouraged.

Conclusion

The three compartments of the pelvis are intertwined. Knowledge of anatomy and physiology aids in taking care of this patient population. A multidisciplinary approach should be considered if the history and physical point to multicompartment problems. Evaluation and treatment planning may also involve a team effort. Surgery on all compartments at the same setting requires coordination and patience but can be in the patients' best interest.

References

1. Haylen B, Maher C, Barber M, et al. Erratum to: An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic organ prolapsed (POP). Int Urogynecolo J. 2016;27:655–84.
2. Swift SE, Tate SB, Nicholas J. Correlation of symptoms with degree of pelvic organ support in a general population of women: what is pelvic organ prolapse? Am J Obstet Gynecol. 2003;189:372–7.
3. The American College of Obstetricians and Gynecologists and the American Urogynecologic Society. Pelvic organ prolapse. Female Pelvic Med Reconstr Surg. 2019;25:397–405.
4. Mant J, Painter R, Vessey M. Epidemiology of genital prolapse: observations from the Oxford family planning association study. Br J Obstet Gynaecol. 1997;107:579–85.
5. Luber KM, Boero S, Choe JY. The demographics of pelvic floor disorders: current observations and future projections. Am J Obstet Gynecol. 2001;184:1496–501.
6. Swift S, Woodman P, O'Boyle A, Kahn M, Valley M, Bland D, Wang W, Schaffer J. Pelvic Organ Support Study (POSST): the distribution, clinical definition, and epidemiologic condition of pelvic organ support defects. Am J Obstet Gyecol. 2005;192(3):795–806.
7. Aigmueller T, Dungl A, Hinterholzer S, Geiss I, Riss P. An estimate of the frequency of surgery for posthysterectomy vault prolapse. Int Urogynecol J. 2010;21:299–302.
8. Barber M, Maher C. Epidemiology and outcome assessment of pelvic organ prolapsed. Int Urogynecol. 2013;24:1783–90.
9. Wu JM, Mathews CA, Conover MM, et al. Lifetime risk of stress incontinence or pelvic organ prolapse surgery. Obstet Gynecol. 2014;123(6):1201–6.
10. Shah AD, Kohli N, Rajan SS, Hoyte L. The age distribution, rates, and types of surgery for POP in the USA. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19:421–8.
11. Nygaard I, Brubaker L, Zyczynski HM, et al. Long-term outcomes following abdominal sacrocolpopexy for pelvic organ prolapse. JAMA. 2013;309:2016–24.
12. Larson KA, Smith T, Berger MB, et al. Long-term patient satisfaction with Michigan four-wall sacrospinous ligament suspension for prolapse. Obstet Gynedol. 2013;122:967–75.
13. Eilber KS, Aplerin M, Khan A, et al. Outcomes of vaginal prolapse surgery among female Medicare beneficiaries: the role of apical support. Obstet Gynecol. 2013;122:981–7.
14. Vergeldt T, Weemhoff M, IntHout J, Kluivers K. Risk factors for pelvic organ prolapse and its recurrence: a systematic review. Int Urogynecol J. 2015;26:1559–73.
15. Barber M, Walters M, Bump RC. Short forms of two condition-specific quality of life questionnaires for women with pelvic floor disorders (PFDI-20 and PFIQ-7). Am J Obstet Gynecol. 2005;193:103–13.
16. Rogers R, Coates K, Kammerer-Doak D, Khalsa S, Qualls C. A short form of the pelvic organ prolapse/urinary incontinence sexual questionnaire (PISQ-12). Int Urogyencology J. 2003;14:164–8.
17. https://www.augs.org/patient-services/pop-q-tool/
18. Hagen S, Stark D, Glazener C, et al. POPPY Trial Collaborators. Individualized pelvic floor muscle training in women with pelvic organ prolapse (POPPY): a multicenter randomized controlled trail. Lancet. 2014;383:796–806.
19. Ismail SI, Bain C, Hagen S. Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women (systematic review). Cochrane Database Syst Rev. 2010;(9):CD007063.
20. Cundiff GW, Smundsen CL, Bent AE, et al. The PESSRI study: symptoms relief outcomes of a randomized crossover trial of the ring and Gellhorn pessaries. Am J Obstet Gynecol. 2007;196:405.

21. von Pechmann WS, Mutone M, Fyffe J, et al. Total colpocleisis with high levator plication for the treatment of advanced pelvic organ prolapse. Am J Obstet Gynecol. 2003;189:121–6.
22. Unger C, Hickman L, Bitchell-Handley B, Barber M, Ridgeway B. The incidence of perioperative adverse events in the very elderly undergoing urogynecological surgery. Female Pelvic Med Reconstr Surg. 2016;22:425–9.
23. Tommaselli GA, Di Carlo C, Formisano C, Fabozzi A, Nappi C. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanlysis. Int Urogynecol J. 2015;26:1253–68.
24. Whiteside JL, Weber AM, Meyn LA, et al. Risk factors for prolapse recurrence after vaginal repair. Am J Obstet Gynecol. 2004;191:1533–8.
25. Nieminen K, Huhtala H, Heinonen PK. Anatomic and functional assessment and risk factors of recurrent prolapse after vaginal sacrospinous fixation. Act Obstet Gynecol Scand. 2003;82:471–8.
26. Diez-Itz I, Aizpitarte I, Becerroa A. Risk factors for the recurrence of pelvic organ prolapse after vaginal surgery: a review at 5 years after surgery. Int Urogynecol J Pelvic Floor Dysfunct. 2007;18:1317–24.
27. Freeman RM, Pantazis K, Thomson A, et al. A randomized controlled trial of abdominal versus laparoscopic sacrocolpopexy for the treatment of post-hysterectomy vaginal vault prolapse. LAS study. Int Urogynecol J. 2013;24:377–84.
28. Jallad K, Ridgeway B, Paraiso MFR, Gurland B, Unger CA. Long-term outcomes after ventral Rectopexy with Sacrocolpo- or Hysteropexy for the treatment of concurrent rectal and pelvic organ prolapse. Female Pelvic Med Reconstr Surg. 2018;24(5):336–40.
29. Chughtai B, Barber M, Mao J, Forde J, Normand S, Sedrakyan A. Association between the amount of vaginal mesh used with mesh erosion and repeated surgery after repairing pelvic organ prolapse and stress urinary incontinence. JAMA Surg. 2017;152:257–63.
30. DHoore A, Cadoni R, Penninckx F. Long-term outcomes of laparoscopic ventral rectopexy for total rectal prolapse. Br J Surg. 2004;91(11):1500–5.
31. Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol. 1997;89(4):501–6.
32. Clark AL, Gregory T, Smith VJ, Edwards R. Epidemiologic evaluation of reoperation for surgically treated pelvic organ prolapse and urinary incontinence. Am J Obstet Gynecol. 2003;189(5):1261–7.
33. Pacquée S, Nawapun K, Claerhout F, Werbrouck E, Veldman J, D'hoore A, Wyndaele J, Verguts J, De Ridder D, Deprest J. Long-term assessment of a prospective cohort of patients undergoing laparoscopic sacrocolpopexy. Obstet Gynecol. 2019;134(2):323–32.
34. Paraiso MF, Barber MD, Muir TW, Walters MD. Rectocele repair: a randomized trial of three surgical techniques including graft augmentation. Am J Obstet Gynecol. 2006;195:1762–71.
35. DeLancey JO. Structural anatomy of the posterior pelvic compartment as it relates to rectocele. Am J Obstet Gynecol. 1999;180:815–23.
36. Peters WA 3rd, Smith MR, Drescher CW. Rectal prolapse in women with other defects of pelvic floor support. Am J Obstet Gynecol. 2001;184(7):1488–94. discussion 1494–5
37. Halligan S, Bartram CI. Is barium trapping in rectoceles significant? Dis Colon Rectum. 1995;38:764–8.
38. Carter D, Gabel MB. Rectocele—does the size matter? Int J Colorect Dis. 2012;27:975–80.
39. da Silva GM, Gurland B, Sleemi A, Levy G. Posterior vaginal wall prolapse does not correlate with fecal symptoms or objective measures of anorectal function. Am J Obstet Gynecol. 2006;195:1742–7.
40. Hicks CW, Weinstein M, Wakamatsu M, Pulliam S, Savitt L, Bordeianou L. Are rectoceles the cause or the result of obstructed defaecation syndrome? A prospective anorectal physiology study. Colorect Dis. 2013;15:993–9.
41. Hicks CW, Weinstein M, Wakamatsu M, Savitt L, Pulliam S, Bordeianou L. In patients with rectoceles and obstructed defecation syndrome, surgery should be the option of last resort. Surgery. 2014;155:659–67.
42. Campagna G, Panico G, Caramazza D, Gallucci V, Pizzacalla S, Ercoli A, Cambia G. Laparoscopic sacrocolpopexy plus ventral rectopexy for multicompartment pelvic organ prolapse. Tech Coloproctol. 2019;23:179–81.
43. Watadani Y, Vogler SA, Warshaw JS, Sueda T, Lowry AC, Madoff RD, Mellgren A. Sacrocolpopexy with rectopexy for pelvic floor prolapse improves bowel function and quality of life. Dis Colon Rectum. 2013;56(12):1415–22.
44. Kapoor DS, Sultan AH, Thakar R, Abulafi MA, Swift RI, Ness W. Management of complex pelvic floor disorders in a multidisciplinary pelvic floor clinic. Color Dis. 2008;10(2):118–23.
45. Smart NJ, Pathak S, Boorman P, Daniels IR. Synthetic or biological mesh use in laparoscopic ventral mesh rectopexy—a systematic review. Colorect Dis. 2013;15:650–4.
46. Oom DM, Gosselink MP, van Wijk JJ, van Dijl VR, Schouten WR. Rectocele repair by anterolateral rectopexy: long-term functional outcome. Colorect Dis 2008;10:925–930.
47. VanderPas Lamb S, Massengill J, Sheridan MJ, Stern LE, von Pechmann W. Safety of combined abdominal sacral colpopexy and sigmoid resection with suture rectopexy: a retrospective cohort study. Female Pelvic Med Reconstr Surg. 2015;21(1):18–24.
48. Barber MD, Brubaker L, Burgio KL, et al. Eunice Kennedy Shriver National Institute of Child Health and Human Development Pelvic Floor Disorders Network. Comparison of 2 transvaginal surgical approaches and perioperative behavioral therapy for apical vaginal prolapse: the OPTIMAL randomized trial. JAMA. 2015;313:2287. (corrections) JAMA 2014;311:1023–1034.
49. Meriwether KV, Balk EM, Antosh DD, et al. Uterine-preserving surgeries for the repair of pelvic organ prolapse: a systematic review with meta-analysis and clinical practice guidelines. Int Urogynecol J. 2019;30(4):505–22.
50. Wang X, Chen Y, Hua K. Pelvic symptoms, body image, and regret after LeFort Colpocleisis: a long-term follow-up. J Minim Invasive Gynecol. 2017;23(3):415–9.
51. Tate SB, Blackwell L, Lorenz DJ, et al. Randomized trial of fascia lata and polypropylene mesh for abdominal sacrocolpopexy: 5 year follow up. Int Urogynecol J. 2011;22:137–43.
52. Maher C. Anterior vaginal compartment surgery. Int Urogynecol J. 2013;24:1791–802.
53. Maher C, Feiner B, Baessler K, Schmid C. Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2013;(4):CD004014.
54. Wei JT, Nugaard I, Richter HE, et al. Pelvic floor disorders network. A midurethral sling to reduce incontinence after vaginal prolapse repair. N Engl J Med. 2012;366:2358–67.

Part VI

Miscellaneous

Pediatric Colorectal Disorders

66

Erin A. Teeple and Kenneth S. Azarow

Key Concepts

- The major principle of operative therapy for Hirschsprung's disease is to bring ganglionated bowel to within 1 cm of the dentate line.
- The ideal surgical treatment of a duplication depends on length and location of duplication, age of child, and relationship to surrounding structures with complete excision being the goal, though not always possible.
- Constipation and fecal incontinence need a full history and physical examination but are managed often successfully by medical management.
- Anorectal malformations often occur with other congenital defects and a mainstay for surgery is an ano rectoplasty.

Hirschsprung's Disease (HD)

Patients with HD present classically during three different periods of life. The first time of presentation is the neonatal period when infants fail to pass meconium in the first 24 hours of life. These infants can present with vomiting, distention, and failure to tolerate feeds as the most common symptoms. Some infants marginally tolerate their first few weeks of feeds (usually breastfed) and subsequently present with enterocolitis, the signs and symptoms of which are explosive and/or bloody stool, vomiting, and fever. Lastly, there are late presenting patients who usually come to attention when either weaning off breast milk or transitioning to solid food. These patients will have significant abdominal distention and significantly dilated colon on contrast studies and usually have a history of requiring laxatives of some sort to assist with bowel movements.

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When suspected, the diagnosis of HD rests with the pathologist. An absence of ganglion cells more than 1 cm proximal to the dentate line is diagnostic of the disease. Suction rectal biopsy, partial-thickness punch biopsy, and full-thickness biopsy are all acceptable means of retrieving tissue depending upon the age of the patient and the need for anesthetic support. With the widespread use of calretinin, which stains ganglion cells, the need for second opinions to locate ganglion cells (or more precisely confirm the absence of ganglion cells) on a hematoxylin and eosin (H&E) slide or assaying for acetylcholinesterase is no longer necessary [1]. For late presenting children over the age of 2, a general anesthetic will be required to obtain tissue for pathologic evaluation. Thus, anorectal manometry can be a triage tool to help determine which patients require rectal biopsy. Failure to demonstrate the receptive relaxation reflex of the internal sphincter is suggestive of HD but not adequate to make a definitive diagnosis.

When diagnosed, the treatment of HD can and should be tailored to the individual patient. Whether to do a primary pull-through (colorectal resection with hand-sewn coloanal anastomosis), a leveling colostomy (colostomy at the level of beginning of ganglion cells), diverting ileostomy, or delay surgery by utilizing rectal irrigations (high colonic saline enemas) should be individualized based upon the patient's signs, symptoms, and age of presentation. Patients presenting with systemic signs of illness due to enterocolitis are at increased risk for significant postoperative enterocolitis, and thus primary pull-through in this population should not be the default [2]. In addition, patients with long-segment disease (especially total colonic HD) are also at increased risk for postoperative enterocolitis, and primary pull-throughs in this population are also not recommended [2]. If diversion is recommended, an experienced pathologist will be required to perform a leveling colostomy as calretinin staining is not available on a frozen specimen. If an experienced pathologist is not available and there is no means to transport the patient to an institution with expertise, a diverting ileostomy will

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suffice in most cases (even in total colonic/total intestinal HD). Lastly, rectal irrigations can be very effective in relieving symptoms and also be effective treatment for enterocolitis. This can allow surgery to be electively scheduled and, in many cases, avoid diversion for families who are resistant to a stoma. This also has the added benefit of teaching the family how to do home irrigations which can be helpful in the event that postoperative enterocolitis occurs [2].

The principle of operative therapy for HD is quite simple: bring ganglionated bowel to within 1 cm of the dentate line [3]. The details of accomplishing this are numerous and very specific. Most HD patients will also have some internal sphincter dysfunction. Thus, each of the common procedures created to accomplish bringing ganglionated bowel distally attempts to deal with internal sphincter dysfunction via a variety of procedure modifications. Although the three main HD operations (Swenson, Soave, and Duhamel; Fig. 66.1) were developed in "the era of open surgery," all can be performed laparoscopically. The Swenson technique brings ganglionated bowel to the distal 1 cm of the rectum after a full-thickness, circumferential resection of the rectum is performed, usually transanally. The Soave technique (first described by Yancy) [4] involves a submucosal transanal rectal dissection with subsequent full-thickness dissection of the rectal wall followed by an anastomosis at 1 cm above the dentate line, leaving a small cuff of aganglionic rectal wall. The Soave and Swenson can also be formed entirely from a perineal approach/transanally. To combat the distal internal sphincter dysfunction and resultant stricture, the Boley modification of the coloanal anastomosis can be applied to either the Swenson or the Soave procedure. Boley described creation of the anastomosis in an angled fashion with anterior being 1 cm from the dentate line and posterior coming within 0.5 cm of the dentate line, thus elongating the anastomosis by essentially creating an elliptical anastomosis and also building a posterior sphincterotomy into the procedure. The Soave has been additionally modified to include a posterior division of the remaining aganglionic rectal wall from below the levators all the way to the level of the anastomosis, thus building in a posterior division of the internal sphincter [5]. The Duhamel technique leaves a segment of aganglionic rectum, and the ganglionated bowel is then anastomosed in an end-to-back fashion just above the level of the dentate line, thus also performing a posterior internal sphincterotomy into the procedure. A critical step is to ensure that any segment of aganglionic rectum proximal to the end-to-back anastomosis is resected as, over time, this can result in expected lack of peristalsis and lack of emptying of this segment with subsequent dilation and stasis into what is known as a "rectal spur" [6]. A Duhamel anastomosis may be chosen with longer-segment HD where retention of part of the rectum, despite being aganglionic, may be beneficial to achieve continence.

With these modifications, all named procedures have success rates that are equal [7]. There are advantages to minimally invasive approaches as far as length of stay, postoperative complications, and postoperative narcotic usage are concerned [7]. When comparing laparoscopic to transanal (perineal) approaches, there are no significant differences[8]. The complications of constipation, enterocolitis, and

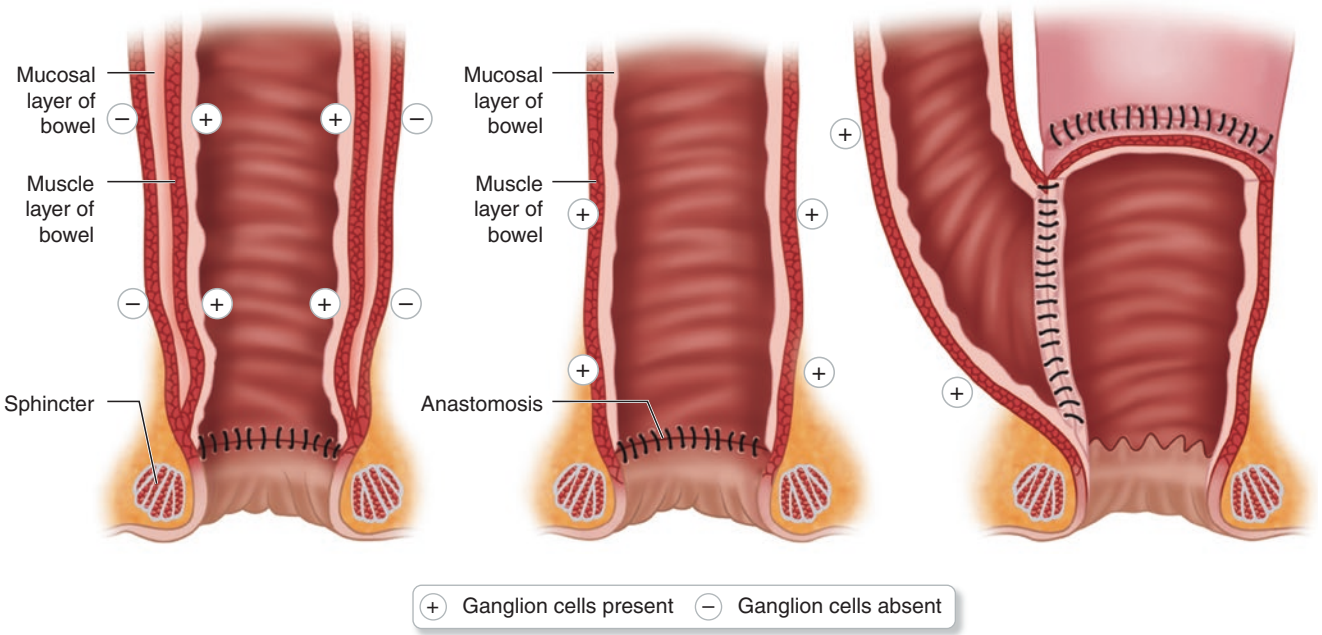

Fig. 66.1 Soave, Swenson, and Duhamel reconstruction for HD

sensory incontinence that limit the success of each procedure have slightly different mechanisms. The Duhamel procedure theoretically is associated with increased stasis of stool in the neorectum due to the remaining distal rectum being unganglionated and the possibility that the proximal end of the rectal portion of the anastomosis will grow into a significant spur. The Swenson and Soave both have risk of circumferential anastomotic strictures (even with the Boley modification) due to some remaining aganglionic rectal wall and will usually require postoperative dilations to avoid development of long-term narrowing which can also lead to enterocolitis.

When complications from HD develop, a systematic approach for each procedure and complication is required. In general, rectal irrigations, dilations, or laxative therapy is the first line of evaluation and treatment. If recurrent symptoms occur, a contrast enema is the first study to be done. Next, a repeat rectal biopsy to ensure that ganglionated cells are present in the neorectum is essential. If ganglion cells are not present due to chronic distention, loss over time, or incorrect pathologic interpretation at the initial procedure, a repeat pull-through (coloanal anastomosis) will be required. If ganglion cells are present within 1 cm of the dentate line and a contrast study shows significant rectal dilation, either anal dilations, internal sphincter Botox injection, or sphincterotomy can be offered [8, 9]. For a significant spur in a Duhamel patient, laparoscopic resection of the spur is required.

In the majority of cases of HD-associated enterocolitis (even significant recurrent disease), patient will overcome their symptoms and "outgrow" most issues by the time they are teenagers. The etiology as to why this pattern of enterocolitis exists is a source of constant study. Theories involving the development and altering of the microbiome are currently evoking the most interest in the scientific community. The composition predisposing microbiota in Hirschsprung-associated enterocolitis (HAEC) is specific to each patient, and total colon resection can change that composition [10]. In addition, relative intestinal immunosuppression could expose Hirschsprung patients to environmental microbes that might not be part of the normal microbiota perhaps leading to a predominance of specific fungi and bacteria that predispose patients to development of HAEC [11].

Adult outcomes in HD are still being elucidated. The main long-term concerns are fecal incontinence which is reported in around 15% and constipation in about 5% [12–16]. Interestingly, bowel quality of life does not seem to be compromised despite these long-term complications of the disease [13–15]. Concerns are higher in those who had longer-segment disease (i.e., standard rectosigmoid aganglionosis vs total colonic aganglionosis) [15]. Also, functionality worsens with increasing age [13, 15], highlighting the importance of care for the aging HD patient. Sacral nerve stimulation is evolving as an adjunctive treatment in some selectively chosen patients.

Colonic Duplications

Enteric duplications are a relatively rare congenital anomaly, occurring in 1 in 100,000 live births and found in 1 of every 4500 autopsies [17]. Sixty to 80% present in the first 2 years of life [18]. Eighty percent are found within the abdomen with the majority being ileal duplications [19]. Twenty percent of patients will have more than one duplication. Genitourinary (GU) anomalies are commonly associated with colon and rectal duplications [18].

Although there are many theories, no exact embryologic cause is known for enteric duplication[20]. Theories include "split notochord" where a traction diverticula is created when the notochord and endoderm split resulting in enteric duplication [20]. This theory explains the associated incidence of spinal cord anomalies and their location on the mesenteric side of the intestinal tract. A second theory is failure of recanalization of the bowel [21]. A third theory is abortive twinning: an incomplete split in the primitive streak which occurs early and late in gestation can explain complete duplication of the colon, bladder, urethra, external genitalia, and upper alimentary tract [22]. Lastly, environmental factors such as hypoxia or trauma could potentially contribute to formation of duplication [23].

Enteric duplications are usually tubular or cystic and closely resemble normal intestinal tract architecture. The duplication cyst may only be partially lined by mucosa, and the mucosa may be different than that of its contiguous bowel. Ectopic mucosa has been described including gastric, pancreatic, transitional, and columnar. Gastric and pancreatic ectopic tissue may cause ulceration, bleeding, and even perforation of the duplication cyst [23, 24]. Hindgut duplications typically contain colonic mucosa and only rarely have ectopic gastric mucosa. As mentioned, they typically occur on the mesenteric side, sharing a blood supply and usually mural elements of musculature and serosa with contiguous bowel. There may be a communication between normal and duplicated bowel, particularly in the longer duplicated segments [25].

Duplication of the colon and rectum makes up 17% of all enteric duplications, ranging from cystic duplication to extensive tubular duplications spanning the entire length of the colon [26]. These can extend to the perineum or vagina as a separate opening. Particularly long duplications and distal duplications are frequently associated with GU and spinal anomalies including fistulae, so this should be investigated preoperatively with contrast and endoscopic studies [27]. Presenting symptoms include constipation, abdominal pain and distention, or stool draining from GU or perineum in the event of a fistula. Rectal duplications can be confused with perirectal abscess and fistula if they become infected. Computed tomography (CT) and magnetic resonance imaging (MRI) are useful to determine the extent of the duplica-

tion as well as the relationship to the spine and GU tract. Ultrasound can be helpful and is the imaging modality of choice in infants, as the cyst will typically have a double layer which is indicative of enteric wall rather than a simple cyst wall [28]. Rectal duplications typically are presacral, rarely anterior, and can be considered as part of a Currarino triad: anorectal stenosis, presacral mass, and sacral anomalies.

Ideal surgical treatment depends on length and location of duplication, age of child, and relationship to surrounding structures. Complete excision is the goal but may not be ideal in all settings, for example, a complete colonic duplication and a small child. Partial resection with long stapled fenestrations to allow normal and duplicated bowel to communicate may be better tolerated in a small child than a total abdominal colectomy (Fig. 66.2) [29]. Fistulae to the GU tract, spine, or perineum must be excised. Isolated rectal duplications often share a common blood supply with normal rectum but can typically be separated from rectal wall and excised in entirety. An infected rectal duplication is recommended to be drained externally rather than internally to protect the operative plane between the native rectum and the cyst wall [30].

For edification, duodenal duplications should not be completely excised due to proximity of the bile and pancreatic ducts. Operative approach should include intubation of the duodenum from above to identify the true lumen, partial excision of the wall opposite the true lumen, and mucosal stripping of the shared wall between the duplication cyst and the true lumen. Any small tears into the true lumen can be primarily repaired and drained. Rarely, cholecystectomy, cholangiogram, and intubation of the CBD into the duodenum are necessary to further identify the anatomy. Cystic duplications of the small intestine usually require intestinal resection as the mesentery adjacent to the duplication cyst is unreliable after cyst excision. Thus, the simplest approach is to resect the bowel with the mesentery and perform a primary anastomosis. As with the large intestine, small bowel tubular duplications can vary in length. In order to avoid lengthy small bowel resections, creating a common lumen with multiple fenestrations or linear division/stapling of the common wall is the preferred approach.

In conclusion, duplications are rare and can present with a variety of symptoms from abdominal fullness to perforation. Ideally, they require complete excision with takedown

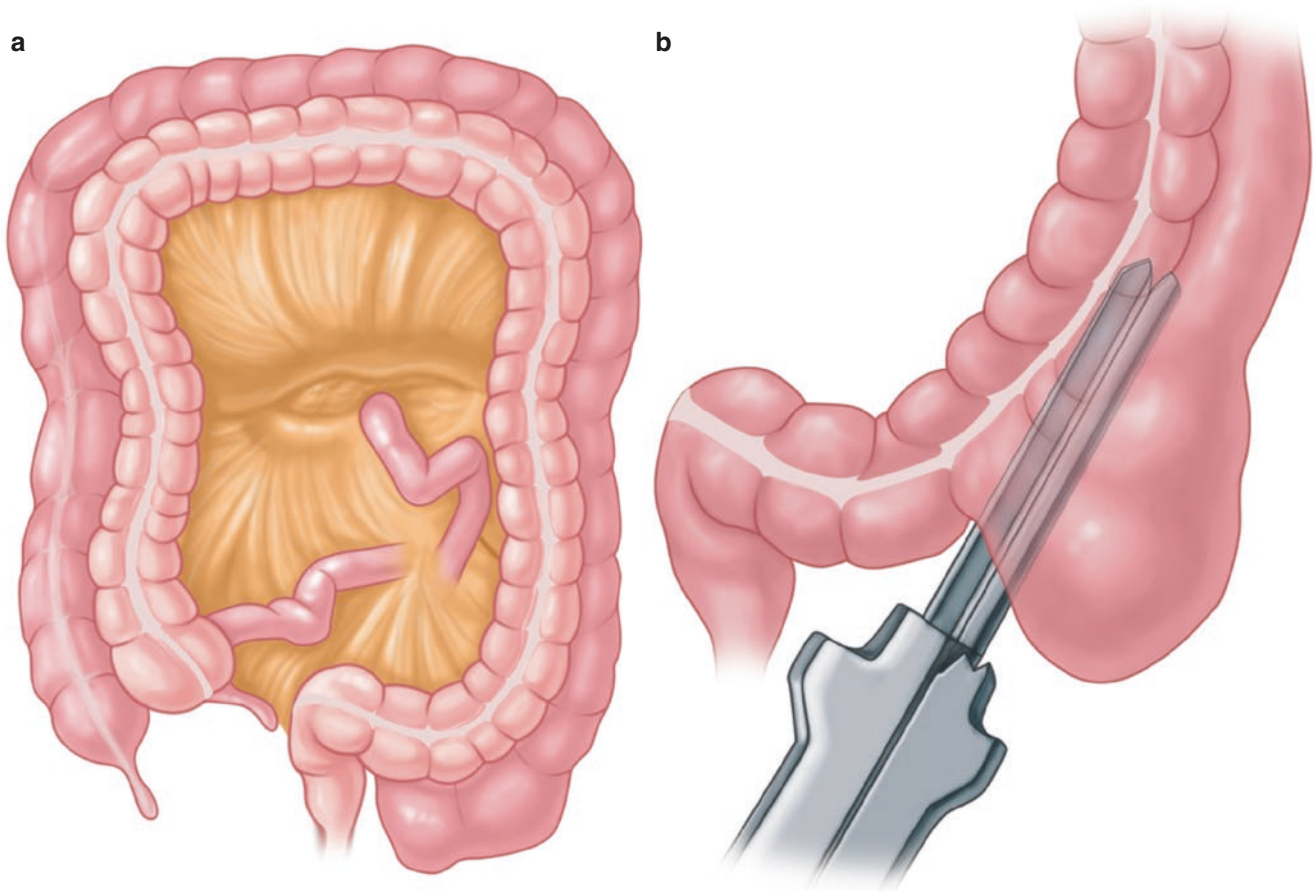

Fig. 66.2 Longitudinal stapling to create common colotomy in long-segment colonic duplication. (**a**) Total colonic duplication. (**b**) Creation of stapled common colotomy for long segment colonic duplication

of any fistulae to prevent symptoms and risk of neoplasm [31]. However, when this would result in intestinal failure, absorptive issues, or damage to critical structures, there are other options including mucosal stripping or wide drainage into a common lumen.

Constipation

Constipation is a common pediatric complaint. It can present with many symptoms including abdominal pain, hard stools, encopresis with fecal incontinence, vomiting, and failure to thrive. Signs can include abdominal distention, rectal prolapse, bright red blood per rectum with anal fissure, and, as a long-term consequence, sigmoid distention with volvulus. Constipation starts within the first year of life in 17–40% of children [32]. Fifty percent of patients referred to gastroenterology for constipation will recover and come off laxatives after 6–12 months. Ten percent will remain on laxatives but be well, and another 40% will need an escalation of therapy beyond laxatives. Fifty percent will come off laxatives after 5 years and 80% will come off after 10 years. If initial referral is delayed and patients present with longer than 3 months of symptoms, recovery is delayed [33]. Common times to present with constipation are in the neonatal period, around the time of toilet training (2–4 years), and after entrance into school where fecal incontinence is more socially pressing. There are many organic problems that can contribute. Celiac and lactose intolerance can commonly predispose to constipation. Any behavioral or musculoskeletal diseases such as autism or cerebral palsy are often associated with a slow transit constipation, anismus and ongoing, refractory constipation. After escalation of medical interventions including osmotic and stimulant laxatives, patients are frequently referred to a surgeon for further evaluation. Also, if there are complications of constipation, a surgeon is frequently enlisted. This section will detail surgical considerations for pediatric constipation.

A detailed history and physical is necessary when evaluating a pediatric patient with constipation. Time to first passage of meconium is an important consideration as Hirschsprung's disease (HD) can present in a delayed fashion. However, if meconium was documented in the first 24 hours, the diagnosis of HD is very unlikely. If no meconium was passed in the initial 48 hours of life, consideration should be given to barium enema looking for a transition zone, and a rectal biopsy should be performed. Anorectal manometry (ARM) looking for a rectoanal inhibitory reflex (RAIR) is unreliable for the first 12 months of life, with a sensitivity ranging from 75% to 90% [34–36]. If HD is discovered, most children who present in a delayed fashion will need diversion to reduce distention of the bowel, allow significant time to treat for enterocolitis, and, ultimately, protect a definitive HD procedure which includes a coloanal anastomosis. If no organic cause of constipation was found but the patient has failed maximal medical treatment, surgical possibilities exist for treatment.

To define the reason for failure of medical management and to direct surgical care, both a sitz marker study to help quantify colonic transit time and colonic manometry in children greater than 2 can be particularly helpful. As in adults, a sitz marker study can help elucidate colonic inertia with a finding of markers remaining throughout the colon or pelvic floor dysfunction where markers are stacked at the puborectalis. Colonic manometry may be useful to predict which patients will respond to antegrade flushes [37, 38]. Identifying and resecting a single dysfunctional segment can improve efficacy of antegrade flushes but may not improve symptomaticity in others [39, 40]. Also, significant bowel dilation will lead to dysmotile bowel that may very well be reversible. Surgical options based on colonic manometry must be tailored to individual patients [41].

Consideration can be given to creation of cecostomy, including a Chait or gastrostomy in the cecum or antegrade continent enterostomy. See the cecostomy portion of this chapter for further information on antegrade flushes. If anismus is a possibility, either by history of withholding, stacked sitz markers along the puborectalis, or anorectal manometry, anal or pelvic floor Botox can be effective in diagnosis and therapy. Anal Botox has been used and studied largely in postoperative HD strictures. Interestingly, there is not always a dose adjustment for size of patient [42, 43]. For medically refractory constipation, consideration can be given to sacral nerve stimulator (SNS), particularly if there are associated urinary symptoms. There are no studies primarily evaluating SNS for constipation in children. Studies in adults do not support implantation for constipation [44–47]. There are retrospective observational studies in pediatrics who note decrease in dependence on ACE flushes and laxatives when the stimulator was implanted for urinary reasons [48, 49]. Of course, if constipation is entirely refractory, fecal diversion is the final step.

Volvulus and perforation of the colon can result from long-standing, refractory constipation. In children, acute and chronic intermittent colonic volvuli are unusual events [50]. Constipation and abnormal colonic fixation are thought to be predisposing factors. Types of volvulus include cecal, transverse colon and sigmoid colon. Presentation varies but usually includes abdominal pain and distention, intolerance to feeds, increased gastrostomy tube output, facial grimace, or expression of pain in the nonverbal population and even peritonitis. Volvulus is diagnosed on abdominal radiograph and confirmed on axial imaging, contrast enema, or colonoscopy. Once discovered, in the case of transverse or sigmoid colon volvulus, the bowel can be attempted to be de-torsed with colonoscopy. This reduces ischemic risk to the colon by straightening the mesentery and may even allow bowel

preparation prior to definitive treatment. Definitive treatment consists of segmental resection and anastomosis. If volvulus is the presenting symptom of constipation, reduction with aggressive medical management may be attempted for transverse colon and sigmoid volvulus, but the rate of failure is high [51–53]. The average age of sigmoid resection in children is 7 years [54]. Postoperatively, due to ongoing dysmotility, the risk of a second volvulus of another segment of the colon should be considered.

If volvulus is present long enough to compromise blood supply to the colon, the presenting symptom may be perforation. Other processes leading to spontaneous perforation include long-standing and increasing dilation of the colon or acute intestinal pseudo-obstruction (Ogilvie's syndrome). Ogilvie's syndrome can present in a postoperative period or occur as a result of any other systemic derangement including but not limited to infection, pancreatitis, electrolyte abnormality, or respiratory process. In the instance of ongoing dilation, the most common site of perforation is the cecum given its proximal position as well as thin wall. This is further supported by the law of Laplace (wall stress = [(transmural pressure) × (radius)]/wall thickness). Should colonic perforation occur, treatment is with segmental resection and primary anastomosis or end colostomy dependent on peritoneal contamination and physiologic status of the patient [55].

Constipation is a common complaint among children, and surgeons are frequently called on to care for the complications of this disease. See the fissure and prolapse portions of the chapter for other complications of constipation in the pediatric patient.

Prolapse

Rectal prolapse is an intussusception of the rectum that by definition involves all layers of the rectum, but in infants and small children with a variety of congenital conditions can involve only the mucosa ("mucosal prolapse"). Prolapse is a common problem in children with a peak incidence in the first year of life and most other occurrences happening under 4 years or around the time of toilet training. Prolapse is a symptom of an underlying condition, usually constipation, but can also be caused by increased abdominal pressure (constipation, staining, chronic cough), acute or chronic diarrhea, parasites or neoplastic disease of the rectum, malnutrition, cystic fibrosis, or pelvic floor weakness.

Most cases of prolapse are mild and resolve spontaneously [56–58]. The initial treatment is typically conservative management of constipation [3]. Parents should be instructed to use stool softeners, or laxatives, avoid prolonged straining, and use proper toilet size to prevent recurrent episodes [4]. If the rectum is prolapsed for a prolonged period of time, manual reduction should occur before edema can make reduction more difficult. Roughly 90% of cases of rectal prolapse that occur in children under the age of 4 will resolve with conservative management and rarely continues after 6 years of age, with children older than 4 being less likely to respond to conservative treatment [3]. Children over 4 years of age are more likely to have neurologic (spinal cord lesions) or muscular defects and require intervention [56–59]. If children fail conservative measures and continue to have rectal prolapse, with ongoing symptoms of pain, rectal bleeding, and perianal excoriation, they may require surgical invention [60–63]. Prior to operative intervention, these children should be screened for cystic fibrosis due to a prevalence of 11.1% in children with rectal prolapse [58–60].

Based on a 2018 survey of the American Pediatric Surgical Association, the most common initial local intervention is the injection of sclerosant [60]. This is thought to be similar to the mechanism of action behind rubber band ligation of internal hemorrhoids, creating scar in the submucosal plane to prevent further prolapse. The methods and content of injections vary highly as some purport a submucosal injection and others advocate trans-serosal injection, scarring the rectal serosa to the perirectal tissues. This is considered the simplest, most benign yet still efficacious intervention [60, 64]. A variety of agents have been described over the years [64–68]. Thirty percent saline was reported with a single injection of 83% and a two-injection cure rate of 97% [65, 66]. Injection of 5% phenol in almond oil results in 91% cure rate after one injection and 100% cure rate after two injections [67]. Ethanol 70% injected results in resolution of 96% of cases after one injection and 98% of cases after two injections [68]. There were few complications seen in these studies including temporary fecal incontinence, temporary limping, bleeding, perirectal inflammation, urinary retention, necrosis of the rectal mucosa, and abscess formation and one death after the injection of phenol [65–69].

Operative interventions are available for refractory cases and can be divided into abdominal or perineal therapies. However, no one operative therapy has been shown to be effective in all cases of rectal prolapse [58–60].

Initially described in 1953 [70], anal encirclement (Thiersch procedure) was recommended as an option for patients with prolapse seconding to weak pelvic floor muscles or associated with cystic fibrosis and is reported to yield success without serious complications [57, 61, 62]. The Thiersch procedure is described as placing an absorbable suture such as a 1-0 PDS circumferentially at the anal opening and securing it over a calibrated Hegar dilator. Another minimally invasive surgical procedure is linear cauterization, which has shown 94% success rate [71]. This is another form of local rectopexy with the submucosal scar being created by electrocautery. Flum, Golladay, and Teitelbaum advocate a combination approach with linear cauterization, sclerotherapy injection, and a Thiersch procedure which they refer

to as a modified Thiersch [62]. In their series they reported a success rate of 67% for patients who underwent a single procedure and a 90% success rate for patients when their patients underwent a combined approach [62].

Patients who continued to experience failures have further surgical options of Altemeier perineal proctosigmoidectomy or abdominal rectopexy. After an Altemeier, some patients did experience temporary fecal incontinence [62]. A posterior sagittal approach rectopexy has been used to treat idiopathic rectal prolapse in children on an ambulatory basis with minimal postoperative pain and normal bowel control. Unfortunately, however up to a 25% recurrence rate was reported [72]. The one study that did not report recurrence was Ekehorn's rectosacropexy which added the placement of a U-shaped suture through the rectal ampulla and tying the suture outside at the sacrococcygeal junction [73]. Ashcraft reported a transcoccygeal rectopexy with puborectalis plication with a success rate of 70%. However, several children developed sigmoid intussusception requiring bowel resection [74]. In one study, children without pelvic floor laxity underwent suture rectopexy to the sacral promontory and suture sigmoidopexy to the left lateral peritoneum without mesh [75]. Laparoscopic posterior levatorplasty has been described for repair of rectosacral hernias where the pelvic floor was lax, treating the prolapse as if it were a true hernia [60, 63]. These procedures were found to be safe and effective with manageable complications.

Currently abdominal rectopexy is thought to be first line for those with irreversible conditions and full-thickness rectal prolapse [76]. As in adults, this can be performed with or without a concurrent sigmoidectomy. Most pediatric surgeons will attempt simple rectopexy with subsequent sigmoidectomy for those that fail pexy alone [5]. Similar to adults, this can be performed laparoscopically or open [58–60, 75]. Laparoscopic rectopexy is a safe and effective treatment for refractory rectal prolapse with approximately a 5% recurrence rate with the only postoperative complication being constipation [58–60]. Laparoscopic sigmoid resection with rectopexy has been controversial in children, but it has been shown to be safe and eliminates the risk of volvulus and has a low morbidity and low recurrence rate [58–60]. Similar to adults, resection rectopexy is preferred in patients with intractable constipation and prolonged transit studies.

Perianal Abscess and Fistula-in-Ano

The treatments of these conditions in children are widely debated in the literature and range from antibiotics and nonoperative management to aggressively probing for a fistula and fistulotomy or fistulectomy. The decision process usually comes down to a weighted belief about attaining adequate source control of an abscess versus creating a fistula-in-ano that can be very difficult to manage surgically and potentially cause recurrence of the infectious process and/or issues with continence. There is currently no consensus as to the best management in the literature [77]. This controversy is in part likely due to the wide range of reported rate of development of fistula-in-ano with a range of 20–85% after perianal abscess management [78, 79]. Further complicating the discussion is the wide range of reports that fistula-in-ano in an infant or toddler can be managed successfully without surgery [78–82].

Perianal abscess and fistula-in-ano are more common under the age of 2, and it is estimated that 0.5–4.3% of all children are affected [79]. Several theories have been hypothesized spanning from gender difference by an androgen excess or androgen-sensitive glands in utero causing a formation of abnormal glands to entrapment of migratory cells from the urogenital sinus during development of the perineum [78, 81–83]. This is a male-predominated disease process; however the ratio of male to female does change with age. In children under 2 years of age, the ratio of males to females is 12:1, while the ratio becomes less extreme after 2 years with a male-to-female ratio of 2–3:1 [80].

The most common positions for perianal abscess and fistula-in-ano are right and left lateral locations [78, 82, 83]. The organisms grown in culture from within the abscess cavities have been found to be gender associated with a significant female predominance growing skin flora (streptococci, *S. aureus*) and a male predominance of enteric flora (*E. coli*, *Klebsiella*, enterococci, *Proteus*) [78]. Although the presence of mixed enteric organisms in the aspirate is suggestive of a fistula, there has been no statically significant correlation between the presence of fistula-in-ano and organisms in culture [80]. There has been a significant increase in the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) in both the hospital and community settings [84–87].

Remarkably, perianal abscess and fistula-in-ano have not been well-studied in the literature. As a result, there are a wide variety of treatment algorithms among pediatric surgeons. Nonoperative management for perianal abscess including advocating hygiene with good diaper care, sitz baths, and antibiotics has been proposed due to the fact that the patients who undergo surgical drainage have up to a 40% rate of development of fistula-in-ano compared to a 16% rate of development of fistula-in-ano without drainage [79]. Also, it is difficult to predict effect on continence when all babies are incontinent at the time of surgery. Therefore, sparing the sphincter if conservative management is sufficient seems prudent. In addition, the fistula may be a result of other underlying disease processes. For example, Christison-Lagay found 10% of their population to be immunocompromised and treated them with nonoperative management without development of subsequent fistula or the need for

operative intervention [79]. Others have advocated similar approaches with treatment of local hygiene and sitz baths for early-stage perianal abscess and a progressive stepwise approach starting with antibiotics and drainage with an 18-gauge needle for more advanced disease [83]. With this approach, if there was no resolution of the collection within 24 hours, an incision and drainage was performed. The rate of recurrent abscess after needle aspiration was 8%, and subsequent development of fistula-in-ano was 11% [83]. Thus, needle aspiration is a viable treatment technique for perianal abscess in children. In line with this approach, our institution has developed a similar step-up algorithm to manage pediatric patients with perianal abscess and fistula (Fig. 66.3).

Counseling families that one third of abscesses will either recur as an abscess or as a fistula-in-ano becomes important in the care of the child. Recurrence of abscess is not decreased by postoperative antibiotic use, but the subsequent formation of fistula-in-ano is [78]. Reports of recurrence range from 12.5% to 50% with no difference between the different types of antibiotics used [78, 79, 82, 83]. Recurrent fistula-in-ano has also been treated with observation with a spontaneous resolution of 17–80% of fistula-in-ano within 1 year [78, 82]. Antibiotic usage did not affect the spontaneous resolution of the fistula-in-ano [78]. Due to the extreme variation in treatment options reported, there has been no consensus on recommended treatment of abscess and fistula-in-ano for children.

For children under the age of 2 years who undergo surgery for perianal abscess, only 15–25% were identified to have a fistula-in-ano at the time of their primary surgery [80, 87]. Thus, one must question the benefit of an extensive search for a fistula given the potential for sphincter injury in very small patients. In children over 8 years, there were both a high recurrence rate at 50% and a high rate of progression to fistula-in-ano of 25% [80]. As a result, a different strategy should be considered in this population. These strategies can include up-front surgery or fibrin glue application in the fistula after the local sepsis is cleared [87]. In addition, a significant portion of this population should be evaluated for immunosuppressive disorders as well as inflammatory bowel

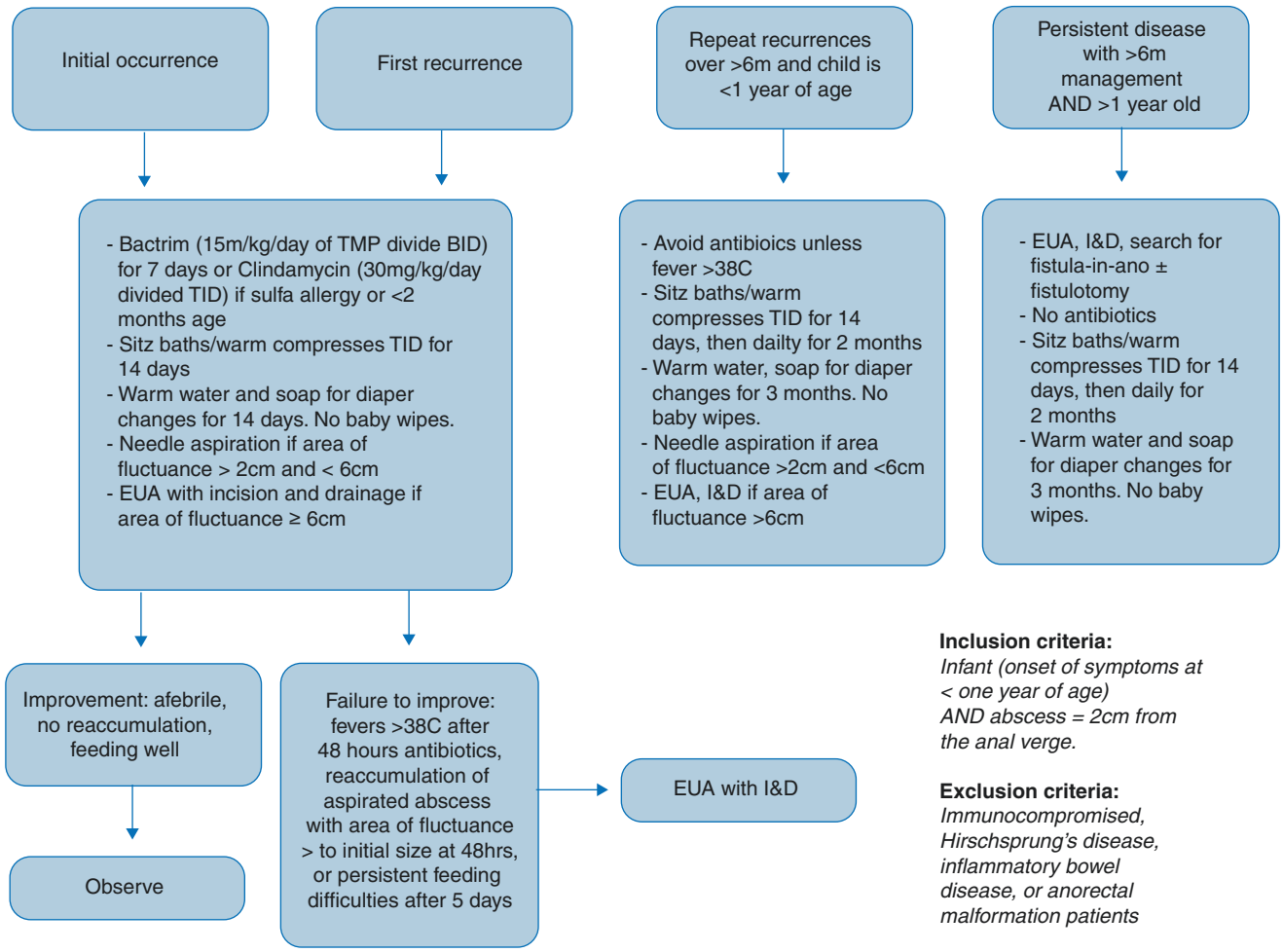

Fig. 66.3 Algorithm for treatment of perianal abscess

disease [77, 80]. Thus, in the inflammatory bowel disease or immunocompromised populations, although perianal sepsis and fistula should be temporized with drainage of the abscess and placement of a draining seton, biologic agents or immunosuppressant therapy should be first-line treatment. As an example, Niyogi successfully used tacrolimus to treat fistulas without the presence of an abscess, and all resolved without operative intervention [80]. Patients as young as 2 years old have been diagnosed with Crohn's disease. Therefore, in a child older than 12 months with recurrent fistula, underlying systemic pathology such as immunosuppression or IBD should be considered and ruled out prior to undertaking any fistula repair.

In summary, perianal abscess is a disease that primarily affects males less than 12 months and should be approached in a stepwise fashion beginning with local therapy and antibiotics, progressing to aspiration, and if necessary incision and drainage. Many of the fistulas-in-ano in this population will spontaneously close without surgical intervention, thus avoiding unnecessary operative interventions. Primary treatment of a fistula-in-ano should be reserved for older children and for those children with a failure to spontaneously resolve as fistula-in-ano seems to be a self-limiting disease in infants [78, 80–82]. While these recommendations are based on current best evidence, prospective randomized trails are needed to further delineate optimum treatment of perianal abscess and fistula-in-ano for infants and children.

Fissures

Anal fissure is a common complication of constipation in children and adults. It represents a longitudinal tear in the distal anal canal and most commonly presents at 2 years of age in children, although it can occur at any age [88]. Pediatric patients present with rectal pain, crying with defecation, hematochezia, or blood on the stools. The fissures in infants may be found anywhere but are more common in the posterior midline. Females, however, more commonly have anterior midline fissures [88–94]. Fissures may also present in association with skin tags or sentinel piles. If the lesions are off the midline or are multiple, a biopsy should be considered to exclude Crohn's disease, malignancy, tuberculosis, sexually transmitted disease, or immunodeficiency [88]. In addition, fissures can be associated with operative management of multiple congenital anomalies including imperforate anus, persistent cloaca, Hirschsprung's disease, ileoanal pull-throughs for polyposis and inflammatory bowel disease, and cystic fibrosis among others [88]. Most anal fissures that appear spontaneously will heal with medical bowel management with recovery rates ranging from 10% to over 95% [88–94]. The higher rate was achieved in a longer study (10 weeks) and with a more intensive bowel regimen with surgical treatment reserved for symptomatic fissures [89–94]. For fissures that do not heal with bowel management and are located within prior surgical fields, nonoperative options such as botulinum toxin injection have become popular [42]. Treatment of constipation in children includes fiber, osmotic laxatives, stimulant laxatives, and rectal suppositories or enemas.

More invasive therapies such as topical nitroglycerin, botulinum toxin injection, calcium channel blockers, anal dilation, anal myectomy, and lateral internal sphincterotomy have all been studied [42, 89–95]. There have been three randomized trials that have evaluated glyceryl trinitrate 2% (GTN). Two of these showed improvement in both the short term (10 days) and at 8 weeks [89–91]. Kenny showed overall 84% healing in both the GTN and placebo groups [89]. Tander and Sönmez separately showed healing in 82–84% of their treatment arm versus 43–50% in the placebo (or lidocaine) groups. They achieved symptomatic relief in 91–94% of the treatment arm versus 10–35% in the placebo (or lidocaine) group [90, 91]. Botulinum toxin can also be used for resolution of anal fissure. Keshtgar showed that children who underwent treatment for anal fissure with transcutaneous botulinum toxin had resolution of their lesion [91].

Anal dilation and anal myectomy of the internal anal sphincter have been performed for constipation with the thought that children with constipation have hypertonicity of their internal anal sphincter and that these modalities would decrease sphincter tone and allow for painless defecation [88]. Double-blinded randomized controlled trials have shown that anal dilation does not benefit children with chronic constipation and that there is no significant difference in outcome with regard to resolution of symptoms [95]. Myectomy of the internal anal sphincter has been used when anal dilation has been unsuccessful. Symptoms were relieved in two thirds of the patients; however, the detrimental effects of fecal incontinence after weakening of the sphincter may not be seen for years [92]. Injection of botulinum toxin into the anal sphincter has been shown to be as effective as myectomy of the sphincter, with resolution of symptoms 94% versus 89%, respectively, without the potential long-term problems [42]. Lateral subcutaneous sphincterotomy was performed for children with a complete resolution of all fissures [93]. A period of inpatient observation and objective evidence of painful defecation is recommended to help avoid misreporting and exaggeration of symptoms and thus unnecessary operations.

In conclusion, asymptomatic lesions are likely to resolve and should be managed expectantly [88, 95]. If intervention is necessary, a trial of topical treatment should be used with reoccurrences again being treated medically and surgery being reserved for continued failures [95]. Any surgical intervention undertaken to the sphincter of a small child or

infant should be done with extreme caution as incontinence and anal stenosis are both reported in up to 30% of children in this age group [95].

Cecostomy

Cecostomy is direct access into the cecum via percutaneous tube or appendix/neo-appendix tacked to the abdominal wall. An antegrade flush is meant to be instilled daily to keep the colon clean and achieve social continence. Cecostomies are used in pediatric patients as an alternative to colostomy as a way to achieve fecal continence.

The antegrade continence enema (ACE) technique was first described by Malone (MACE) in 1990 [96]. He used the appendix to create access to the cecum to provide antegrade enemas. This resulted in controlled stooling with mechanical reduction in fecal burden and ideally reduction in fecal incontinence episodes. Since his original description, the procedure has had several modifications, including creating an antireflux mechanism by wrapping the appendix in the wall of the cecum. This prevents stool from leaking retrograde from the cecum while the catheter is removed. Another modification is the use of laparoscopy for creation of the MACE. If no appendix is available, a conduit can be created using a transverse cecal flap or spiraled piece of small bowel. Other mechanisms of providing access to the cecum to establish an antegrade enema program are via a surgically or radiographically placed percutaneous cecostomy [97, 98]. A surgically fashioned cecostomy involves sewing the cecum to the anterior wall and placing a tube or low-profile gastrostomy through an anterior abdominal wall trephination into the cecum. Gastrostomy or jejunostomy tubes can be used. However, to minimize leakage, granulation tissue, and epithelialization of the cecostomy, Dr. Peter Chait created a low-profile, small-caliber self-retaining coiled tube (Fig. 66.4). Drs. Chait and Shandling first described radiographically

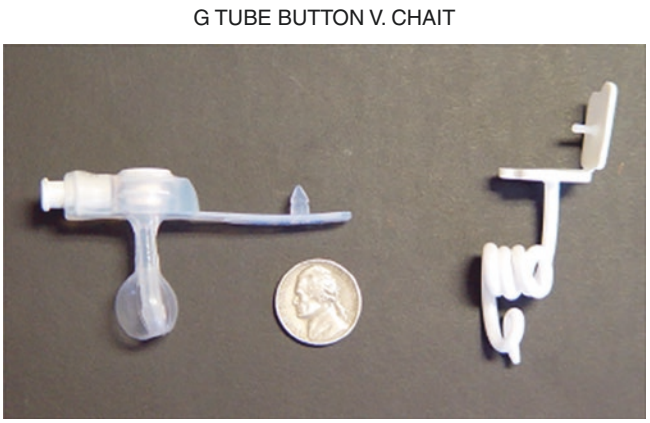

Fig. 66.4 Gastrostomy button versus Chait

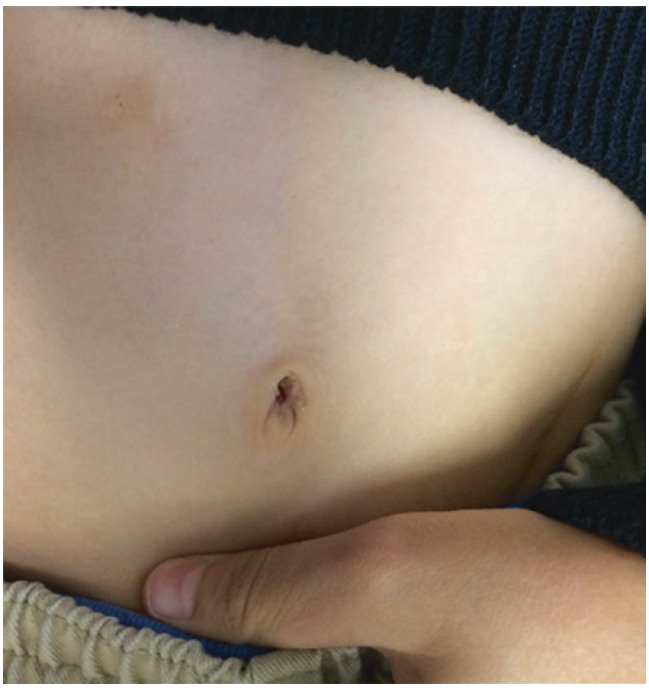

Fig. 66.5 Umbilical antegrade continent enterostomy (ACE) site

placed cecostomies [99]. Each approach to cecostomy carries its own risks and benefits. After surgical creation of an appendicostomy (ACE), a catheter is placed in the orifice nightly, the flush is administered typically via gravity, and then the tube is removed. Benefits include ability to remove the tube so there is no permanent foreign body and cosmesis. Because it is typically located within the umbilicus, the orifice is not noticeable once the tube is removed (Fig. 66.5). Potential complications include stenosis of the aperture and tract as well as injury to the appendix resulting in superficial or deep space infection. Intraluminal knotting of the catheter can also occur making removal difficult. Because a percutaneous cecostomy tube typically remains in place, the tract does not have to be manipulated daily. The drawbacks of this approach include permanent foreign body in the abdominal wall, formation of granulation tissue, potential dislodgement, and potential need for sedation to facilitate tube replacement or exchange. Complications common to all approaches include leakage at the skin and skin infection. Both carry equivalent likelihood of continence, and outcomes surrounding superiority of either are mixed [100, 101].

Prior to placement of antegrade enema access, investigation should be undertaken to help gauge if antegrade enemas will be successful at achieving social continence. A retrograde enema program can be initiated. If a temporary retrograde enema program is successful, antegrade access typically will also be ultimately successful. As mentioned, colonic manometry can also be a useful adjunct to help predict success of an antegrade enema program [33,

37, 102, 103]. Those with generalized dysmotility or those who do not respond to a bisacodyl challenge are less likely to be successful with cecostomy. At our institution, postoperatively, flushes are then escalated through the antegrade enemas over the postoperative days to achieve 20 milliliters per kilogram normal saline in a nightly flush. The child will sit on the toilet and begin the flush via gravity drainage through the cecostomy. They will sit on the toilet for an average of 45 minutes, allowing the flush to pass through the colon and anus along with a large quantity of stool. If saline alone is ineffective at achieving fecal continence during the day or if children do not tolerate sitting on the toilet for 45 minutes, additives can be dissolved into the antegrade enemas, including irritant laxatives, lubricants, and promotility laxatives. The percentile success of antegrade enemas is variable dependent on underlying disease process. Some children with cerebral palsy and other movement and communication disorders seem to be higher risk for refractory constipation and soiling due to their potential for significant dysmotility [104].

A new consideration in cecostomies is the adjunctive use of sacral nerve stimulation (SNS). Many patients with cecostomies will receive SNS for urinary indications. Rarely will it be implanted for constipation alone as the failure rate for this indication is quite high [105, 106]. However, in those patients who received SNS for other indications, 45% ultimately had their cecostomy closed [107]. Although interesting, more research is needed around SNS and constipation.

In summary, cecostomy can be created in a variety of techniques, each with its own advantages and disadvantages. Antegrade flushes are a common method of achieving social fecal continence and an attempt to avoid a permanent colostomy.

Transitional Care in the Pediatric Colorectal Patient: Anorectal Malformation, HD

Transitional care for the complex pediatric colorectal patient is becoming more important as this population ages. It is widely known that there is a disconnect as these patients outgrow their pediatric care but do not necessarily seek care at an adult institution [108]. The reasons for this disconnect are still under investigation. It is critical to identify the main patient populations with congenital disease that may seek the care of an adult colorectal surgeon. Facilitating access to adult colorectal surgeons and adult gastroenterologists is a requirement prior to managing the problems that may be encountered.

Anorectal malformation (ARM) has a large spectrum of severity, ranging from congenital anal stenosis to cloaca. ARM presents in the newborn period with a rate of about 1 in 2000–4000 live births. The severity of bowel dysfunction typically correlates with the level of fistula. Those with a higher fistula (e.g., rectal-bladder neck or cloaca) have worse bowel outcomes. This is likely due to the lack of embryologic development of important pelvic floor functionality as well as other associated congenital anomalies. Sixty percent of ARM patients have associated genitourinary, skeletal, and spinal anomalies [109]. Thirty percent will report long-term issues with urinary incontinence. Around 10% of men will report issues with erectile dysfunction and 15% with ejaculatory dysfunction. Unfortunately, female sexual dysfunction rates have not been adequately studied.

In general, these patients will undergo a posterior sagittal anorectoplasty in infancy. To summarize, this operation approaches the rectum from a Kraske (posterior sagittal) approach and separates it from the genital (female) or urologic (male) structures and places it within the identified pelvic floor and external anal sphincters. Of the patients with more proximal fistulas, 30–50% of these patients are constipated [110, 111]. Stimulant laxatives have been the intervention of choice in this disease process as osmotic laxatives are known to increase fecal leakage in these patients with compromised sphincter function. Around 20% of adults with ARM report fecal incontinence (FI) episodes weekly [112]. Intervention for FI includes a fine balance of diet, fiber, and antimotility agents. Implantation of sacral nerve stimulator (SNS) may be a reasonable option if at least one of the S3 nerve roots remains intact as many of these patients will have significant sacral anomalies. After medical interventions have failed, consideration is often given to creation of access for antegrade flushes via cecostomy (see cecostomy portion of this chapter). This is typically a Chait (a percutaneous tube placed in the cecum) or a Malone antegrade continent enterostomy (MACE). A MACE is typically fashioned by using the cecum to create an antireflux valve at the base of the appendix and subsequently attaching the appendix to the anterior abdominal wall, usually at the umbilicus. If the appendix is unavailable, the cecum can be tubularized. The ACE is catheterized nightly for an antegrade flush. The flush can include a variety of agents including saline, polyethylene glycol, glycerin, as well as a variety of other stimulant or lubricating agents. This flush is performed nightly and ideally results in socially acceptable fecal continence during the day. Escalation of fecal leakage indicates that the flush is no longer effective and needs to be changed in some manner.

Issues with cecostomies occasionally will come to an adult colon and rectal surgeon. Excessive granulation tissue at the stoma can be managed with local care consisting typically of either topical steroids or silver nitrate. Stenosis at the ACE is typically improved with a local surgical flap such as a VY advancement flap. Stenosis of the skin around a Chait tube can often be managed with local dilation. Prolapse of the ACE can lead to ongoing soilage. This would need a local revision of the ACE, taking care not to damage the tenuous blood

supply of the appendix/conduit. If there is retrograde drainage of stool from the MACE and the patient is not severely constipated, the MACE would need revision of the antireflux mechanism. MACE flush management in the pediatric sector is typically performed by the surgeon. During transition to adult care, this responsibility is typically taken on by the adult gastroenterologist. Clear and ongoing communication between pediatric surgeon and adult provider is paramount in maintaining continence for these young adults. Another reason ARM patients may seek an adult colorectal surgeon is rectal prolapse, which is usually a symptom of long-standing constipation. The constipation should be addressed prior to limited Altemeier where the redundant rectum is excised and sewn directly to skin as there is no anus.

Hirschsprung's disease (HD) is another congenital diagnosis which requires transitional care and may ultimately present to an adult colorectal surgeon. HD is an absence of ganglion cells in the distal bowel creating a functional obstruction. Early in life, the aganglionic segment is removed and/or bypassed, and the ganglionated segment is brought down to the anus with a hand-sewn coloanal anastomosis (see HD section for further details on variable operative approaches). Eighty-five percent of HD has ganglion cells in the rectosigmoid area resulting in a short-segment resection. Long segment is defined as ganglion cells identified proximal to the middle colic vessels. Short-segment disease can be resected through either a transanal or an intra-abdominal technique. Intra-abdominal approaches are used in longer-segment disease. Many advocate for the use of adjunctive laparoscopy to find the level of transition and mobilize the colon to minimize the trauma to the anal sphincters during a transanal approach. Previous data indicated that long-term bowel functioning was optimistic after repair for HD disease, finding only frequency of bowel movements to differ in HD adults compared to non-HD controls [113]. Many studies have found that initial problems with constipation and FI improve as children enter adulthood [16, 113, 114]. However, this optimistic view has recently been questioned, finding that many adults still struggle with constipation and incomplete evacuation [115]. There is also concern that functional bowel outcomes may deteriorate in an aging population [116]. Further data is clearly needed to further elucidate long-term outcomes, particularly of transanal endorectal pull-through. Hirschsprung-associated enterocolitis (HAEC) is a common postoperative complication of HD regardless of surgical approach. It is thought to be a result of multiple etiologies ranging from internal sphincter achalasia to an abnormal processing of bacteria by HD bowel. The initial treatment, regardless of etiology or age, is with retrograde rectal saline irrigations and antibiotics. About 50% will experience at least 1 episode of HAEC postoperatively and 20% will have >4 episodes. The increasing number of episodes of postoperative HAEC correlates with increasing problems with social continence [113]. Many patients will "outgrow" recurrent HAEC after 5 years of age, and ongoing medical management includes prophylaxis with antibiotics, prebiotics, or probiotics. For those with life-threatening episodes of HAEC or when medical management has no effect, surgical management ranges from injection of Botox or sphincterotomy to creation of a stoma or an ACE. For patients with ongoing fecal incontinence after HD repair, consideration should be given to SNS or creation of ACE when appropriate with the goal of establishing social continence.

Some of the other pediatric bowel management patients that may ultimately seek the care of an adult colorectal surgeon include inflammatory bowel disease, familial adenomatous polyposis, mitochondrial cytopathy, colonic inertia, pelvic floor dysfunction, as well as other behavior and musculoskeletal disorders. Although the pediatric surgeon is heavily involved in the care of these patients as children, they will typically transition to an adult GI provider and be referred to the adult colorectal surgeon via this venue.

Transitional care should begin at age 12 years. The discussion should start with the patient and the family about what will be needed including provider, family, and patient readiness. An appropriately skilled adult provider should be identified. There should be clear communication between the pediatric and adult provider including a joint visit if possible and appropriate. Completion of transition should occur sometime between 16 and 21 years of age with the pediatric provider remaining available to the adult provider for ongoing discussion and questions. Transition of the complex colorectal patient should be a "clearly executed transition rather than a drift away from pediatric care" [117].

References

1. Guinard-Samuel V, Bonnard A, De Lagausie P, et al. Calretinin immunohistochemistry: a simple and efficient tool to diagnose Hirschsprung disease. Mod Pathol. 2009;22:1379–84.
2. Fryckman P, Short S. Hirschsprung-associated enterocolitis: prevention and therapy. Semin Pediatr Surg. 2012;21(4):328–35.
3. Swenson O. A new surgical treatment for Hirschsprung's disease. Surgery. 1950;28(2):371–83.
4. Yancey AG, Cromartie JE Jr, Ford JR, et al. A modification of the Swenson technique for congenital megacolon. J Natl Med Assoc. 1952;44(5):356–63.
5. Boley S. New modification of the surgical treatment of Hirschsprung's disease. Surgery. 1964;56:1015–7.
6. Canty T. Modified Duhamel procedure for treatment of Hirschsprung's disease in infancy and childhood: review of 41 consecutive cases. J Pediatr Surg. 1982;17(6):773–8.
7. Zhang S, Li J, Hu Y, et al. Comparison of laparoscopic-assisted operations and laparotomy operations for the treatment of Hirschsprung disease: evidence from a meta-analysis. Medicine. 2015;94(39):1–7. https://doi.org/10.1097/MD.0000000000001632.
8. Thomson D, Allin B, Long A-M, et al. Laparoscopic assistance for primary transanal pull-through in Hirschsprung's disease: a sys-

tematic review and meta-analysis. BMJ Open. 2015;5:e006063. https://doi.org/10.1136/bmjopen-2014-006063.
9. Roorda D, Abeln Z, Oosterlaan J, et al. Botulinum toxin injections after surgery for Hirschsprung disease: systematic review and meta-analysis. World J Gastroenterol. 2019;25(25):3268–80.
10. Prato AP, Bartow-McKenney C, Hudspeth K, et al. A metagenomics study on Hirschsprung's disease associated enterocolitis: biodiversity and gut microbial homeostasis depend on resection length and patient's clinical history. Front Pediatr. 2019;7:326. https://doi.org/10.3389/fped.2019.00326.
11. Frykman P, Nordenskjöld A, Kawaguchi A, et al. Characterization of bacterial and fungal microbiome in children with Hirschsprung disease with and without a history of enterocolitis: a multicenter study. Plos One. https://doi.org/10.1371/journal.pone.0124172 April 24, 2015.
12. Heikkinen M, Rintala RJ, Louhimo I. Bowel function and quality of life in adult patients with operated Hirschsprung's disease. Pediatr Surg Int. 1995;10:342–4.
13. Jarvi K, Laitakari EM, Koivusalo A, Rintala RJ, Pakarinen MP. Bowel function and gastrointestinal quality of life among adults operated for Hirschsprung disease during childhood: a population-based study. Ann Surg. 2010;252:977–81.
14. Neuvonen MI, Kyrklund K, Rintala RJ, Pakarinen MP. Bowel function and quality of life after transanal endorectal pull-through for Hirschsprung disease: controlled outcomes up to adulthood. Ann Surg. 2017;265:622–9.
15. Drissi F, Meurette G, Baayen C, et al. Long-term outcome of Hirschsprung disease: impact on quality of life and social condition at adult age. Dis Col Rectum. 2019;62(6):727–73.
16. Onishi S, Nakame K, Kaji T, et al. The bowel function and quality of life of Hirschsprung disease patients who have reached 18 years of age or older – the long-term outcomes after undergoing the transabdominal soave procedure. J Pediatr Surg. 2017;52(12):2001–5. https://doi.org/10.1016/j.jpedsurg.2017.08.036. Epub 2017 Sep 2
17. Ildstad ST, et al. Duplications of the alimentary tract. Clinical characteristics, preferred treatment and associated malformations. Ann Surg. 1988;208:184.
18. Laje P, Flake AW, Adzick NS. Prenatal diagnosis and postnatal resection of intraabdominal enteric duplications. J Peds Surg. 2010;45:1554.
19. Bower RJ, Sieber WK, Kiesewetter WB. Alimentary tract duplications in children. Ann Surg. 1978;188:669.
20. Bentley JF, Smith JR. Developmental posterior enteric remnants and spinal malformations: the split notochord syndrome. Arch Dis Chil. 1960;35:76.
21. Bremer JL. Diverticula and duplications of the intestinal tract. Arch Path. 1952;38:132.
22. Beach PD, et al. Duplication of the primitive hindgut of the human being. Surgery. 1961;49:779.
23. Mellish RW, Koop CE. Clinical manifestations of duplication of the bowel. Pediatrics. 1961;27:397.
24. Puligandla PS, Nguyen LT, St-Vil D, et al. Gastrointestinal duplications. J Pediatr Surg. 2003;38(05):740–4.
25. Jeziorczak PM, Warner BW. Enteric duplication. Clin Colon Rectal Surg. 2018;31:127–31.
26. Kottra JJ, Dodds WJ. Duplication of the large bowel. Am J Roentgenol Radium Therapy, Nucl Med. 1971;113:310.
27. Yousefzadeh DK, et al. Tubular colonic duplication – review of 1876-1981 literature. Pediatr Radiol. 1983;13:65.
28. Barr LL, Hayden CK Jr, Stansberry SD, Swischuk LE. Enteric duplication cysts in children: are their ultrasonographic wall characteristics diagnostic? Pediatr Radiol. 1990;20(05):326–8.
29. Yucesan S, Zorludemir U, Olcay I. Complete duplication of the colon. J Peds Surg. 1986;21:962.
30. LaQuaglia MP, et al. Rectal duplications. J Peds Surg. 1990;25:980.
31. Stern LE, Warner BW. Gastrointestinal duplications. Semin Pediatr Surg. 2000;9:135.
32. Loening-Baucke V. Constipation in early childhood: patient characteristics, treatment, and long-term follow up. Gut. 1993;34:1400–4.
33. Tabbers MM, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Ped Gastro Nut. 2014;58(2):258–74.
34. Tang YF, Chen JG, An HJ, et al. High-resolution anorectal manometry in newborns: normative values and diagnostic utility in Hirschsprung disease. Neurogastroenterol Motil. 2014;26(11):1565–72. https://doi.org/10.1111/nmo.12423. Epub 2014 Sep 27
35. Loening-Baucke V, et al. Anorectal manometry for the exclusion of Hirschsprung's disease in neonates. J Pediatr Gastroenterol Nutr. 1985;4:596.
36. Enríquez Zarabozo E, Núñez Núñez R, Ayuso Velasco R, et al. Anorectal manometry in the neonatal diagnosis of Hirschsprung's disease. Cir Pediatr. 2010;23(1):40–5.
37. Rodriguez L, Nurko S, Flores A. Factors associated with successful decrease and discontinuation of antegrade continence enemas (ACE) in children with defecation disorders: a study evaluating the effect of ACE on colon motility. Neurogastroenterol Motil. 2013;25:140–e81.
38. van den Berg MM, Di Lorenzo C, van Ginkel R, Mousa HM, Benninga MA. Barostat testing in children with functional gastrointestinal disorders. Curr Gastroenterol Rep. 2006;8:224–9.
39. Bonilla SF, Flores A, Jackson C-CA, Chwals WJ, Orkin BA. Management of pediatric patients with refractory constipation who fail cecostomy. J Pediatr Surg. 2013;48:1931–5.
40. Christison-Lagay ER, Rodriguez L, Kurtz M, Pierre KS, Doody DP, Goldstein AM. Antegrade colonic enemas and intestinal diversion are highly effective in the management of children with intractable constipation. J Pediatr Surg. 2010;45:213–9.
41. Rodriguez L, Sood M, Di Lorenzo C, Saps M. An ANMS-NASPGHAN consensus document on anorectal and colonic manometry in children. Neurogastroenterol Motil. 2017;29(1). https://doi.org/10.1111/nmo.12944. Epub 2016 Oct 9.
42. Roorda D, Abeln ZA, Oosterlaan J, van Heurn LW, Derikx JP. Botulinum toxin injections after surgery for Hirschsprung disease: systematic review and meta-analysis. World J Gastroenterol. 2019;25(25):3268–80. https://doi.org/10.3748/wjg.v25.i25.3268.
43. Halleran DR, Lu PL, Ahmad H, et al. Anal sphincter botulinum toxin injection in children with functional anorectal and colonic disorders: a large institutional study and review of the literature focusing on complications. J Pediatr Surg. 2019;54(11):2305–10. https://doi.org/10.1016/j.jpedsurg.2019.03.020. Epub 2019 Apr 23
44. Zerbib F, Siproudhis L, Lehur PA, Germain C, Mion F, Leroi AM, Coffin B, Le Sidaner A, Vitton V, Bouyssou-Cellier C, Chene G, CONSTIMOD study investigators. Randomized clinical trial of sacral nerve stimulation for refractory constipation. Br J Surg. 2017;104(3):205–13. https://doi.org/10.1002/bjs.10326. Epub 2016 Oct 25
45. Thaha MA, Abukar AA, Thin NN, Ramsanahie A, Knowles CH. Sacral nerve stimulation for faecal incontinence and constipation in adults. Cochrane Database Syst Rev. 2015;(8):CD004464. https://doi.org/10.1002/14651858.CD004464.pub3. Review
46. Ortiz H, de Miguel M, Rinaldi M, Oteiza F, Altomare DF. Functional outcome of sacral nerve stimulation in patients with severe constipation. Dis Colon Rectum. 2012;55(8):876–80. https://doi.org/10.1097/DCR.0b013e31825bc9af.
47. Maeda Y, Lundby L, Buntzen S, Laurberg S. Sacral nerve stimulation for constipation: suboptimal outcome and adverse events.

Dis Colon Rectum. 2010;53(7):995–9. https://doi.org/10.1007/DCR.0b013e3181d64207.
48. Sulkowski JP, Nacion KM, Deans KJ, Minneci PC, Levitt MA, Mousa HM, Alpert SA, Teich S. Sacral nerve stimulation: a promising therapy for fecal and urinary incontinence and constipation in children. J Pediatr Surg. 2015;50(10):1644–7. https://doi.org/10.1016/j.jpedsurg.2015.03.043. Epub 2015 Mar 26
49. Lu PL, Asti L, Lodwick DL, et al. Sacral nerve stimulation allows for decreased antegrade continence enema use in children with severe constipation. J Pediatr Surg. 2017;52(4):558–62. https://doi.org/10.1016/j.jpedsurg.2016.11.003. Epub 2016 Nov 10
50. Samuel M, Boddy SA, Capps S. Volvulus of the transverse and sigmoid colon. Pediatr Surg Int. 2000;16(7):522–4.
51. Asipu D, Jaffray B. Treatment of severe childhood constipation with restorative proctocolectomy. Arch Dis Child. 2010;95(11):867–70.
52. Ballantyne GH, et al. Volvulus of the colon. Incidence and mortality. Ann Surg. 1985;202(1):83–92.
53. Brothers TE, Strodel WE, Eckhauser FE. Endoscopy in colonic volvulus. Ann Surg. 1987;206(1):1–4.
54. Salas S, Angel CA, Salas N, et al. Sigmoid volvulus in children and adolescents. JACS. 2000;190(6):717–23.
55. Szmulowicz U, Hull T. Colonic physiology. In: Beck DE, Roberts PL, Saclarides TJ, Senagore AJ, Stamos ML, Wexner SD, ed, editors. The ASCRS textbook of colon and rectal surgery. Springer: New York. 2nd ed. 2011.
56. Antao B, Bradley V, Roberts JP, Shawis R. Management of rectal prolapse in children. Dis Colon Rectum. 2005;48:1620–5.
57. Malyshev YI, Gulin VA. Our experience with the treatment of rectal prolapse in infants and children. Am J Proctol. 1973;24:470–2.
58. Hintz GC, Zou VZ, Baird R. Sclerotherapy for rectal prolapse in children: a systematic review and meta-analysis. J Pediatr Surg. 2019;54(5):1083–8. https://doi.org/10.1016/j.jpedsurg.2019.01.033.
59. Morrison ZD, LaPlant M, Hess D, Segura B, Saltzman D. A systematic review of management options in pediatric rectal prolapse. J Pediatr Surg. 2019;54(9):1782–7. https://doi.org/10.1016/j.jpedsurg.2019.03.002.
60. Alfred Francois Trappey III, Galganski L, Saadai P, Stephenson J, Stark R, Farmer DL, Langer JC, Hirose S. Surgical management of pediatric rectal prolapse: a survey of the American Pediatric Surgical Association (APSA). J Pediatr Surg. 2019;54(10):2149–54. https://doi.org/10.1016/j.jpedsurg.2019.02.017.
61. Laituri CA, Garey CL, Fraser JD, et al. 15-year experience in the treatment of rectal prolapse in children. J Pediatr Surg. 2010;45:1607–9.
62. Flum AS, Golladay ES, Teitelbaum DH. Recurrent rectal prolapse following primary surgical treatment. Pediatr Surg Int. 2010;26:427–31.
63. Ismail M, Gabr K, Shalaby R. Laparoscopic management of persistent complete rectal prolapse in children. J Pediatr Surg. 2010;45:533–9.
64. Chan WK, Kay SM, Laberge J, Gallucci JG, Bensoussan AL, Yazbeck S. Injection sclerotherapy in the treatment of rectal prolapse in infants and children. J Pediatr Surg. 1998;33:225–58.
65. Kay N, Zachary RB. The treatment of rectal prolapse in children with injections of 30 percent saline solutions. J Pediatr Surg. 1970;5:334–7.
66. Dutta BN, Das AK. Treatment of prolapse rectum in children with injections of sclerosing agents. J Indian Med Assoc. 1977;69:275–6.
67. Wyllie GG. The injection treatment of rectal prolapse. J Pediatr Surg. 1979;14:62–4.
68. Bahador A, Foroutan HR, Hosseini S, Davani S. Effect of submucosal alcohol injection on prolonged rectal prolapse in infants and children. J Indian Assoc Pediatr Surg. 2008;13(1):11–3.
69. Philip AT, Marraffa JM. Death following injection sclerotherapy due to phenol toxicity. J Forensic Sci. 2012;57(05):1372–5.
70. Gabriel WB. Thiersch's operation for anal incontinence and minor degrees of rectal prolapse. Am J Surg. 1953;86(05):583–90.
71. High DW, Hertzler JH, Phillippart AI, Benson CD. Linear cauterization for the treatment of rectal prolapse in infants and children. Surg Gynecol Obstet. 1982;154:400–2.
72. Pena A, Hong A. The posterior sagittal trans-sphincteric and transrectal approach. Tech Coloproctol. 2003;7:35–44.
73. Sanders S, Vural O, Unal M. Management of rectal prolapse in children: Ekehorn's rectosacropexy. Pediatr Surg Int. 1999;15:111–4.
74. Ashcraft KW, Garred JL, Holder TM, Amoury RA, Sharp RJ, Murphy JP. Rectal prolapse: 17-year experience with the posterior repair and suspension. J Pediatr Surg. 1990;25:992–5.
75. Puri B. Rectal prolapse in children: laparoscopic suture rectopexy is a suitable alternative. J Indian Assoc Pediatr Surg. 2010;15:47–9.
76. Rentea RM, St. Peter SD. Pediatric rectal prolapse. Clin Colon Rectal Surg. 2018;31:108–16.
77. Buddicom E, Jamieson A, Beaslley S, King S. Perianal abscess in children: aiming for optimal management. ANZ J Surg. 2012;82:60–2.
78. Afsarlar CE, et al. Perianal abscess and fistula-in-ano in children: clinical characteristic, management and outcome. Pediatr Surg Int. 2011;27:1063–8.
79. Christison-Lagay ER, et al. Nonoperative management of perianal abscess in infants is associate with decreased risk for fistula formation. Pediatrics. 2007;120:e548–52.
80. Niyogi A, Agarwal T, Broadhurst J, Abel RM. Management of perianal abscess and fistula-in-ano in children. Eur J Pediatr Surg. 2010;20:35–9.
81. Al-Salem AH, Laing W, Talwalker V. Fistula- in-ano in infancy and childhood. J Pediaric Surg. 1994;29:436–8.
82. Watanabe Y, Todani T, Yamamoto S. Conservative management of fistula in ano in infants. Pediatr Surg Int. 1998;13:274–6.
83. Serour F, Gorenstein A. Characteristics of perianal abscess and fistula-in-ano in healthy children. World J Surg. 2006;30:467–72.
84. Karamatsu ML, Thorp AW, Brown L. Changes in community-associated methicillin-resistant Staphylococcus aureus skin and soft tissue infections presenting to pediatric emergency department. Pediatr Emerg Care. 2012;28:131–5.
85. Alt AL, Routh JC, Ashley RA, Boyce TG, Kramer SA. Superficial genitourinary abscesses in children: emergence of methicillin resistant Staphylococcus aureus. J Urol. 2008;180:1472–5.
86. Woods DL, Amrute KV. Trends of genital and nongenital community-acquired methicillin-resistant Staphylococcus aureus infections in urban pediatric population. J Low Genit Tract Dis. 2012;17:6–11.
87. Liao F-T, Chang C-J. Initial Experience with Fibrin Glue Treatment of Anal Fistulae in Children. Am Surg. 2018;84(6):1105–9.
88. Özdamar MY, Hirik E. Anal fissure epidemiology and related diseases in children. South Clin Ist Euras. 2018;29(4):295–300. https://doi.org/10.14744/scie.2018.84803.
89. Kenny SE, Irvine T, Driver CP, et al. Double blinded randomised controlled trial of topical glyceryl trinitrate in anal fissure. Arch Dis Child. 2001;85:404–7.
90. Tander B, Guven A, Demirbag S, et al. A prospective, randomized, double-blinded, placebo-controlled trial of glyceryl-trinitrate ointment in the treatment of children with anal fissure. J Pediatr Surg. 1999;34:1810–2.
91. Sonmez K, Demirogullari B, Ekingen G, et al. Randomized, placebo controlled treatment of anal fissure by lidocaine, EMLA, and GTN in children. J Pediatr Surg. 2002;37:1313–6.
92. Keshtgar AS, Ward HC, Clayden GS. Transcutaneous needle-free injection of botulinum toxin: a novel treatment of childhood constipation and anal fissure. J Pediatr Surg. 2009;44:1791–8.

93. Cohen A, Dehn T. Lateral subcutaneous sphincterotomy for treatment of anal fissure in children. Br J Surg. 1995;82:1341–2.
94. Joda AE, Al-Mayoof AF. Efficacy of nitroglycerine ointment in the treatment of pediatric anal fissure. J Pediatric Surg. 2017;52(11):1782–6.
95. Nelson RL, Thomas K, Morgan J, Jones A. Non surgical therapy for anal fissure. Cochrane Systematic Review – Intervention Version published: 15 February 2012. https://doi.org/10.1002/14651858.CD003431.pub3.
96. Malone PS, Ransley PG, Kiely EM. Preliminary report: the antegrade continence enema. Lancet. 1990;336(8725):1217–8.
97. Rivera MT, et al. Percutaneous colonoscopic cecostomy for management of chronic constipation in children. Gastrointest Endosc. 2001;53(2):225–8.
98. Cascio S, et al. MACE or caecostomy button for idiopathic constipation in children: a comparison of complications and outcomes. Pediatr Surg Int. 2004;20(7):484–7.
99. Shandling B, Chait PG, Richards HF. Percutaneous cecostomy: a new technique in the management of fecal incontinence. J Pediatr Surg. 1996;31(4):534–7.
100. Li C, Shanahan S, Livingston MH, Walton JM. Malone appendicostomy versus cecostomy tube insertion for children with intractable constipation: a systematic review and meta-analysis. J Pediatr Surg. 2018;53(5):885–91.
101. Halleran DR, Vilanova-Sanchez A, Rentea RM, et al. A comparison of Malone appendicostomy and cecostomy for antegrade access as adjuncts to a bowel management program for patients with functional constipation or fecal incontinence. J Pediatr Surg. 2019;54(1):123–8.
102. van den Berg MM, Hogan M, Caniano DA, et al. Colonic manometry as predictor of cecostomy success in children with defecation disorders. J Pediatr Surg. 2006;41:730–6.
103. Pensabene L, Youssef NN, Griffiths JM, et al. Colonic manometry in children with defecatory disorders. Role in diagnosis and management. Am J Gastroenterol. 2003;98:1052–7.
104. Mugie SM, et al. Ten-year experience using antegrade enemas in children. J Pediatr. 2012;161(4):700–4.
105. Gortazar de las Casas S, Rubio-Pérez I, Saavedra Ambrosy J, et al. Sacral nerve stimulation for constipation: long-term outcomes. Tech Coloproctol. 2019;23:559–64.
106. Schiano di Visconte M, Pasquali A, Cipolat Mis T, et al. Sacral nerve stimulation in slow-transit constipation: effectiveness at 5-year follow-up. Int J Color Dis. 2019;34(9):1529–40.
107. Lu PL, Asti L, Lodwick DL, et al. Sacral nerve stimulation allows for decreased antegrade continence enema use in children with severe constipation. J Pediatr Surg. 2017 Apr;52(4):558–62.
108. Cairo SB, Gasior A, Rollins MD, Rothstein DH. Challenges in transition of care for patients with anorectal malformations: a systematic review and recommendations for comprehensive care. Delivery of Surgical Care Committee of the American Academy of Pediatrics Section on Surgery. Dis Colon Rectum. 2018;61(3):390–9. https://doi.org/10.1097/DCR.0000000000001033.
109. Springford LR, Connor MJ, Jones K, Kapetanakis VV, Giuliani S. Prevalence of active long-term problems in patients with anorectal malformations: a systemic review. Dis Colon Rectum. 2016;59(6):570–80.
110. Versteegh HP, van Rooij IA, Levitt MA, et al. Long-term follow-up of functional outcome in patients with a cloacal malformation: a systematic review. J Pediatr Surg. 2013;48(11):2343–50. https://doi.org/10.1016/j.jpedsurg.2013.08.027.
111. Kyrklund K, Pakarinen MP, Koivusalo A, et al. Long-term bowel functional outcomes in rectourethral fistula treated with PSARP: controlled results after 4–29 years of follow-up. J Pediatr Surg. 2014;49:1635–42.
112. Danielson J, Karlbom U, Graf W, Wester T. Outcome in adults with anorectal malformations in relation to modern classification – which patients do we need to follow beyond childhood? J Pediatr Surg. 2017;52(3):463–8. https://doi.org/10.1016/j.jpedsurg.2016.10.051. Epub 2016 Nov 15
113. Neuvonen MA, Kyrklund K, Rintala RJ, Pakarinen MP. Bowel function and quality of life after transanal endorectal pull-through for Hirschsprung disease. Ann Surg. 2017;265:622–9.
114. Drissi F, Meurette G, Baayen C, Wyart V, et al. Long-term outcome of Hirschsprung disease: impact on quality of life and social condition at adult age. Dis Colon Rectum. 2019;62(6):727–32.
115. Meinds RJ, van der Steeg AFW, Sloots CEJ, et al. Long-term functional outcomes and quality of life in patients with Hirschsprung's disease. Br J Surg. 2019;106(4):499–507. https://doi.org/10.1002/bjs.11059. Epub 2019 Jan 17
116. Rintala RJ, Pakarinen MP. Long-term outcomes of Hirschsprung's disease. Semin Pediatr Surg. 2012;21:336–43.
117. American Academy of Pediatrics, American Academy of Family Physicians and American College of Physicians, Transitions Clinical Report Authoring Group. Clinical report – supporting health care transition from adolescence to adulthood in the medical home. Pediatrics. 2011;128:182–202.

Considerations for Geriatric Patients Undergoing Colorectal Surgery

67

Nicole M. Saur and Kirsten Bass Wilkins

Key Concepts

- Frailty affects a large number of our current patients and needs to be assessed.
- Prehabilitation is associated with improved outcomes.
- Enhanced recovery is useful and impactful for older patients and those with comorbidities, though all aspects of the program may not be applicable to each patient.
- Organ-specific recovery, including cognitive function, is critically important.

Introduction

Fifty-six percent of new colorectal cancer diagnoses in the United States are in patients older than 65 years of age [1]. An average 75-year-old male in good health has 18 years of life expectancy, while an 82-year-old has 10 years. However, the presence of severe comorbidities decreases life expectancy to 6 and 2 years, respectively for these patients [2]. While there still exists lack of consensus about the age cut-off to define geriatric patients (65 vs 70 vs 75 years old), there is consensus that patients should not be treated solely based on their age [3]. Despite this knowledge, as surgeons we still struggle to appropriately treat geriatric patients and especially those with cancer who have been shown to be susceptible to inappropriate care, either undertreatment based on their chronological age or overtreatment for their degree of frailty [4]. This chapter will help surgeons evaluate for and optimize frailty and focus on outcomes that matter most to patients.

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Frailty Screening

Frailty is a state of reduced tolerance to surgical stress secondary to progressive and lifelong physiological decline [5]. For example, a fit and a frail patient may undergo the same surgery with similar perioperative courses, but a frail patient has a significant functional decline after surgery and requires a prolonged recovery period and has a high probability of dying in the first year. On the other hand, the fit patient recovers quickly from surgery, is discharged from the hospital, and is able to resume all of his/her functional activity as before surgery. Therefore, assessing frailty before surgery is critical for surgical decision making by surgeons, patients, their caregivers, and the multidisciplinary team.

The gold standard for assessing frailty is comprehensive geriatric assessment (CGA), a multidimensional, interdisciplinary assessment of patients, typically performed by geriatricians [6]. The main domains assessed in the CGA are functional status, comorbidities, cognition and mental health status, nutrition, social status and support, fatigue, and assessment for polypharmacy and presence of geriatric syndromes [7]. There are a wide range of tools used for geriatric assessment, but there is currently no consensus on what tools are most useful. There appears to be a rate of frailty between 25% and 46% based on the study and tool used [8]. A study showed that less than a quarter of surgeons routinely collaborate with geriatricians [9]. Moreover, the number of geriatricians is limited with only approximately 7000 practicing geriatricians in the United States [10]. As a result, it is crucial for surgeons to become familiar with components of the CGA and to screen for frailty in the surgical clinic. There are a number of tools available, which are described below and summarized in Table 67.1. The tool chosen is not as important as the universal nature of screening. All surgical patients should be screened for frailty as we have all seen frail patients with Crohn's disease at 30 years of age and fit 80-year-old patients in our practices. With universal screening of older and frail-

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Table 67.1 Summary of commonly used frailty screening tests [11]

Test	Acronym	Range of possible scores	Frailty indicator threshold	Purpose
Eastern Collaborative Oncology Group Performance Status	ECOG PS	0–4	≥1	Evaluation of cancer burden on functional status
Katz Activities of Daily Living	ADL	0–6	<5	Evaluation of functional independence
Mini-Cog	Mini-Cog	0–5	≤2	Detection of cognitive impairment in older adults therefore suitable for a more thorough evaluation
Flemish version of the Triage Risk Screening Test	fTRST	0–6	≥2	Detection of hospitalized geriatric patients at risk for frailty
Timed Up and Go Test	TUG	Not applicable	≥20 s	10 feet (3 meters) walking test to determine gait speed
G8	G8	0–17	≤14	Detection of oncogeriatric patients who may benefit from comprehensive geriatric assessment
Nutritional risk screening	NRS	Normal to severely impaired nutritional status	Moderately to severely impaired	Evaluation of nutritional status taking into account BMI, weight loss, and food intake
American Society of Anesthesiologists score	ASA	1–5	Not applicable	Evaluation of preoperative general clinical condition and estimation of anesthesiologic risk
Charlson age comorbidity index	CACI	0–42	≥6	Evaluation of cumulative burden of patient's comorbidities

appearing patients, sparse resources are utilized for patients who need them most, and patients are optimized based on their individual frailty.

Domains of Geriatric Assessment (GA)

Functional Assessment

One of the most important domains of GA is functional assessment preoperatively. Assessing basic and instrumental activities of daily living [12] allow the clinician to determine the patient's ability to care for themselves. Common questions include: Are you able to prepare meal for yourself? Who does the house cleaning? and Do you take your medications on your own? These questions can easily be asked as part of the standard presurgical patient interview. Assessing gait speed and balance is an important objective assessment of patient's functional status. A simple Timed Up and Go (TUG) test [13] can be performed in the surgical clinic in less than a minute. The patient is asked to rise from their chair without using their arms, walk 10 ft (3 m), turn and walk back to the chair, and sit down. A time of greater than 20 seconds has been shown to be predictive of surgical complications. In the PREOP study, a prolonged TUG time was associated with a 50% rate of major complications compared to the rate of complications in the patients with a normal TUG of 13.6%. Furthermore, the authors compared the sensitivity of the TUG vs the American Society of Anesthesiologists (ASA) score to predict development of major complications and showed that the absolute risk for patients with prolonged TUG was 50% while the absolute risk for patients with ASA 3 or 4 was 24.8% [14].

Cognitive Function

Patients who are cognitively impaired preoperatively are at higher risk for postoperative delirium [15]. Many instruments are available to assess cognitive function of older adults. The time needed to complete these assessments range from 2 to 3 minutes for Mini-Cog [16] to more than 20 minutes for tests such as the Mini-Mental Status Exam [17]. The Mini-Cog is a simple test that includes a three-word recall and clock drawing. The patient must place the numbers correctly on the clock and set the time correctly to get full credit for the clock drawing. The test is scored out of 5 points. If the patient is able to recall all three words (3 points) and draw the clock with the appropriate time displayed (2 points), they receive a maximum score of 5.

Polypharmacy

It is imperative to review a patient's medication list. It gives you an idea on comorbid conditions that patient has, the severity (e.g., taking five different blood pressure medications versus one), and the possibility of medications interfering with anesthesia during the surgical procedure. When feasible, consult with a pharmacist for patients having excessive polypharmacy (e.g., more than ten medications).

Nutritional Assessment

With more emphasis on prehabilitation and optimization, assessing nutritional status of patients is essential. This will allow for a timely referral to dietician for improvement in nutritional status of patients while the preoperative workup and optimization are completed.

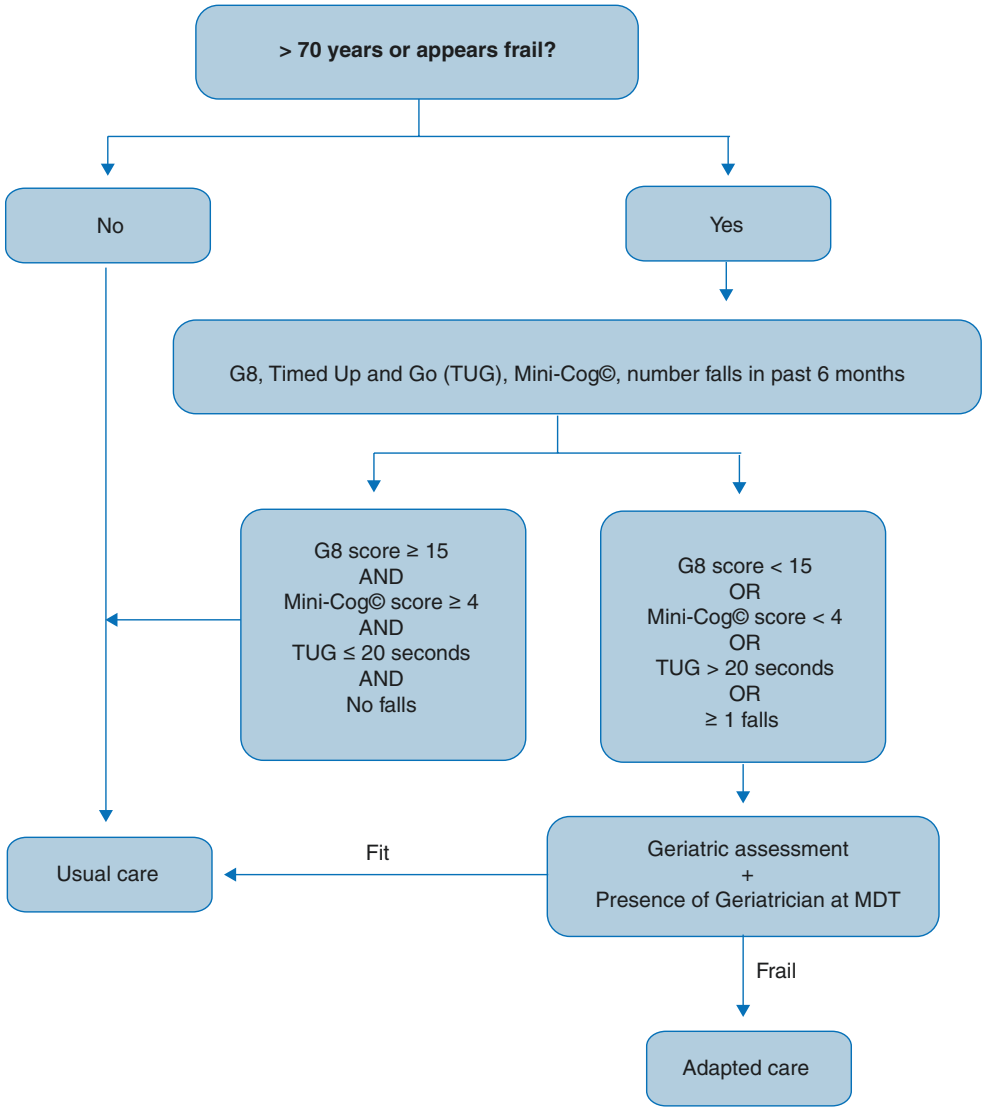

Fig. 67.1 A proposed algorithm to screen for frailty in the surgical office setting. Of note, the tools chosen are not as important as the universal nature of screening [18]

Social Support

Frail patients are more likely to have functional decline after surgery, and, as a result, they rely on their social support to provide care for them. One would assume that a patient living alone is fit. However, we know that they are vulnerable based on their lack of support if they have functional decline after surgery [11]. Assessing social support of a patient before surgery will allow preemptive involvement of the social worker and case manager during the perioperative period. Important questions to address are whether patient lives alone, if the spouse/partner/family member can take care of patient if needed during the perioperative period, how the patient came to clinic, and if they have any issues with transportation.

Patient's Wishes

Another key aspect of the frailty assessment is the discussion of the patient's goals and wishes regarding their diagnosis and their care. This should not be overlooked as it will guide their care from start to finish. If the patient has a cancer diagnosis, their wishes should be presented at the multidisciplinary care discussion [18]. In addition, it should be noted that patients may change their goals throughout treatment and the discussion should be ongoing.

Figure 67.1 presents an algorithm for simple office-based frailty evaluation to trigger additional referrals. Of note, this is an example of tests that can be combined for simple office-based frailty screening in less than 5 minutes. However, there are many frailty screening tools, and the most important recommendation is that *any* tool is utilized to screen for frailty.

Prehabilitation

Prehabilitation refers to interventions in the preoperative waiting period designed to optimize the patient's physical condition in order to reduce perioperative morbidity and pro-

mote an earlier return to preoperative functional status. Due to lack of uniformity of prehabilitation models in the literature, it is difficult to generalize the benefits of the various interventions studied. However, most meta-analyses do point toward decreased postoperative morbidity in geriatric patients who have participated in prehabilitation programs [18–24].

Prehabilitation programs should be multidimensional and include optimization of medical comorbidities, physical strength, nutritional status, and psychological well-being. There is no consensus of the appropriate duration of prehabilitation, but most models suggest that 4–6 weeks of preoperative intervention is sufficient to result in meaningful change [25, 26]. While patients may be anxious to proceed with surgery as soon as possible, it is the responsibility of the surgeon to explain the benefits of prehabilitation to the patient and family when patients have modifiable frailty factors. Furthermore, patients should be assured that cancer and overall outcome will not be compromised by this delay from the time of cancer diagnosis to operative intervention [27]. In fact, as patients become stronger, they may be more likely to be able to successfully complete definitive cancer treatment plans including surgery and adjuvant chemotherapy. Rectal cancer patients undergoing neoadjuvant chemotherapy and radiation are ideal patients to undergo prehabilitation as it may help them maintain strength during the neoadjuvant treatment period and be in a better condition to undergo radical surgery [18]. This is discussed further in section "Personalized Treatment of Rectal Cancer".

Medical prehabilitation includes the management and optimization of comorbid conditions such as diabetes, thyroid function, and cardiopulmonary status. Smoking cessation is paramount in reducing perioperative complications. Reduction of excessive alcohol intake will decrease the problems associated with alcohol withdrawal and delirium. Reduction of polypharmacy should also be a goal in coordination with a pharmacist. All of the above should be undertaken with coordinated care with a geriatrician whenever possible [28].

Preoperative cardiopulmonary fitness has been linked to postoperative outcomes in patients undergoing major abdominal surgery. One objective measure of cardiopulmonary fitness is the cardiopulmonary exercise test (CPET), which determines the ventilatory anaerobic threshold (VAT). Studies have demonstrated an association between a low VAT and postoperative morbidity in major noncardiac surgery. While CPET is considered the gold standard method of evaluation, it may not be readily available in all settings [29]. An easy alternative that can be utilized is the 6-min walk test or TUG. These screening tools require no specialized equipment or training to obtain meaningful results, which can be tracked over time [30].

Prehabilitation exercise programs are not standardized, but may include a combination of resistance and endurance training and breathing exercises at least 2–3 times a week for 30–45 minute sessions throughout the duration of the preoperative period. The exercise program may be completed under the guidance of a physiotherapist and supplemented with exercises to be completed at home. Of course, it is difficult to ensure compliance with the exercise program when it is solely completed in the home setting. Despite the heterogeneity of the prehabilitation exercise programs in the literature, they all aim to improve muscle strength and have been linked with better postoperative outcomes. In fact, Minnella et al. reported that colorectal surgery patients with poor baseline walking capacity were most likely to demonstrate meaningful improvement in physical function from prehabilitation [24]. This highlights the importance of the timely identification of patients with poor functional status so that they can benefit from prolonged physical prehabilitation.

Of note, in a follow-up study, the same group reported that almost 30% of colorectal patients do not respond to the prehabilitation [31], and another recently performed prospective, randomized study showed no benefit when they compared prehabilitation to rehabilitation [26]. Therefore, it remains necessary to identify the factors responsible for poor outcomes and determine what is best utilized to improve these factors. It is unclear if tumor stage or anabolic resistance affect the functional capacity of these patients to respond to exercise or nutritional optimization. There is a need for well-designed prospective studies to evaluate for a metabolic mechanism for failure of prehabilitation in some patients. In addition, the impact of prehabilitation on healthcare systems, timing and type of oncologic treatment, tumor progression, surgical stress response, and postoperative complications needs to be studied further [25].

Preoperative malnutrition is common in geriatric patients and has been linked to worse perioperative outcomes. Sarcopenia is also an important predictor of perioperative outcomes, and sarcopenia can occur in underweight, normal weight, and overweight patients. Thus, nutritional evaluation and supplementation are an important aspect of any prehabilitation program. Patients should be referred to a dietician early in the preoperative period and a full nutritional assessment undertaken. Patients should be given nutritional support with a targeted protein intake of 1.2–1.5 g/kg/day. Whey protein supplementation given prior to exercise may improve functional exercise capacity. Gillis et al., in a systematic review and meta-analysis, found that nutritional prehabilitation alone or combined with an exercise program decreased length of hospital stay following surgery and accelerated the return to presurgical functional capacity [21].

An additional aspect of prehabilitation addresses the psychological needs of patients facing the challenges of a possible cancer diagnosis and a major surgery and life-altering changes that may entail. Therefore, efforts should be made to address the anxiety and depression that is frequently present

in these patients. Anxiety-decreasing and relaxation strategies should be implemented by a psychologist whenever possible. It has been demonstrated that symptoms of anxiety and depression decrease when measured using the Hospital Anxiety and Depression Scale (HADS) when prehabilitation is utilized [22].

In summary, multimodal prehabilitation that focuses on medical optimization, improved functional capacity, optimal nutritional status, and decreased anxiety and depression should be the goal for geriatric patients undergoing colorectal surgery. While programs are not standardized to date, making it difficult to compare different prehabilitation studies, it is clear that prehabilitation does have a positive effect in postoperative outcomes.

Surgical Considerations

Enhanced recovery (ER) pathways have been shown to decrease perioperative complications and promote a more rapid recovery from surgery. This is a multidisciplinary approach that involves participation of the patient, patient's support system, surgeon, anesthesiologist, nurses, dieticians, and physiotherapists. The approach involves the utilization of evidence-based preoperative, intraoperative, and postoperative strategies to achieve these goals. These pathways are addressed in greater detail in this textbook, but some of the key elements are patient and family preoperative education, carbohydrate loading before surgery, early oral intake, goal-directed intravenous fluid therapy, avoidance of drains and nasogastric tubes, early ambulation, multimodal opiate-sparing pain control, and minimally invasive surgery. Studies have demonstrated that ER pathways are feasible to utilize in geriatric patients without an increase in perioperative complications and with the same benefits as those seen in younger patients [18, 23, 32–36]. Of course, care should be taken to modify certain aspects of ER pathways in older patients as in younger patients. For instance, NSAID use and extreme fluid restriction use should be avoided in patients with baseline renal insufficiency. Patients with known diabetes and gastroparesis should be monitored closely with the implementation of early feeding to reduce chances of aspiration.

Minimally invasive surgery should be offered to geriatric patients when deemed appropriate. Age alone should not be a contraindication to offering a patient laparoscopic surgery, and laparoscopic colorectal surgery is feasible in the geriatric population [18, 23, 37–40]. Consideration should be given to the hemodynamic changes secondary to the intraabdominal pressure associated with pneumoperitoneum. In that regard, laparoscopic surgery may not be appropriate for a patient with severely compromised cardiac ejection fraction or severe preexisting pulmonary compromise. However, this is not solely based on age, but on the overall preoperative risk assessment. Redo surgery and rectal cancer surgery is not a contraindication to laparoscopic surgery in geriatric patients, but as in all laparoscopic surgery, only experienced and facile laparoscopic surgeons should offer geriatric patients minimally invasive surgery so as to avoid prolonged time under general anesthesia and to prevent late conversion to open surgery.

If a geriatric patient is not considered a good candidate for minimally invasive surgery, components of the ER pathway should still be utilized as geriatric patients have been shown to benefit from such an approach even when open surgery is utilized [41].

Emergency colorectal surgery in geriatric patients has higher rates of morbidity and mortality. These outcomes are worse as frailty increases. Obviously, emergency surgery does not allow for medical optimization and the other components of prehabilitation which are useful at reducing morbidity. Emergency surgery is unavoidable in certain scenarios, and the patient and family should be informed of the increased risks and the extended time expected for a functional recovery. Zattoni et al. showed that the Flemish Triage Risk Screening Tool (fTRST) could be used in the emergency setting. The fTRST includes just five questions that can be asked of the patient or the caregiver in the emergency department: presence of cognitive decline (2 points), living alone or no help from partner/family available (1 point), reduced mobility or falls in the past 6 months (1 point), hospitalized in the past 3 months (1 point), and polypharmacy (≥ 5 different medications; 1 point). A score of 2 or greater was effective in predicting increased morbidity, mortality, and length of stay [42]. This data can be utilized to help patients and their caregivers decide on a treatment path and have an accurate prediction of their likelihood to survive surgery. As the population ages, there should be consideration for the continuation of "screening" for colorectal cancer in geriatric patients so as to avoid such emergency encounters secondary to advanced colorectal cancer [18, 43].

There are times when palliative surgery may be offered to geriatric patients with advanced disease. For instance, a patient in severe pain from an obstructing cancer with multiple liver metastases may be offered a diverting ostomy or colonic stent. However, "palliative" surgery should be avoided in geriatric patients undergoing surgery if there is a chance for cure. Surgeons should not be biased to do a lesser operation in a geriatric patient based on age alone. For instance, a patient with an obstructing sigmoid colon cancer without metastatic disease should not be simply given a diverting ostomy if the patient could tolerate resection of the primary lesion based on oncologic principles. As in younger patients, there should be the goal to achieve an R0 oncologic resection whenever possible in the medically optimized patient. Geriatric patients with node-positive disease should be considered for adjuvant chemotherapy based on

their postoperative frailty and a personal decision regarding treatment made between the patient and oncologist. While geriatric patients do have overall decreased survival from all causes, disease-specific survival is the same in geriatric colorectal cancer patients when they are offered standard-of-care cancer treatment [44]. There will obviously be situations when the risks of surgery far outweigh any perceived benefits of the procedure. In those situations, it is the role of the surgeon to educate the patient and the family about the futility of surgery and refer the patient to hospice or palliative care. This will be discussed further in section "Personalized Treatment of Rectal Cancer".

Postoperative Management

Geriatric patients, especially when frail, are at risk for postoperative complications. Even with optimal frailty screening and prehabilitation, patients have less chance to return to their preoperative functional status when they suffer complications. In the colorectal cohort of the Geriatric Oncology Surgical Assessment and Functional Recovery After Surgery (GOSAFE) study, patients who experienced one or more Clavien-Dindo complication had double the rate of functional decline when compared to the entire cohort (59 vs 31 percent) [45].

Geriatric comanagement is a system of collaboration between geriatrics and surgery teams with the goal of prevention and management of geriatric syndromes and complications [46]. The benefits of geriatric comanagement have been demonstrated in the orthopedic surgery population and include decreased length of stay, morbidity, and mortality [47–49].

Shahrokni et al. presented data on 1009 patients that were geriatric comanaged versus 846 that were managed by the surgery service alone after cancer surgery. They found that the adjusted rate of 90-day mortality was lower in geriatric-managed group versus the surgery-managed group (4.3% and 9.2%, respectively; 95% CI around difference − 7.3%, −2.5%; *p*-value <0.0001) [50].

Additional benefits of comanagement include early recognition and management of geriatric syndromes, such as delirium and falls. Patients who have experienced a prior delirium, who are dependent on caregivers, or who have cognitive impairment have an increased risk of delirium in the perioperative period. This increased risk should be identified preoperatively and communicated to the patient and caregiver in order to reduce the stress that comes with the development of delirium and to improve communication of early symptoms. When increased risk is present, delirium prevention measures should be taken, including improving orientation and safety, mobilization, and maintaining the day-night rhythm. A recent systematic review and meta-analysis demonstrated that these multifactorial interventions can reduce the risk of delirium, with an odds ratio of 0.47 (95% CI 0.38–0.58) [51].

If needed, rehabilitation can be utilized in older patients to maintain baseline function and slow the functional decline due to surgery. This process should start at admission as part of a multimodality program and continue beyond discharge. In order to maintain functional status, the focus of rehabilitation should be to restore daily living skills and mobility. Bedrest should be avoided at all costs because even a limited time can lead to a rapid loss of muscle mass, which is difficult to reverse [52].

Functional Recovery and Patient-Reported Outcomes

Functional recovery is as important as achieving low morbidity and mortality and good oncologic outcomes in geriatric patients undergoing colorectal surgery. Functional recovery includes distinct aspects including return to preoperative independence as well as organ-specific recovery. These functional aspects are perhaps even more important to geriatric patients than 5-year disease-free and overall survival since the expected life expectancy is already decreased in the very old patients. Thus, patients and families must be adequately informed of the possible functional consequences of surgery in order to make decisions which will lead to good functional recovery and increased health-related quality of life [11, 18].

Regaining functional independence requires the return to preoperative cognitive status and achieving adequate nutritional status, the ability to perform activities of daily living, and the ability to ambulate proficiently. As discussed above, one of the purposes of aggressive prehabilitation is to assure expedited functional recovery. Early hospital discharge and appropriate use of rehabilitation also contributes to the achievement of these goals [18].

Organ-specific functional recovery includes return of bowel, bladder, and sexual function. Bowel functional recovery is multifactorial and should include not only restoration of intestinal continuity but also assessment of function in patients who have achieved that continuity. Of particular concern are problems with fecal incontinence and bowel dysfunction associated with low anterior resection syndrome (LARS). These outcomes should be objectively measured using validated instruments such as the Cleveland Clinic Fecal Incontinence Score and the LARS score. Fecal incontinence in geriatric patients is a frequent reason for nursing home placement [18].

Therefore, a thoughtful discussion should be undertaken prior to surgery in geriatric patients when restoration of intestinal continuity is likely to result in fecal incontinence. For instance, an older woman with poor sphincter tone

would be expected to have better functional outcome with a permanent colostomy as opposed to a coloanal anastomosis following surgery for a distal rectal cancer. There is also evidence that diverting loop ileostomy reversal occurs less frequently in geriatric patients. Readmission to the hospital from ileostomy complications such as dehydration and acute renal insufficiency is not uncommon and potentially less tolerated in the geriatric population. This is not to say that diverting ileostomy should be avoided in geriatric patients, but careful patient selection is required to achieve acceptable outcomes in this population. When it is unlikely that a patient will undergo ileostomy reversal, it is probably better to offer the patient a permanent colostomy. This alleviates the potential complications from the ileostomy itself, but also potential complications from a second surgery to reverse the ileostomy. There is evidence to suggest that geriatric patients are able to tolerate a permanent colostomy as well as a restorative procedure and that geriatric patients with a stoma have the same health-related quality of life (HRQL) as geriatric patients without a stoma [53]. In addition, geriatric patients undergoing treatment for rectal cancer also need to be informed regarding the increased chances of bladder and sexual function that occur not only following pelvic surgery but also from neoadjuvant treatment from chemotherapy and radiation [54].

The prospective, international Geriatric Oncology Surgical Assessment and Functional Recovery After Surgery (GOSAFE) study recently finished enrollment of over 1000 geriatric patients undergoing curative cancer surgery [11]. Early results suggest that complete functional recovery (ADL score > 4, Mini-Cog >2, TUG <20) occurred in 26% of patients. On the other hand, decreased functional capacity was seen in 31% of patients alive at 90 days. In the same cohort, quality of life improved 90 days after surgery (mean EQ-5D index from 0.76 to 0.80) with the main drivers being improvement in pain and anxiety/depression [45]. Final results are forthcoming with the hope of giving patients a real-world prediction of their likelihood of functional recovery and their quality of life after surgery.

In evaluating quality of life, goals, and patient-reported outcomes, the International Consortium for Health Outcomes Measurement (ICHOM) has done considerable work. They aptly point out in Fig. 67.2 that outcomes that matter to patients related to cancer and related to being older often overlap. These overlapping points such as pain, function, and mobility likely have considerable improvement when successful surgery is undertaken [55].

Personalized Treatment of Rectal Cancer

Rectal cancer management is complex, and geriatric patients are complex. In an attempt to mitigate the complexity and offer rectal cancer patients personalized treat-

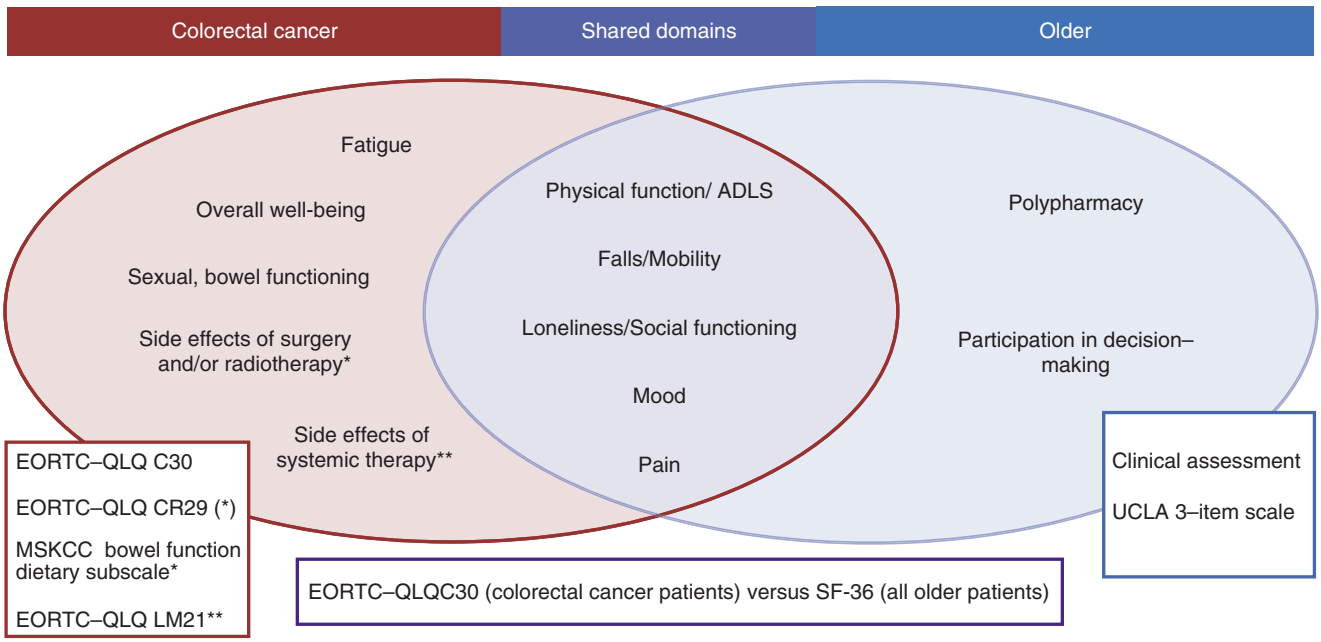

Fig. 67.2 Domains of the International Consortium for Health Outcomes Measurement (ICHOM) patient-reported outcome measures (PROMs) for patients with colorectal cancer and older persons. Several domains are assessed by both outcome measure sets, suggesting the outcome measures for colorectal cancer patients can be adapted to older patients, and with the addition of clinical assessment for polypharmacy and UCLA three-item scale for participation in decision-making, a comprehensive set for older colorectal cancer patients would be achieved. (Reused with permission from Doolin et al. [55]. Copyright © 2020 Elsevier)

ment of their rectal cancer, an interdisciplinary task force was created. The task force was comprised of 29 members representing the following organizations: the European Society of Surgical Oncology (ESSO), European Society of Coloproctology (ESCP), International Society of Geriatric Oncology (SIOG), and American College of Surgeons Commission on Cancer (ACS CoC) [18]. The recommendations of the group are summarized in Table 67.2, and a treatment algorithm is presented in Fig. 67.3.

Table 67.2 Summary of expert recommendations for the management of geriatric patients with rectal cancer [18]

General recommendations	All management decisions for an elderly patient with rectal cancer should consider: Physiological age Life expectancy Risks versus benefits of treatment vs nontreatment Treatment tolerance Patient goals/wishes Possible treatment barriers
Multidisciplinary team	Frailty and not chronological age should be used in risk stratification Mandatory frailty screening: ex; G8, Mini-Cog, Timed Up and Go, history of falls If frail, geriatrician should be routinely involved in multidisciplinary team If patient is fit, should treat with algorithms developed for younger patients
Patient optimization	Multidimensional prehabilitation should be utilized pretreatment and especially considered in the window for neoadjuvant chemoradiation (nCRT) Required elements include exercise, nutrition, treatment of anxiety/depression
Surgical treatment	Rectal resection with total mesorectal excision (TME): Open/laparoscopic/robotic/transanal TME (taTME) techniques for TME surgery are not contraindicated based on chronological age alone and should be considered in elderly patients Laparoscopy: Laparoscopy is safe and effective in the elderly population and should be utilized as the preferred option by experienced surgeons Robotic approaches can be considered based on surgeon preference, but have not been shown to be superior to laparoscopy and are associated with higher costs taTME: taTME is advised when utilized by expert surgeons as it has shown to be associated with decreased conversion rates. It should be noted that long-term data are lacking Local excision (LE): Clinicians should balance oncologic outcomes with goals of care/frailty LE is not recommended after radiation therapy secondary to increased morbidity Surgical emergencies: Efforts should be made to preempt surgical emergencies (bleeding, obstruction, perforation) and treat them early when they occur
Treatment of locally advanced disease	Neoadjuvant chemoradiotherapy: Can be considered to increase local control but should be noted that increased toxicity can prevent potentially curative surgery Capecitabine is contraindicated in renal failure Contact X-ray brachytherapy can be used as an adjunct for small residual tumors (<3 cm) following external beam radiation therapy (EBRT) or as monotherapy for early rectal cancer (cT1) less than 3 cm, in order to increase rate of complete clinical response, but is only available at selected centers EBRT +/− contact radiation can be considered for patients not suitable for surgery in order to improve local control Watch and wait: Should be considered in elderly patients with complete clinical response, but need experienced MD expertise by surgeons/radiologist/medical oncologist and radiation oncologist to be performed safely No single reliable predictive factor of complete response is available, but can evaluate size and rate of tumor shrinkage as useful prognosticators Required to take into account patient's goals/wishes Adjuvant chemotherapy: Adjuvant chemotherapy after nCRT and surgery is not advised in geriatric patients

Table 67.2 (continued)

Treatment of synchronous liver metastases	Liver metastasis: Liver surgery should only be performed with curative intent Neoadjuvant chemotherapy and radiation therapy (if indicated) is suggested, if primary asymptomatic Synchronous resections should be avoided
Outcomes	Enhanced recovery pathways: Should be applied to elderly patients based on reduced length of stay and overall complications Most important elements to include are early discontinuation of intravenous fluids, early oral intake, timely removal of the urinary catheter (when possible given pelvic dissection), early mobilization, very limited administration of opioids, and adoption of minimally invasive surgery Involvement of both patients and caregivers is crucial to increase compliance Functional recovery: Should be recorded as pivotal posttreatment endpoint, especially in the elderly Consideration should be given to the morbidity of "permanent" diverting loop ileostomy and prediction used to preferentially perform colostomies in patients who are not likely to undergo reversal Patient-reported outcome measures (PROMs): PROMs should no longer be considered secondary outcomes and instead be recorded by the clinical team posttreatment Prospective observational studies are needed to define outcomes Healthcare cost: Recommend shift toward value-based care as target for finance allocation Focus should be on early diagnosis and frailty assessment as tools to help contain costs

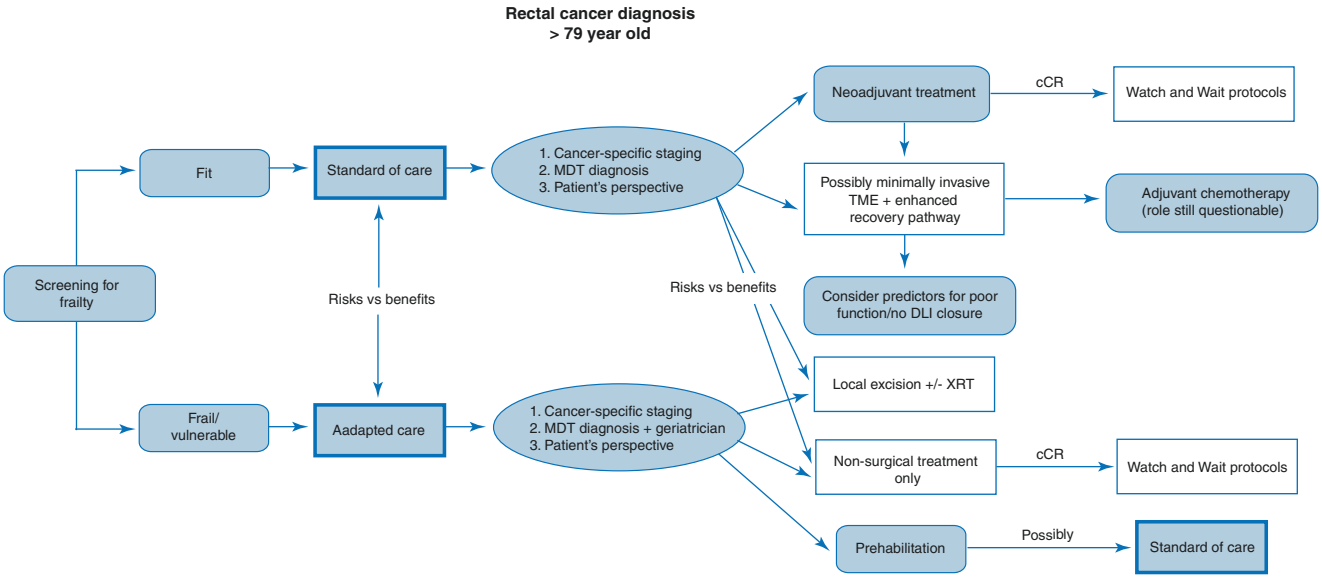

Fig. 67.3 Proposed treatment pathway for geriatric patients with rectal cancer. The treatment pathway is proposed for elderly patients with rectal cancer to guide treatment. It should be noted that treatment should be personalized for the individual patient with input from the patient and the treating multidisciplinary team [18]

One of the key findings stressed by the task force is presented in Fig. 67.4. The long-held historic belief was that older patients could not handle the surgical stress of rectal cancer surgery. However, with a better understanding of frailty and measures to improve fitness, improvement in both open and minimally invasive total mesorectal excision (TME) techniques leading to fewer complications and more efficient recovery, and improved perioperative care, TME surgery has become feasible in well-selected older adults. Therefore, since frailty rather than age has been established as the primary surgical risk factor, TME surgery is currently advised for all rectal patients who can undergo the extensive procedure, independent of their chronological age [18].

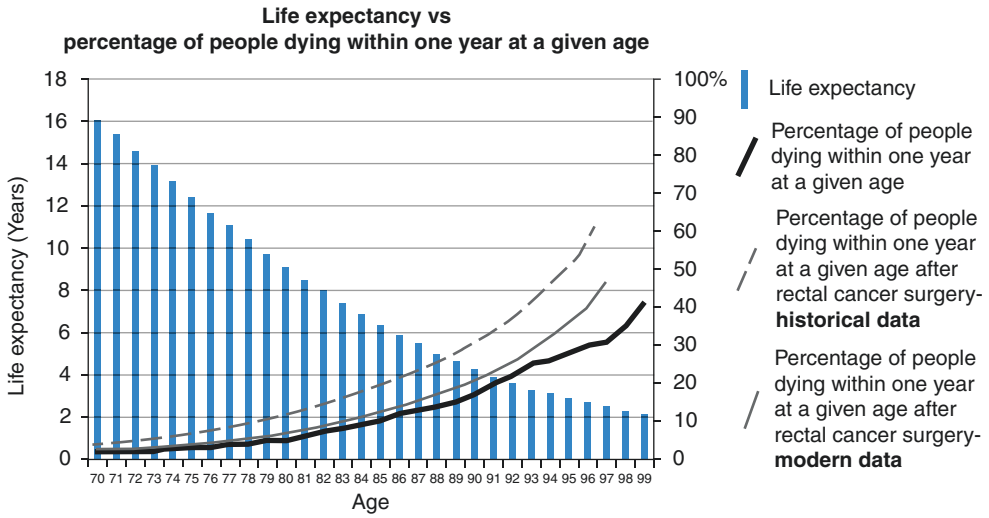

Fig. 67.4 The impact of rectal cancer surgery on life expectancy in geriatric patients. The graph demonstrates life expectancy in the elderly, which is generally higher, at a given age, than previously believed. Using historical data, total mesorectal excision was associated with an increased mortality and was, therefore, not advised. Modern surgical data suggest that elderly patients undergoing surgery today have a similar life expectancy to their peers without rectal cancer. Therefore, in properly selected patients, rectal cancer surgery is advised. (Original Data obtained from: 1. http://opendata.cbs.nl/statline/#/CBS/en/. Central Bureau of Statistics, Dutch life expectancy per year and change of dying within 1 year in the Dutch population 2015. 2. Kankerzorg in beeld – de oudere patient, chapter darmkanker by van Erning FN, Lemmens VEPP, Dekker JWT, Maas Haam, Rutten HJT, page 101–116, 2016 published by IKNL the Dutch Cancer Registry. 3. Rutten et al. [56] Reproduced with Permission (ref 18).)

Conclusions

Geriatric patients require multimodality, multispecialty intervention to improve their care. Patient goals and wishes should be identified and addressed early in the course of care. All patients should undergo office-based frailty screening with referral to a geriatric specialist if they are deemed to be frail. Frailty should be optimized with multimodality prehabilitation, and we expect prehabilitation programs to continue to evolve with changing evidence. Perioperative principles applied to all patients should be utilized in geriatric patients as well, including minimally invasive surgery and enhanced recovery programs. Geriatric comanagement has been shown to improve postoperative outcomes and identify and treat geriatric syndromes, such as delirium, early. Functional recovery and patient-reported outcomes are as important as cancer-related outcomes, especially in geriatric patients. These outcomes should be measured and the expected outcomes discussed with patients preoperatively.

Geriatric surgical patients are complex, especially those with rectal cancer. The treatment strategies and algorithms presented here can guide surgeons to provide personalized care and avoid undertreatment of patients based on their age and overtreatment of patients based on their frailty. This is an exciting time in treating geriatric colorectal patients as there has never been more interest in or study of the topic. As the continuing study results continue to be presented, we expect care of older patients will continue to improve and their care will continue to be challenging and rewarding for surgeons.

References

1. Siegel RL, Miller KD, Fedewa SA, et al. Colorectal cancer statistics, 2017. CA Cancer J Clin. 2017;67(3):177–93. https://doi.org/10.3322/caac.21395.
2. Walter LC, Covinsky KE. Cancer screening in elderly patients: a framework for individualized decision making. JAMA. 2001;285(21):2750–6.
3. Shahrokni A, Alexander K. The age of talking about age alone is over. Ann Surg Oncol. 2019;26(1):12–4. https://doi.org/10.1245/s10434-018-6983-7.
4. Lawler M, Selby P, Aapro MS, et al. Ageism in cancer care: time to change the mindset. BMJ. 2014;348:g1614.
5. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. Lancet. 2013;381:752–62.
6. Korc-Grodzicki B, Holmes HM, Shahrokni A. Geriatric assessment for oncologists. Cancer Biol Med. 2015;12:261–74.
7. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol. 2014;32(24):2595–603. https://doi.org/10.1200/JCO.2013.54.8347.
8. Fagard K, Leonard S, Deschodt M, et al. The impact of frailty on postoperative outcomes in individuals aged 65 and over undergoing elective surgery for colorectal cancer: a systematic review. J Geriatr Oncol. 2016;7(6):479–91. https://doi.org/10.1016/j.jgo.2016.06.001.

9. Ghignone F, Van Leeuwen B, Montroni I, et al. The assessment and management of older cancer patients: a SIOG surgical task force survey on surgeons' attitudes. Eur J Surg Oncol (EJSO). 2016;42:297–302.
10. Kottek A, Bates T, Spetz MJ. The roles and value of geriatricians in healthcare teams: a landscape analysis. San Francisco: UCSF Health Workforce Research Center on Long-Term Care; 2017.
11. Montroni I, Rostoft S, Spinelli A, et al. GOSAFE – Geriatric Oncology Surgical Assessment and Functional rEcovery after Surgery: early analysis on 977 patients. J Geriatr Oncol. 2019;S1879-4068(19)30168-7.; https://doi.org/10.1016/j.jgo.2019.06.017.
12. Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. J Am Geriatr Soc. 1983;31:721–7.
13. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39:142–8.
14. Huisman M, Audisio R, Ugolini G, et al. Screening for predictors of adverse outcome in onco-geriatric surgical patients: a multicenter prospective cohort study. Eur J Surg Oncol. 2015;41:844–51.
15. Rudolph JL, Jones RN, Rasmussen LS, et al. Independent vascular and cognitive risk factors for postoperative delirium. Am J Med. 2007;120:807–13.
16. Borson S, Scanlan J, Brush M, et al. The Mini-Cog: a cognitive 'vital signs' measure for dementia screening in multi-lingual elderly. Int J Geriatr Psychiatry. 2000;15:1021–7.
17. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc. 1992;40:922–35.
18. Montroni I, Ugolini G, Saur NM, et al. Personalized management of elderly patients with rectal cancer: expert recommendations of the European Society of Surgical Oncology, European Society of Coloproctology, International Society of Geriatric Oncology, and American College of Surgeons Commission on Cancer. Eur J Surg Oncol. 2018;44:1685–702.
19. Berkel AEM, Bongers BC, van Kamp M-JS, et al. The effects of prehabilitation versus usual care to reduce postoperative complications in high-risk patients with colorectal cancer or dysplasia scheduled for elective colorectal resection: study protocol of a randomized controlled trial. BMC Gastroenterol. 2018;18(29):1–14.
20. Moran J, Guinan E, McCormick P, et al. The ability of prehabilitation to influence postoperative outcome after intra-abdominal operation: a systematic review and meta-analysis. Surgery. 2016;160:1189–201.
21. Gillis C, Buhler K, Bresee L, et al. Effects of nutritional prehabilitation, with and without exercise, on outcomes of patients who undergo colorectal surgery: a systematic review and meta-analysis. Gastroenterology. 2018;155:391–410.
22. Hijazi Y, Gondal U, Aziz O. A systematic review of prehabilitation programs in abdominal cancer surgery. Int J Surg. 2017;39:156–62.
23. Souwer ETD, Bastiaannet E, de Bruijn S, et al. Comprehensive multidisciplinary care program for elderly colorectal cancer patients: "from prehabilitation to independence". Eur J Surg Oncol. 2018;44:1894–900.
24. Minnella EM, Awasthi R, Gillis C, et al. Patients with poor baseline walking capacity are most likely to improve their functional status with multimodal prehabilitation. Surgery. 2016;160:1070–9.
25. Carli F, Bessissow A, Awasthi R, Liberman S. Prehabilitation: finally utilizing frailty screening data. Eur J Surg Oncol. 2020;46(3):321–5. https://doi.org/10.1016/j.ejso.2020.01.001.
26. Carli F, Bousquet-Dion G, Awasthi R, et al. Effect of multimodal prehabilitation vs postoperative rehabilitation on 30-day postoperative complications for frail patients undergoing resection of colorectal cancer: a randomized clinical trial [published online ahead of print, 2020 Jan 22]. JAMA Surg. 2020;155:e195474. https://doi.org/10.1001/jamasurg.2019.5474.
27. Curtis NJ, West MA, Salib E, et al. Time from colorectal cancer diagnosis to laparoscopic curative surgery-is there a safe window for prehabilitation? Int J Color Dis. 2018;33:979–83.
28. Van Rooijen S, Carli F, Dalton SO, et al. Preoperative modifiable risk factors in colorectal surgery: an observational cohort study identifying the possible value of prehabilitation. Acta Oncol. 2017;56(2):329–34.
29. Lee CHA, Kong JC, Ismail H, et al. Systematic review and meta-analysis of objective assessment of physical fitness in patients undergoing colorectal cancer surgery. Dis Colon Rectum. 2018;61(3):400–9.
30. Northgraves MJ, Arunachalam L, Madden LA, et al. Feasibility of a novel exercise prehabilitation programme in patients scheduled for elective colorectal surgery: a feasibility randomised controlled trial [published online ahead of print, 2019 Nov 12]. Support Care Cancer. 2019. https://doi.org/10.1007/s00520-019-05098-0.
31. Minnella EM, Liberman AS, Charlebois P, et al. The impact of improved functional capacity before surgery on postoperative complications: a study in colorectal cancer. Acta Oncol. 2019;58(5):573–8. https://doi.org/10.1080/0284186X.2018.1557343.
32. Zeng WG, Liu MJ, Zhou ZX, et al. Enhanced recovery programme following laparoscopic colorectal resection for elderly patients. ANZ J Surg. 2018;88:582–6.
33. Hallam S, Rickard F, Reeves N, et al. Compliance with enhanced recovery protocols in elderly patients undergoing colorectal resection. Ann R Coll Surg Engl. 2018;100:570–9.
34. Slieker J, Frauche P, Jurt J, et al. Enhanced recovery ERAS for elderly: a safe and beneficial pathway in colorectal surgery. Int J Color Dis. 2017;32:215–21.
35. Launay-Savary M-V, Mathonnet M, Theissen A, et al. Are enhanced recovery programs in colorectal surgery feasible and useful in the elderly? A systematic review of the literature. J Visc Surg. 2017;154:29–35.
36. Pirrera B, Lucchi A, Gabbianelli C, et al. E.R.A.S. pathway in colorectal surgery in elderly: our experience: a retrospective cohort study. Int J Surg. 2017;43:101–6.
37. Ho B, Lewis A, Paz B. Laparoscopy can safely be performed in frail patients undergoing colon resection for cancer. Am Surg. 2017;83(10):1179–83.
38. Otsuka K, Kimura T, Hakozaki M, et al. Comparative benefits if laparoscopic surgery for colorectal cancer in octogenarians: a case-matched comparison of short- and long-term outcomes with middle-aged patients. Surg Today. 2017;47:587–94.
39. Kazama K, Aoyama T, Hayashi T, et al. Evaluation of short-term outcomes of laparoscopic-assisted surgery for colorectal cancer in elderly patients aged over 75 years old: a multi-institutional study (YSURG1401). BMC Surg. 2017;17(29):1–6.
40. Devoto L, Celentano V, Cohen R, et al. Colorectal cancer surgery in the very elderly patient: a systematic review of laparoscopic versus open colorectal resection. Int J Color Dis. 2017;32:1237–42.
41. Difronzo LA, Yamin N, Patel K, et al. Benefits of early feeding and early hospital discharge in elderly patients undergoing open colon resection. J Am Coll Surg. 2003;197:747–52.
42. Zattoni D, Montroni I, Saur NM, et al. A simple screening tool to predict outcomes in older adults undergoing emergency general surgery. J Am Geriatr Soc. 2019;67(2):309–16. https://doi.org/10.1111/jgs.15627.
43. Pirrera B, Vaccari S, Cuicchi D, et al. Impact of octogenerians on surgical outcome in colorectal cancer. Int J Surg. 2016;35:28–33.
44. Mothes H, Bauschke A, Schuele S, et al. Surgery for colorectal cancer in elderly patients: how can we improve outcome? J Cancer Res Clin Oncol. 2017;143:1879–89.

45. Saur N, Montroni I, Ugolini G, et al. Outcomes that matter to patients? The Geriatric Oncology Surgical Assessment and Functional rEcovery after Surgery (GOSAFE) study: subgroup analysis of 440 patients undergoing colorectal cancer surgery. J Geriatric Oncol. 2019;10(6S1):S11-S9.
46. Grigoryan KV, Javedan H, Rudolph JL. Ortho-geriatric care models and outcomes in hip fracture patients: a systematic review and meta-analysis. J Orthop Trauma. 2014;28(3):e49.
47. Friedman SM, Mendelson DA, Bingham KW, Kates SL. Impact of a comanaged geriatric fracture center on short-term hip fracture outcomes. Arch Intern Med. 2009;169(18):1712–7.
48. Moyet J, Deschasse G, Marquant B, Mertl P, Bloch F. Which is the optimal orthogeriatric care model to prevent mortality of elderly subjects post hip fractures? A systematic review and meta-analysis based on current clinical practice. Int Orthop. 2019;43(6):1449–54. https://doi.org/10.1007/s00264-018-3928-5. Epub 2018 Apr 24.
49. Friedman SM, Mendelson DA, Kates SL, McCann RM. Geriatric co-management of proximal femur fractures: total quality management and protocol-driven care result in better outcomes for a frail patient population. J Am Geriatr Soc. 2008;56(7):1349–56.
50. Shahrokni A, Tin A, Sarraf S. Reduced 90-day postoperative mortality through geriatric comanagement after cancer surgery. J Clin Oncol. 2019;37(suppl; abstr 11512).
51. Hshieh TT, Yue J, Oh E, Puelle M, Dowal S, Travison T, et al. Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. JAMA Intern Med. 2015;175(4):512e20.
52. Rostoft S, Hamaker ME. Basic geriatric principles for colorectal surgeons: how to optimize assessment and care of older patients in the perioperative period. Eur J Surg Oncol. 2020;46(3):310–5. https://doi.org/10.1016/j.ejso.2019.07.027.
53. Orsini RG, Thong MS, van de Poll-Franse LV, et al. Quality of life of older rectal cancer patients is not impaired by a permanent stoma. Eur J Surg Oncol. 2013;39(2):164–70. https://doi.org/10.1016/j.ejso.2012.10.005.
54. Haak HE, Maas M, Lambregts DMJ, Beets-Tan RGH, Beets GL, Dutch Watch-and-Wait Consortium. Is watch and wait a safe and effective way to treat rectal cancer in older patients? Eur J Surg Oncol. 2020;46(3):358–62. https://doi.org/10.1016/j.ejso.2020.01.005.
55. Doolin JW, Halpin M, Berry JL, Hshieh T, Zerillo JA. Why focus on patient-reported outcome measures in older colorectal cancer patients? Eur J Surg Oncol. 2020;46(3):394–401. https://doi.org/10.1016/j.ejso.2019.07.028.
56. Rutten HJ, Dulk d, Lemmens VE, van de Velde CJ, Marjinen CA. Controversies of total mesorectal excision for rectal cancer in elderly patients. Lancet Oncol. 2008;9(5)):494–501.

Healthcare Economics

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Walter R. Peters and Teresa deBeche-Adams

Key Concepts

- This textbook is dedicated to improving the quality of care provided to individual patients suffering from diseases of the small intestine, colon, rectum, and anus. That care does not occur in a vacuum, but within an incredibly complex healthcare economic environment.
- Decisions made by healthcare systems, insurers, employers, government agencies, pharmaceutical companies, medical device manufacturers, professional societies, and individual providers can often be understood only when viewed in the context of the entire system.
- Our patients make healthcare decisions, including whether, when, and where to seek care, from the perspective of their individual healthcare economic realities.
- This chapter will provide an overview of the complex healthcare environment in which we work, the issues that fuel the healthcare reform discussion, and the current payment system under which US surgeons are compensated.

Healthcare Economics: A Global Perspective

> The U.S. healthcare system is on a dangerous path, with a toxic combination of high costs, uneven quality, frequent errors, and limited access to care. Michael E. Porter, *Redefining Health Care: Creating Value-Based Competition on Results* [1].

Healthcare spending represents a large portion of the gross domestic product (GDP) of the economy in every developed country, but no country spends more on healthcare than the United States. This has not always been the case, but since the 1980s, the growth in US spending on healthcare has steadily outpaced that of all other major economies [2]. US healthcare expenditures in 2018 were $3.6 trillion, which was estimated to represent 16.9–17.7% of GDP, or $11,172 per person [3, 4]. By comparison, Switzerland had the second-highest expenditures at 12.2% of GDP, or $7317 per person. All other major industrialized nations spent a smaller portion of their GDP on healthcare, including Germany (11.2%), Japan (10.9%), and the United Kingdom (9.8%) [5]. While spending less on healthcare, many members of the Organisation for Economic Co-operation and Development (OECD) have achieved universal or near-universal access to core healthcare services. In 2018, only 90.8% of the US population had health insurance coverage, ranking the United States 35th out of 36 OECD countries [5].

Despite massive spending on healthcare, common outcome metrics for the United States are not exceptional. The US life expectancy at birth (78.6 years in 2018) is the lowest of the G7 economies, trailing Japan (84.2 years), Italy (83 years), France (82.6 years), Canada (82 years), the United Kingdom (81.3 years), and Germany (81.1 years). US life expectancy at birth ranks 28th out of 36 member countries of the OECD. Cancer outcomes in the United States are consistently better than the average of the OECD countries, including 5-year survival for colon cancer and rectal cancer, but avoidable mortality rates are higher than average [5].

Why does the United States spend so much more on healthcare than other advanced nations? The two primary determinants of total healthcare spending are the quantity of resources utilized and the prices paid for those resources. It might be anticipated that differences in healthcare delivery systems and the social determinants of disease, such as smoking, obesity, education, nutritional support, and opioid addiction, might result in differences in utilization of resources between the world's developed countries. Numerous reviews of OECD and other data sets have found that utilization of resources in the United States is similar to that of other countries. The United States has similar numbers of hospital beds,

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physicians, and nurses as other countries, although there is higher utilization of advanced imaging and some common surgical procedures than the OECD average [6–8].

Prices for healthcare resources, however, are substantially higher in the United States than in other countries. Healthcare is labor-intensive, and wealthy countries, like the United States, generally have higher wages than less affluent countries. Remuneration for generalist physicians, specialist physicians, and nurses in the United States were highest in a comparison of 11 high-income countries, both in absolute terms and relative to the average non-healthcare worker [7]. Pharmaceutical prices are also far higher in the United States than in other countries. The same comparison of 11 high-income countries found that a sample of commonly prescribed drugs cost nearly twice as much in the United States as the average price across all 11 countries [7]. Pharmaceutical expenditures per capita in the United States are more than double the OECD average [5]. The United States also spends more on administrative costs than other countries, due to the fragmented and complex system of healthcare financing. Administrative costs represent 8% of the total healthcare expenditure in the United States, more than double the costs in other high-income countries. In 2015, US administrative costs, $787 per capita, were almost nine times higher than the OECD average of $90 [6, 7, 9].

There are a variety of healthcare delivery models currently in use around the world. The United Kingdom, for example, provides universal care through the National Health Service, which is funded largely through general tax revenues. Canada relies on provinces and territories to plan and co-fund a universal public insurance program. Switzerland utilizes federally mandated health insurance to fund healthcare delivery, but much of the regulation of the system is delegated to cantons and municipalities [10–12]. Financing of the US healthcare system is more complex, with a mixture of payers for specific populations.

US Healthcare Finance

The federal government is the largest single purchaser of healthcare services in the United States. While employer-sponsored health plans provide benefits for 49% of Americans, this coverage is administered through a mixture of private insurance companies and self-funded plans. Medicaid (20%), Medicare (14%), and military programs (1%) provide insurance coverage for 35% of the US population [13]. Total Federal spending on healthcare programs totaled over $1 trillion in 2018, representing approximately 25% of the Federal budget [4, 14].

Medicare

Medicare was one of the signature achievements of President Lyndon Johnson's Great Society legislative agenda in 1965. Passed over the long-standing objection of the AMA, Medicare was created to compliment Social Security in providing a safety net for retired Americans [15]. It is entirely funded by the federal government and provides a broad array of healthcare services for retired individuals over age 65 and patients with end-stage renal disease, amyotrophic lateral sclerosis, and permanent disability. Medicare initially consisted of two complimentary plans, one for hospital care and the other for physician services, but has expanded its offerings over the past five decades. Part A, also known as the Hospital Insurance program, provides coverage to all eligible Americans for inpatient hospital, skilled nursing facility, some home health visits, and hospice care. It is primarily funded through the collection of payroll taxes from both employers and employees. Part B requires voluntary enrollment and offers coverage for medically necessary or preventive services by qualified providers. It is funded through general tax revenues and participant premiums [16, 17]. Medicare Part C, now called Medicare Advantage (MA), was authorized in 1982 to provide Medicare recipients an alternative to traditional fee-for-service Medicare Part B. MA plans are administered by private insurers who receive capitated payments from Medicare to cover all Part A and Part B services. Enrollees in Medicare Advantage continue to pay the premium for Part B and may be required to pay a supplemental premium. These plans typically offer extended coverage for services not covered by Medicare Part B, including dental, vision, and fitness services. MA plans have grown in popularity over the past decade; in 2019, 34% of Medicare recipients were enrolled in MA plans [17, 18]. The Medicare Modernization Act of 2003 (MMA) authorized Medicare Part D, a voluntary program to provide prescription drug coverage. These benefits are administered by private insurers as either stand-alone prescription drug plans (PDPs) or as part of a Medicare Advantage plan. These plans have become very popular, and by 2019, 70% of Medicare beneficiaries had Part D benefits [17, 19].

Medicaid

Medicaid was also established in 1965, as a companion to Medicare, with the goal of providing healthcare insurance for the poor. Unlike Medicare, the Medicaid program is a partnership between the states and the federal government. The federal government sets core eligibility and benefit requirements, while the individual states administer the pro-

gram and have flexibility to expand eligibility, define covered services, and choose the healthcare delivery model. Funding is provided jointly by the federal government and the states with the federal contribution ranging from 50% to 78%, depending on the state's per capita income. Federal matching funds are provided for low-income children and their parents, pregnant women, the elderly, and those with disabilities. In addition, the Affordable Care Act requires the federal government to provide 90% of the funding for newly eligible adults under age 65 with incomes at or below 138 percent of the Federal Poverty Level (FPL) in states that elect to expand Medicaid coverage. The Children's Health Insurance Program (CHIP) is a supplemental program that was authorized in 1997 and provides additional federal funds to allow states to extend insurance coverage to uninsured children whose families have incomes above the Medicaid threshold. Medicaid has become an integral part of the US healthcare system, providing coverage for 20% of the population, and is especially important for certain at-risk populations. In most states, approximately half of all deliveries and over 60% of nursing home residents are covered by Medicaid. Children represent 43% of Medicaid enrollees nationwide [20–22].

Employer-Sponsored Insurance

Many employers sponsor insurance coverage for their workers and dependents, which now covers almost half of all Americans. The practice began during World War II when wage and price controls prevented employers from raising wages, but insurance coverage could be offered as a benefit to attract or retain workers. Because health insurance was very inexpensive at the time, and because the cost was considered a pre-tax business expense, not taxable for the worker, the practice continued after the war. Since 2014, the Patient Protections and Affordable Care Act of 2010 (ACA) mandates that employers with more than 50 employees offer affordable health insurance to their employees or pay a penalty. A recent survey found that 56% of small businesses (<200 employees) and 99% of large businesses (≥200 employees) offered health insurance benefits to at least some groups of employees in 2019. However, only 61% of workers at companies offering insurance benefits were enrolled in a plan offered by the company. As the cost of health insurance has increased over the past decades, employers have begun shifting more of the cost to their employees in the form of higher deductibles and greater cost sharing. The average cost for family coverage through an employer-sponsored plan in 2019 was $20,576 with the employee responsible for 30% of the premium, on average. The portion of the premium paid by the employee has increased more rapidly over the past 5 years (22%) than wages (14%) or inflation (8%) [23].

Individual (Non-group) Insurance

While a robust market has existed for the sale and purchase of large-group health insurance policies, the same was not always true for policies sold to individuals not covered by an employer-sponsored plan. Title I of the ACA established insurance exchanges, or markets, in each state to allow individuals and small businesses a greater opportunity to purchase coverage for themselves or their employees at competitive prices [24]. These individual policies now provide coverage for approximately 6% of Americans.

Healthcare and Politics

The role of government in healthcare finance has been a topic of vigorous political debate for at least the last 75 years. President Truman first advocated for national health insurance in 1945 and 1949. He was met with overwhelming opposition from the Republican-controlled Congress and the American Medical Association. Medicare and Medicaid were hotly debated in 1965 and were enacted only after President Johnson brokered numerous compromises to achieve passage [15]. Healthcare reform efforts by President Clinton in 1993–1994 failed to garner bipartisan support and ended with the loss of the Democratic majority in Congress [25]. The Affordable Care Act was passed on a strictly party-line vote and has continued to engender strong opposition from those who opposed its passage [26]. As our political landscape has become increasingly polarized, several healthcare policy topics will remain in the public discussion for the foreseeable future. These topics are relevant to surgeons because they impact our patient's ability and willingness to seek medical care and they influence a wide range of financial decisions made by healthcare providers.

The Future of the ACA

The Affordable Care Act was designed to increase the number of Americans with insurance coverage by several mechanisms. Employers with more than 50 employees were required to provide health insurance or pay a penalty, the "Employer Mandate." Individuals were required to show proof of insurance or pay a penalty, a requirement known as the "Individual Mandate." Healthcare insurance exchanges

were established in every state to give individuals a market in which to purchase insurance coverage. Finally, states were required to expand Medicaid eligibility to include those earning up to 138% of the FPL in order to continue receiving the federal contribution for Medicaid coverage. The federal government was to cover the entire increased cost of expanding Medicaid coverage for 5 years and at least 90% of the cost thereafter.

The constitutionality of the ACA was immediately challenged, and in 2012 the Supreme Court ruled in *National Federation of Independent Business v. Sebelius* that the Individual Mandate was valid under Congress' taxing authority but that states could not be required to expand Medicaid eligibility, substantially undermining one of the key tactics to expand insurance coverage. Despite this, 36 states and the District of Columbia have expanded Medicaid eligibility, resulting in greater variation between states in Medicaid eligibility and coverage. Medicaid enrollment increased 34% from 2013 to 2019 in states that expanded Medicaid, while non-expansion states saw an increase of only 9.1% [27].

Efforts to weaken or repeal the ACA have increased since the election of 2016. An attempt to repeal the ACA failed by one vote in the US Senate in 2017. Later that year, Congress reduced the penalty, or tax, for failing to purchase insurance as required by the Individual Mandate to $0. This has resulted in renewed legal challenges to the constitutionality of the ACA, arguing that without such a penalty, Congress has no right to mandate an individual obtain coverage. This litigation has pitted states against one another and will ultimately be decided by the Supreme Court [28]. Other efforts to weaken the ACA have included state-imposed work requirements on Medicaid recipients, refusal of 14 states to expand Medicaid, efforts to reduce enrollment through the exchanges, and policy changes intended to destabilize the exchange markets [26]. The debate about the future of the ACA, whether to repeal or strengthen it, will continue following the elections of 2020.

Underinsurance

Even with healthcare insurance coverage, some individuals cannot afford or gain access to healthcare. The National Health Interview Survey found that enrollment in high deductible health plans, defined as those with >$1300 deductible for individuals and >$2600 for families, has increased from 14.8% of employer-based coverage in 2007 to 43.4% in 2017 [29]. Average deductibles for employer-based coverage have increased by 162% from 2009 to 2019. A survey of individuals with employer-based coverage found that 40% reported that they have problems affording healthcare insurance or medical bills. Approximately half said that they, or a family member, had postponed healthcare or prescriptions due to cost within the past 12 months [23].

The ACA relied upon the expansion of Medicaid eligibility to extend coverage to millions of Americans. However, traditionally low fee schedules have resulted in many physicians limiting the number of Medicaid patients they will see. A 2015 survey of primary care physicians found that only 71.6% were accepting new Medicaid patients, compared to 77.4% for new Medicare patients and 92.4% for new private insurance patients [30]. The provision of health insurance, whether through Medicaid or employer-based plans, does not guarantee access to healthcare services if patients cannot afford their deductible or find a provider willing to accept their form of insurance.

Surprise Medical Billing

Surprise medical billing refers to unexpected charges incurred by an insured patient for healthcare services provided by an out-of-network physician or facility. This may occur in the case of a medical emergency but also may occur when patients undergo elective surgery at in-network facilities by in-network surgeons. Other physicians that are not chosen by the patient, such as an anesthesiologist, pathologist, or radiologist, may not be in the patient's network and can bill the patient directly for whatever fee they believe is appropriate. These "surprise bills" may be paid fully, partially, or not at all by the patient's insurance carrier. The provider may then "balance bill" the patient for any amount not paid by the insurance company.

A recent study of 347,000 patients who underwent elective surgical procedures performed by in-network surgeons at in-network facilities over a 5-year period found out-of-network bills associated with 20.5% of cases. The mean potential "balance bill" was $2011. More complex procedures and cases with complications were more likely to result in an out-of-network bill. Anesthesiologists and surgical assistants were the most likely providers to submit an out-of-network charge [31].

Surprise medical bills are a symptom of the fragmented nature of healthcare delivery. They are a source of frustration to patients and can result in significant financial hardship. This issue has attracted bipartisan attention in Congress, and many legislative solutions have been proposed. The debate is likely to continue after the 2020 elections..

Rural Hospital Closures

Since 2005, 170 hospitals in rural counties have closed, including 19 in 2019. A 2020 study found that 354 rural hos-

pitals in 40 states, 25% of the nation's rural hospitals, were financially stressed and at risk of closing unless their financial situations improved [32]. Rural hospitals struggle to survive in today's healthcare economic environment for several reasons. Population declines and a shift to outpatient services have left many hospitals with too many inpatient beds. It is more costly to provide technologically advanced care for a smaller patient base. Patients with the means to do so are often willing to travel to larger facilities for elective care. Rural hospitals are often left with a payer mix including increased shares of Medicare, Medicaid, and unfunded patients. This problem has been exacerbated in states that have not expanded Medicaid eligibility; between 2010 and 2018, approximately two-thirds of rural hospital closures occurred in non-expansion states [33]. Medicaid expansion has been associated with improved financial performance and lessened risk of closure, especially for rural hospitals [34]. The threatened loss of rural hospitals has been the subject of Congressional proposals, but a solution has not yet been found. Possible policy solutions include payment reforms to support rural hospitals, Medicaid expansion, or changes in healthcare delivery models, such as telehealth, to enable delivery of care in rural areas.

Physician Reimbursement: The Quality Payment Program

The processes by which a surgeon's care is described and compensated makes up another complex part of the healthcare economic environment. Because of the federal government's role as the largest single payer for healthcare services, the Centers for Medicare and Medicaid Services (CMS) payment programs are extremely important for surgeons to understand.

Medicare Access and Children's Health Insurance Program Reauthorization Act of 2015 (MACRA)

MACRA was passed with bipartisan support and signed into law on April 16, 2015. It repealed the sustainable growth rate (SGR) approach to Medicare fee schedule adjustments and prepared the way for Medicare to reward clinicians for value rather than volume. Under the SGR approach, an annual physician fee schedule update would be released which carried the threat of a negative adjustment in payments to physicians. Designed as a method to ensure that the yearly increase in the expense per Medicare beneficiary did not exceed the growth in GDP, the fee schedule could be suspended or adjusted by Congress. This temporary "doc fix" only served to defer a permanent solution to the flawed payment system [35].

MACRA created a new payment system, the Quality Payment Program (QPP). It streamlined multiple quality programs under the new Merit-Based Incentive Payments System (MIPS) and provided bonus payments for participation in eligible alternative payment models (APMs). CMS released the final rule governing the QPP in October of 2016 declaring that provider performance during calendar year (CY) 2017 would determine reimbursement for CY 2019. This left little time for physicians to understand the QPP before its implementation and resulted in significant implications for practices that caused concern on the part of many surgeons. Not all physicians are required to participate in QPP; CMS estimated that a low-volume threshold would exempt one-third of Medicare physicians. Physicians seeing fewer than 100 Medicare patients annually or submitting less than $30,000 in Medicare Part B allowable charges were exempt from reporting requirements in 2017; therefore, their Medicare fee schedule remained flat in CY 2019. While an exemption from the QPPs new requirements might have seemed beneficial to providers, in a world where practice expenses and cost of living increase every year, a flat fee schedule is an impractical long-term strategy for success [35].

In September 2018, a new funding opportunity was announced by CMS through the "Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) Funding Opportunity: Measure Development for the Quality Payment Program." Cooperative agreements provided a unique opportunity to partner with clinicians, patients, and other stakeholders to give financial (up to $30 million) and limited technical support to develop, improve, update, or expand measures to use in the QPP. The CMS Quality Measure Development Plan set up initial priority areas to include outcome measures (e.g., patient-reported outcome and functional status measures), patient experience measures, care coordination measures, and measures of appropriate use of services. The goal of these measures is to minimize administrative burden on clinicians, improve outcomes for patients, and drive increased value in care. It is critical that the expertise and insight of those on the front lines be leveraged to develop measures that are relevant and contribute to building a truly value-based healthcare system [35].

To better understand the two value-based payment model pathways developed for the QPP, the Merit-Based Incentive Payment System (MIPS) and the alternative payment model (APS), we will discuss each in further detail.

Merit-Based Incentive Payment System (MIPS)

The Merit-Based Incentive Payment System (MIPS) was designed to connect payments to quality and cost-efficient care, motivate improvement in care processes and health outcomes, increase the use of healthcare information, and reduce the cost of care. This track includes three renamed quality programs (quality, cost, and promoting interoperability) and added a new performance category (improvement activities). The quality element of the score replaced the Physician Quality Reporting System (PQRS). Cost is predicated on the Value-Based Payment Modifier (VBPM), and PI replaced meaningful use. An MIPS score is assigned to each participating provider based on these components. Performance in each category is weighted and used to calculate a final score (0–100). As a reference point, the threshold for the 2019 performance period was 30 points. Payment adjustments are based on performance from 2 years prior (e.g., the MIPS score based on 2017 data was used to adjust the Medicare fee schedule beginning in CY 2019). Initial adjustments ranged from −4% to +4% but will gradually increase to ±9% by 2022 [36].

MIPS is designed to be budget neutral, meaning that the money withheld in penalties will be used to offset positive adjustments to the fee schedule. Whereby CMS made it relatively easy for a provider to evade penalty in 2019, it is unlikely that there will be large sums available in the future to pay incentives. MACRA did set aside an additional $500 million to reward "exceptional" providers based on quality metrics. Exceptional performers that meet the additional performance threshold could receive a further sliding scale positive payment adjustment of up to 10%. The exceptional performance threshold for the 2019 period was set at 75 points. Exceptional performance adjustments occur outside of budget neutrality [35].

Providers can report MIPS data as individuals, as a group, or as both an individual and a group. A group is classified as two or more providers under the same taxpayer identification number (TIN). Reporting as a group may be easier, especially for physicians employed in a large group practice. It is important to note, however, that all providers within the group will receive the same MIPS score and that score may be based on quality metrics that have nothing to do with an individual provider's practice. For instance, a colorectal surgeon employed in a large multi-specialty group practice may have a quality score determined by primary care metrics (e.g., smoking cessation, diabetic retinal eye exam, breast cancer and colorectal cancer screening, etc.) due to the ease in capturing and reporting of this data. Certain eligible providers can report data as an individual and as part of a group holding the same TIN. Under this reporting, the clinician is evaluated across all four MIPS categories on their individual performance and on the group's performance. The final score is calculated for each evaluation as an individual and under the group's TIN. The clinician will receive a payment adjustment based on the higher of the two scores [36].

Advanced Alternative Payment Model (A-APM)

A much smaller percentage of physicians participate in the QPP through an Advanced APM (A-APM). This track offers a 5% incentive for achieving threshold levels of payments or patients through advanced APMs. If these thresholds are achieved, physicians are excluded from the MIPS reporting requirements and payment adjustment. Under the ACA, accountable care organizations (ACOs) were established through the Medicare Shared Savings Program. Although they are an alternative payment model, over 90% of ACOs are not considered to be advanced APMs because they do not accept significant financial risk for the outcomes of their associated patients.

The Executive Summary of the MACRA Final Rule explicitly states that one of the aims of the QPP is to "promote adoption of alternative payment models that align incentives across healthcare stakeholders." It also gives fair warning that "we expect the quality payment program to evolve over multiple years in order to achieve our national goals." Although most physicians will initially participate in MIPS, the incentives will continue to reward conversion to an A-APM, increasing pressure on smaller practices to join larger organizations [35, 36].

Coding Systems

For most surgical trainees, the mundane clerical practice of billing and coding is overshadowed by their desire to master the cognitive and technical skills of surgical care. Their professional education also includes ethical, professional, and interpersonal skill development which further leads to decreased emphasis on billing literacy. Unfortunately, once the young surgeon embarks on their clinical career, the importance of accurate and knowledgeable billing and coding practices becomes immediately apparent. Incorrect coding can result in significant financial penalties by CMS if the claims are ever audited. As the rendering surgeon becomes more proficient in the knowledge of coding systems, they are able to accurately describe the services that were provided using the appropriate language. There is no better person to specify the details of a procedure correctly than the surgeon who performed it.

Billing and coding provide benefit beyond converting clinical effort into financial reward. Employment contracts may include requirements for maintaining appropriate records to support claims for a surgeon's work. Institutions

may also use this data to make employment decisions, career advancement promotions, and resource allocations. Surgical case scheduling and clinical protocol assignment, such as ERP, may be based upon the surgeon's procedure code used for booking the case. Research and quality improvement projects are generally populated within databases based on filters applied in coding systems. For all these reasons, it behooves a surgeon to become familiar with surgical coding and billing practices.

As a basic principle, codes can be broken down into two categories—diagnosis codes or procedural codes. In addition, hospitals and physicians use separate systems of coding to describe surgical services. For example, inpatient surgical procedures are documented by the surgeon using the CPT® coding system, while the hospital will report based on ICD-10-PCS procedural codes (see below). This can prove quite difficult when clinicians realize that hospitals are using a completely different language regarding procedural coding. Here we will discuss the coding systems used in the United States today.

ICD-10

The International Classification of Diseases, Tenth Revision (ICD-10), is an international coding system utilized by clinicians, researchers, governments, and policymakers to accurately describe diseases and health conditions [37, 38]. Responsibility for managing and periodically updating the ICD has been granted by the United Nations to the World Health Organization since 1946 [37]. Under the electronic reporting standards of HIPAA, the Department of Health and Human Services (HHS) requires the use of ICD-10, which in the United States consists of two parts: ICD-10-CM (Clinical Modification) is used for *diagnosis* coding in all US healthcare settings, while ICD-10-PCS (Procedure Coding System) is used to describe *procedures* performed in inpatient hospital settings [39]. When a surgeon performs a procedure in an inpatient setting, the hospital or facility reports that procedure using ICD-10-PCS.

CPT®

Current Procedural Terminology (CPT®) is the coding system that surgeons deal with most frequently. CPT® is a registered trademark of the American Medical Association (AMA). The first set of CPT® codes were published in 1966 and developed to provide a standard method of coding *procedures* for insurance claims, medical records, and statistical tracking. They are copyrighted by the AMA which is responsible for regular revisions and additions to the list of codes. CMS has mandated the use of CPT® codes to report services covered by Medicare Part B and for hospital outpatient surgeries since 1983. All operative procedures, office visits, or hospital encounters with a patient can be described with a five-digit CPT® code to aid in billing purposes. These codes are also designated as a standard for electronic transmission of healthcare information under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 [40].

Given the complexity and variety of the services provided by surgeons, it is not surprising that there are several rules, algorithms, and modifiers that may be necessary to accurately describe a service. Category I codes make up the most numerous group of CPT® codes and describe a wide range of services, including evaluation and management services (E/M codes), and diagnostic or therapeutic procedures. Category II codes are supplemental codes used for data gathering and performance measurement, thereby decreasing the need for record abstraction and chart review. These are not billable codes. Category III codes are used as temporary tracking codes to collect data and assess new technologies or procedures that do not meet the criteria for a Category I code. They are noticeably different from Category I codes with their numeric alpha format. For example, 0249T was used for transanal hemorrhoidal dearterialization (THD) until a Category I code was established—46948. No work RVUs are assigned to these codes, so there is no payment established for these procedures in a payer's fee schedule.

There is a well-defined process for the creation of a new CPT® Category I code or for a Category III code to become a Category I code. The AMA CPT® Editorial Panel, the group charged with maintaining the CPT® code set, is the receiving party for a CPT® code application submission. The panel meets three times per year to review applications for new or revised codes and to delete codes when necessary. The process for approval of a Category I code can take between 18 and 26 months. These procedures must have demonstrated clinical efficacy supported by literature, be commonly practiced across the United States, have FDA approval if a drug or device is involved, and have a minimum of five peer-reviewed journal articles that include US patient populations and a minimum level of evidence. The literature required to obtain such a code is many times incomplete, and without the requisite literature, a request for a Category I code would be summarily denied. The literature requirement is the most common cause for denial of a new code application [40, 41].

Once a Category I code is approved by the AMA CPT® Editorial Panel, the code is turned over to the AMA Specialty Society Relative Value Scale Update Committee, also known as the RUC. This Committee is tasked with assigning a value for the code and includes multiple medical professionals. Most of the members are appointed by major national medical specialty societies recognized by the American Board of Medical Specialties. The remaining members arise

from subspecialties with relatively large numbers of physicians in patient care or specialties that report high percentages of Medicare expenditures. The ASCRS does not hold a permanent seat on the RUC but has held one of the 2-year rotating seats about every 4–6 years. The RUC meets three times a year following the CPT® Editorial Panel meetings to develop recommendations for work relative value units (wRVUs) assigned to new or edited CPT® codes which are then submitted to CMS. Though recommendations are provided by the RUC, the final decision for Medicare payments ultimately lies with CMS [41].

DRG

Diagnosis-related groups (DRG) is the classification system utilized by CMS to determine payments to hospitals for care provided under the Inpatient Prospective Payment System (IPPS). Patients are assigned to the appropriate DRG based upon a primary diagnosis, up to 25 other diagnoses, and up to 25 procedures performed during the stay [42]. Accurate coding of the primary diagnosis and surgical procedure(s) is essential to insure that the hospital will receive the full reimbursement it is due for the care provided. The DRG system is yet another coding language to be understood when identifying populations of patients within a healthcare system's databases [43].

Codes Become Payments

After a billable patient service is performed, from an office evaluation (E/M code) to a surgical procedure, a CPT® code is used to describe the service. The coded service description then makes its way to the payer, where the claim is evaluated on several parameters—if the service provided is covered by the insurance contract, if the claim is supported by necessary documentation, and if the claim has been properly submitted. If the code fulfills the criteria, the payer will transmit payment based on the contractual fee schedule. There is also a "timely filing requirement," ranging from as little as 120 days for some commercial payers up to 1 year for Medicare, which dictates the window of time in which claims must be filed [43].

Surgical procedures as described by CPT® codes may be supplemented by a two-digit modifier to further describe a procedure code without changing its definition. CPT® modifiers (also referred to as Level I modifiers) are used to add information or adjust care descriptions to provide extra details concerning a procedure or service provided. The 2020 CPT® code list includes 35 modifiers that may be joined to a five-digit code to provide greater clarity [44]. The most used modifier in the office would be modifier −57, the decision made for surgery. For procedures that require "substantially greater" than the typical work, modifier −22 may be added to the CPT® code. If the submitted documentation supports the use of the modifier to the satisfaction of the payer, it may result in increased reimbursement to the surgeon. The documentation must specifically indicate the reason for the increased work, for example, a patient undergoing a subsequent laparotomy that is found to have diffuse, dense adhesions. The operative note is obligated to contain the reason for the increased work—"Diffuse, dense adhesions were encountered from previous laparotomies"—and the magnitude of the increase, "… that prolonged the procedure by at least X amount of time." In the case of multiple procedures performed during the same surgery, modifier −51 may be used to indicate the portion that was designated as the secondary procedure. This is usually reimbursed at a discounted rate (50%) as the majority of the work during the surgery was completed for the primary procedure (e.g., placement of laparoscopic trocars, postoperative care) [43, 45].

In addition to modifiers, add-on codes can be used to provide additional detail about a primary procedure. Add-on codes are five-digit CPT® codes that describe procedures commonly performed with other listed procedures. They cannot be billed as stand-alone procedures and are excluded from using the −51 modifier as a secondary procedure [44]. The add-on codes most used by colorectal surgeons are open (44139) and laparoscopic (44213) mobilization of the splenic flexure in conjunction with a partial colectomy. These codes can only be used in conjunction with open and laparoscopic colectomy codes and are not subject to multiple procedure payment reduction (MPPR) [43].

There are still surgical procedures for which no established code seems to perfectly describe the operation. If there is doubt as to the correctness of a listed code, the alternative is to use an "Unlisted Code." These codes are used for procedures that do not fit any of the descriptions provided in the list of CPT® procedure codes. In order to receive payment for an unlisted procedure, submission to the payer of the operative report is requisite to document the service, as well as an explanation of the procedure with suggested comparable procedures. A negotiation with the payer will then be used to determine reimbursement. This is often a labor-intensive process compared to the normal claim submission, and as such, most providers avoid using unlisted codes unless no other code or combination of codes can accurately describe the procedure [43].

References

1. Porter ME, Teisberg EO. Redefining health care: creating value-based competition on results. Boston: Harvard Business School Press; 2006.
2. Health expenditure and financing [Internet]. OECD. Stat. 2019 [Cited 4 Apr 2020]. Available from: https://stats.oecd.org/viewhtml.aspx?datasetcode=SHA&lang=en.
3. Keehan SP, Cuckler GA, Poisal JA, Sisko AM, Smith SD, Madison AJ, et al. National health expenditure projections, 2019–28: expected rebound in prices drives rising spending growth. Health Aff. 2020;39(4):704–14.
4. U.S. Centers for Medicare & Medicaid Services. NHE Fact Sheet | CMS [Internet]. 2019 [Cited 6 Apr 2020]. Available from: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NHE-Fact-Sheet.
5. OECD. OECD health at a glance. OECD iLibrary [Internet]. 2019 [Cited 5 Apr 2020]. Available from: https://www.oecd-ilibrary.org/social-issues-migration-health/health-at-a-glance-2019_4dd50c09-en.
6. Anderson GF, Reinhardt UE, Hussey PS, Petrosyan V. It's the prices, stupid: why the United States is so different from other countries. Health Aff. 2003;22(3):89–105.
7. Papanicolas I, Woskie LR, Jha AK. Health care spending in the United States and other high-income countries. JAMA. 2018;319(10):1024–39.
8. Anderson GFGF, Hussey P, Petrosyan V. It's still the prices, stupid: why the US spends so much on health care, and a tribute to UWE Reinhardt. Health Aff. 2019;38(1):87–95.
9. Tikkanen R. The Commonwealth Fund multinational comparisons of health systems data, 2017 [Internet]. Cited 5 Apr 2020. Available from: https://www.commonwealthfund.org/publications/other-publication/2017/nov/multinational-comparisons-health-systems-data-2017.
10. Thorlby R, Arora S. England: international health care system profiles [Internet]. The Commonwealth Fund. Cited 5 Apr 2020. Available from: https://international.commonwealthfund.org/countries/england/.
11. Allin S, Rudoler D. Canada: international health care system profiles [Internet]. The Commonwealth Fund. Cited 5 Apr 2020. Available from: https://international.commonwealthfund.org/countries/canada/.
12. Sturny I. Switzerland: international health care system profiles [Internet]. The Commonwealth Fund. Cited 5 Apr 2020. Available from: https://international.commonwealthfund.org/countries/switzerland/.
13. Health insurance coverage of the total population, multiple sources of coverage [Internet]. Kaiser Family Foundation. Cited 5 Apr 2020. Available from: https://www.kff.org/other/state-indicator/health-insurance-coverage-of-the-total-population-multiple-sources-of-coverage/?currentTimeframe=0&selectedRows=%257B%2522wrapups%2522:%257B%2522united-states%2522:%257B%257D%257D%257D&sortModel=%257B%2522colId%2522:%2522Location%2522,%2522sort%25.
14. Congressional Budget Office. The federal budget in 2018: an infographic [Internet]. 2019 [Cited 6 Apr 2020]. Available from: https://www.cbo.gov/publication/55342.
15. Zelizer JE. How medicare was made. New Yorker [Internet]. 2015 [Cited 1 May 2020]. p. 1–10. Available from: https://www.newyorker.com/news/news-desk/medicare-made.
16. Medicare.gov: the official U.S. government site for Medicare | Medicare [Internet]. Cited 1 May 2020. Available from: https://www.medicare.gov/.
17. A primer on medicare financing | The Henry J. Kaiser Family Foundation [Internet]. Cited 2 May 2020. Available from: https://www.kff.org/report-section/a-primer-on-medicare-what-is-medicare/.
18. Foundation THJKF. Medicare advantage [Internet]. 2019 [Cited 1 May 2020]. Available from: http://kff.org/medicare/fact-sheet/medicare-advantage/.
19. Cubanski J, Damico A, Neuman T. 10 Things to know about medicare part D coverage and costs in 2019 [Internet]. Kaiser Family Foundation Data Note. 2019 [Cited 2 May 2020]. Available from: https://www.kff.org/medicare/issue-brief/10-things-to-know-about-medicare-part-d-coverage-and-costs-in-2019/.
20. Hinton E, Rudowitz R, Diaz M, Singer N. 10 Things to know about medicaid managed care | The Henry J. Kaiser Family Foundation [Internet]. 2019 [Cited 3 May 2020]. p. 1–11. Available from: https://www.kff.org/medicaid/issue-brief/10-things-to-know-about-medicaid-setting-the-facts-straight/.
21. Kaiser Family Foundation. Federal medical assistance percentage (FMAP) for medicaid and multiplier | The Henry J. Kaiser Family Foundation [Internet]. Kaiser Family Foundation. 2017 [Cited 3 May 2020]. Available from: https://www.kff.org/medicaid/state-indicator/federal-matching-rate-and-multiplier/?activeTab=map&currentTimeframe=0&selectedDistributions=fmap-percentage&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D.
22. Brooks T. CHIP funding has been extended, what's next for children's health coverage? [Internet]. Health Aff. 2018 [Cited 3 May 2020]. Available from: https://www.healthaffairs.org/do/10.1377/hblog20180130.116879/full/.
23. Claxton G, Rae M, Damico A, Young G, McDermott D, Whitmore H. Health benefits in 2019: premiums inch higher, employers respond to federal policy. Health Aff. 2019;38(10):1–10.
24. PUBLIC LAW 111–148—MAR. 23, 2010 [Internet]. 2010. p. 1–906. Available from: https://www.govinfo.gov/content/pkg/PLAW-111publ148/pdf/PLAW-111publ148.pdf.
25. Skocpol T, Heclo H, Mongan JJ, Weir M. The rise and resounding demise of the Clinton plan. Vol. 14. Health Affairs. Project HOPE – The People-to-People Health Foundation, Inc.; 1995. p. 66–104.
26. Oberlander J. The ten years' war: politics, partisanship, and the ACA. Health Aff. 2020;39(3):471–8.
27. Medicaid enrollment changes following the ACA: MACPAC [Internet]. Medicaid and CHIP Payment and Access Commission. Cited 3 May 2020. Available from: https://www.macpac.gov/subtopic/medicaid-enrollment-changes-following-the-aca/.
28. Musumeci M. Explaining Texas v. U.S.: a guide to the case challenging the ACA | The Henry J. Kaiser Family Foundation [Internet]. Kaiser Family Foundation. 2020 [Cited 3 May 2020]. Available from: https://www.kff.org/health-reform/issue-brief/explaining-texas-v-u-s-a-guide-to-the-case-challenging-the-aca/.
29. Cohen RA, Zammitti EP. High-deductible health plan enrollment among adults aged 18–64 with employment-based insurance coverage [Internet]. NCHS Data Brief No. 317, August 2018. 2018 [Cited 3 May 2020]. Available from: https://www.cdc.gov/nchs/products/databriefs/db317.htm.
30. QuickStats: percentage of office-based primary care physicians accepting new patients, by source of payment accepted — national electronic health records survey, 2015 | MMWR [Internet]. Cited 4 May 2020. Available from: https://www.cdc.gov/mmwr/volumes/66/wr/mm6628a9.htm.
31. Chhabra KR, Sheetz KH, Nuliyalu U, Dekhne MS, Ryan AM, Dimick JB. Out-of-network bills for privately insured patients undergoing elective surgery with in-network primary surgeons and facilities. JAMA. 2020;323(6):538–47.
32. Mosley D, Debehnke D, Gaskell S, Weil A, 2020 A. 2020 Rural hospital sustainability index trends in rural hospital financial via-

bility, community essentiality, and patient outmigration [Internet]. Cited 9 May 2020. Available from: https://guidehouse.com/-/media/www/site/insights/healthcare/2020/guidehouse-navigant-2020-rural-analysis.pdf.
33. Iglehart JK. The challenging quest to improve rural health care. N Engl J Med [Internet]. 2018 [Cited 9 May 2020];378(5):473–9. Available from: http://www.nejm.org/doi/10.1056/NEJMhpr1707176.
34. Lindrooth RC, Perraillon MC, Hardy RY, Tung GJ. Understanding the relationship between Medicaid expansions and hospital closures. Health Aff [Internet]. 2018;37(1):111–20. Available from: https://www.healthaffairs.org/doi/full/10.1377/hlthaff.2017.0976.
35. MACRA: MIPS & APMs | CMS [Internet]. Cited 9 May 2020. Available from: https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/Value-Based-Programs/MACRA-MIPS-and-APMs/MACRA-MIPS-and-APMs.
36. Peters WR, Colvin D, Cohen J. What every colorectal surgeon should know about the medicare access and children's health insurance program reauthorization act of 2015. Dis Colon Rectum [Internet]. 2017 [Cited 10 May 2020];60(9):879–80. Available from: http://journals.lww.com/00003453-201709000-00003.
37. Topaz M, Shafran-Topaz L, Bowles KH. ICD-9 to ICD-10: evolution, revolution, and current debates in the United States. Perspect Heal Inf Manag [Internet]. 2013 [Cited 14 July 2019];10(Spring):1d. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23805064.
38. WHO | International classification of diseases, 11th revision (ICD-11). WHO [Internet]. 2019 [Cited 14 July 2019]. Available from: https://www.who.int/classifications/icd/en/.
39. Averill RF, Mullin RL, Steinbeck BA, Goldfield NI. Development of the ICD-10 Procedure Coding System (ICD-10-PCS) [Internet]. Cited 9 May 2020. Available from: https://www.cms.gov/Medicare/Coding/ICD10/downloads/pcs_final_report2012.pdf.
40. Dotson P. CPT® Codes: what are they, why are they necessary, and how are they developed? Adv Wound Care [Internet]. 2013 [Cited 8 July 2019];2(10):583–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24761332.
41. Eberhardt J, Harb W. Current procedural terminology codes – why are they important? Dis Colon Rectum [Internet]. 2018 [Cited 10 May 2020];61(10):1128–9. Available from: http://journals.lww.com/00003453-201810000-00002.
42. MS-DRG Classifications and Software | CMS [Internet]. Cited 10 May 2020. Available from: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/MS-DRG-Classifications-and-Software.
43. Peters WR. Billing/coding tips from the pros: how important is this stuff, and what does the future hold? Semin Colon Rectal Surg [Internet]. 2020 [Cited 10 May 2020];31(1). Available from: https://www.clinicalkey.com/#!/content/journal/1-s2.0-S1043148919300673.
44. American Medical Association. CPT® 2020 Professional Edition. 2020.
45. Just the facts: multiple procedure payment reductions (MPPR) – AAPC Knowledge Center [Internet]. Cited 18 Aug 2019. Available from: https://www.aapc.com/blog/41773-mppr-facts/.

Ethical Considerations (Conflict of Interest, Surgical Innovation, and End of Life)

69

W. Donald Buie and Anthony R. MacLean

Key Concepts

- Conflict of interest can take many forms—each are critical to understanding, addressing, and disclosing.
- Reporting conflict of interest can affect study outcomes.
- Introduction of new technologies into practice needs to balance progression of the field of medicine versus placing patients at undue and unnecessary risk.
- Providing excellent and ethical end-of-life care requires attention to three principles: effective communication, accurate prognostication, and sound decision-making.

> Only one rule in surgical ethics need concern you: that action on your part which best conserves the interests of your patient. Martin H. Fischer (1879–1962)

Conflict of Interest in Surgical Research

Conflict of interest (COI) is common within the surgical literature but is neither consistently acknowledged nor transparently reported. COI exists when "professional judgement concerning a primary interest (such as a patients' welfare or validity in research) may be influenced by a secondary interest (such as financial gain)" [1–5]. Researchers are obliged to identify and mitigate the effect of all sources of bias, including COI. While it may be impossible to completely avoid COI, it must be dealt with transparently. This section will explore individual COI as it applies to surgical research including classification, effect on outcomes, reporting, management strategies, relationship to the peer review process, and future directions.

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Classification

Individual COI can be classified as financial, intellectual, or professional (Table 69.1) and includes any relationship or belief that may impact an individuals' ability to approach a scientific question with an open mind. While there is some debate as to the relative importance of each of these categories, any type of COI has the potential to have a negative effect on the integrity of the investigators and the veracity of the scientific process.

Financial COI

This is the most easily identified, and the most likely to undermine the credibility of the author(s), the journal, and the science. It usually involves industry and industry-sponsored trials and may include direct or indirect financial support as outlined in Table 69.1. Physician industry relationships are diverse ranging from a sponsored lunch to full research support [6–8]. Interpretation of a significant finan-

Table 69.1 Conflict of interest in surgical research

Financial	
	Grants (for profit and not for profit)
	Employment
	Personal fees (consultant)
	Non-monetary support
	Drugs/equipment, supplies
	Patent(s)
	Stocks, bonds, stock options, other securities (equity)
	Other (gifts, trips, meals expenses, paid expert testimony)
Nonfinancial	
Intellectual	Personal views, ideas, moral convictions
	Strong opinions on theoretic approach
Professional	Personal relationships
	Academic competition
	Peer recognition, public acclaim

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cial COI is situational and depends on financial details, the degree of involvement, the timing and place of the relationship, and any attempts to mitigate the effect. Even small gifts or an exchange of services may have an effect on attitudes and decisions [9–11]. The importance of industry investigator relationships is borne out by advances in technology such as laparoscopic surgery, transanal endoscopic microsurgery, and colonoscopy. Preserving these relationships is vital to surgical advancement, but there is a need for regulation to control unprofessional behavior from individuals who are willing to compromise themselves for personal gain.

Non-financial

Nonfinancial COIs, both intellectual and professional, are more subtle and difficult to measure, but are no less dangerous to the scientific process (Table 69.1). Intellectual COIs include personal views, ideas or moral convictions, and strong theoretical opinions. A researcher for example, may be unable to provide an unbiased review of a manuscript that contradicts his/her views. Professional COIs includes personal relationships (friendship or enmity), academic issues, and peer/public recognition and acclaim. Academic pressures including the need for funding, promotion, or publication can affect the quality of scientific investigation. However, there is limited evidence regarding the relative contribution and importance of nonfinancial COIs to scientific bias.

Most authors have argued there is no meaningful conceptual and few practical differences between financial and nonfinancial COIs [12]. The two are often intertwined, influential, and require similar management [13, 14]. Other authors have suggested that nonfinancial interests are virtually always present and should be considered an interest but not necessarily a conflict [15]. However, by definition successful researchers are biased having developed a strong belief in both their ideas and theoretical approach. In addition, there is both sociologic and psychologic evidence that, given the correct circumstances, people are as likely to be influenced to change behavior by nonfinancial incentives as they are by financial incentives. The desire to conform or reciprocate to avoid social disapproval can be a very strong motivator for behavioral change [16–18]. Clearly both external and internal values, goals, and obligations can contribute to nonfinancial COIs.

Determining Conflict of Interest

How do we determine when a conflict of interest is present? In an editorial, Fineberg put forth *the reasonable person standard*; a conflict of interest exists when "a reasonable person would interpret the…circumstances pertaining to a situation as potentially sufficient to influence the judgment of the physician in question" [19]. In other words, would an uninterested observer conclude that the physician is able to make an informed and unbiased judgment or decision? Determination of COI is ultimately subjective and based on the perception of a reasonable person. However, the most important question is not whether a conflict of interest exists but whether it "presents an unacceptable risk of undue influence or bias" [20]. Practically speaking, there is a need for specific guidelines and policies that can be applied universally and transparently to grade significant COI.

It is important to judge every situation on its own merits and avoid being too prescriptive eliminating potentially useful viewpoints. While the opinions and ideas of recognized experts with reported COIs should be carefully vetted prior to acceptance due to the potential for recognized bias, other experts without any financial COIs should be no less scrutinized as they may harbor hidden nonfinancial biases which could subtly affect the framing of an argument or the interpretation of evidence [21].

Reporting COI and the Effect on Study Outcomes

Scientific journals have relied on self-reporting of financial and nonfinancial COIs with varying success [22]. Most journals now require a COI statement to be completed with submission of a manuscript, yet a significant number of relevant COIs still go unreported [23]. To increase transparency and reporting of financial COIs, the Physician Payments Sunshine Act was passed in 2010 which mandated that manufacturers of drugs, medical devices, and biological products report all of their financial transactions with clinicians having a National Provider Identifier (NPI) number. These transactions are publicly available through the Open Payments Database (OPD), which was designed to allow industry-reported COI to be compared with author self-disclosure [24, 25].

There is a significant body of evidence examining the effect of financial COIs on study outcomes. Primary studies that are industry sponsored, both pharmaceutical and medical device, are more often favorable to the sponsor's product when compared to studies with independent sponsorship [26]. This association has also been demonstrated for meta-analysis, systematic reviews, editorials, and letters to the editor [27]. Industry influence includes setting the research agenda, obfuscating important research questions with secondary studies, selective analysis, selective reporting, and selective interpretation of results and conclusions [28–32]. The latter was reinforced in the aftermath of the Vioxx scandal where despite a lack of scientific evidence, an excess of cardiovascular events in the Vioxx arm were falsely ascribed

to a presumed cardioprotective effect of naproxen (control) rather than an increase in thrombogenic potential from Vioxx. Selective interpretation combined with selective reporting and aggressive marketing caused harm to an unknown number of patients prior to the drug being pulled emphasizing the need for oversight and attention to detail when entering into a relationship with industry [33].

Failure to disclose COI is also associated with conclusions that are significantly more likely to favor industry. Cherla et al. used the OPD to investigate the impact of financial COI and found a 70.3% discordance of reported COI between surgeons and industry. Surgeons who failed to disclose developed conclusions that were more likely to favor industry when compared to surgeons without COI [34]. Similarly, a prospective blinded review of 100 consecutive articles on ventral hernia found that authors with COI both self-reported and not reported were twice as likely to report results favorable to industry compared to authors with no COI [35]. Most of the articles (82%) had a relevant COI, and up to one quarter of relevant COIs were not disclosed.

These findings are not confined to primary research. Reporting of individual financial COI in systematic reviews ranges from 17% to 65% [36–39]. Systematic reviews are generally viewed as higher-quality evidence, and thus the potential for disseminating biased conclusions is significant. Recently, a review of opioid practice guidelines published between 2007 and 2013 demonstrated significant unreported financial COI from panelists who produced guidelines that were otherwise judged to be of high methodological quality [40]. The principles of managing COI in guideline panels were outlined in 2011 by the Institute of Medicine but have not been widely adopted [41, 42]. Clearly, guidelines for reporting COI must include primary and secondary research [43].

Management Strategies for Primary and Secondary Research

COI cannot always be avoided, but like all forms of bias, it needs to be managed as transparently and effectively as possible. There are four main strategies: disclosure, elimination, balance, and exclusion. Each strategy is useful in specific situations and has its own strengths and weaknesses [5].

Disclosure

Disclosure is the most frequently used strategy for managing financial COI. It cannot reduce or eliminate bias, but when complete and transparent, the scientific community has the opportunity to evaluate it. Disclosure is usually post hoc and thus is prone to selection bias; investigators disclose only what they want the scientific community to see; thus, financial interests may remain hidden or incompletely reported [22]. Nonfinancial interests including personal views, ideas, and moral convictions are central to an individuals' character and cannot be separated, while other nonfinancial issues, such as previous publications espousing a specific position, may already be a matter of public record. Disclosure of nonfinancial interests may be inhibited by ethical and privacy concerns. Disclosure of a large number of nonfinancial COIs may also distract from a more significant financial COI. For these reasons some authors have questioned the value of extensive disclosure of nonfinancial interests [5].

Disclosure may be associated with several inappropriate assumptions. It does not suggest that the investigators' judgment has been affected nor should it be interpreted to mean that the investigator is biased. Furthermore, it should not be used to interpret the appropriateness or value of a financial relationship [19]. From the investigator's viewpoint, potential unintended effects following disclosure include moral licensing, where the individual, having disclosed their conflicts, feels entitled to say and do what they want. In addition, disclosure of financial COIs by a surgeon in a high-profile advisory role may be interpreted as a sign of expertise inflating their standing and influence as a speaker [44, 45]. Thus disclosure, while necessary, is not always sufficient, and the COI should be judged as any other form of bias when evaluating the validity and generalizability of a study.

Elimination

Elimination works best for financial COIs where the investigator can divest himself/herself of the relationship prior to undertaking the research. Unfortunately, nonfinancial interests cannot be divested from either the investigator or the research for reasons listed above. Elimination is best performed a priori, preferably in the planning stage.

Balance

When planning a study, the participating individuals should ensure that there is balanced representation of financial and nonfinancial biases among the researchers. It may be ideal for two groups with differing viewpoints to participate equally in trial design with a neutral party leading data collection and analysis. Balance is also important in guideline development where all sides of scientific debate can be evaluated and incorporated [46].

Exclusion

Individuals who might be influenced by a secondary interest should be excluded from evaluation and interpretation of results, although they may selectively participate in trial development. Surgeons with a financial interest in a company that would benefit from the recommendations of a guideline panel should be excluded from guideline development and authorship. Again, it is difficult to exclude on the basis of personal views and beliefs which adds to the diver-

sity of scientific discourse and healthy discussion. If all dissenting views are excluded, the homogeneity of the remaining researchers may result in unintentional bias [46]. It cannot be assumed that the remaining investigators are unbiased or without relevant interests or personal beliefs.

COI and the Peer Review Process

Mitigating the effect of COI within the realm of scientific enquiry is the responsibility of all participants including investigators/authors, reviewers, editors, and editorial staff. Investigators must assess the effect of COI during planning, implementation, analysis, and writing.

Disclosure and exclusion are the primary strategies and require transparency to be effective. Authors are required to disclose all financial and nonfinancial COIs that might be perceived to bias their work. The ICMJE form "Disclosure of Conflicts of Interest" has been adopted by most journals including DCR and must be submitted with any completed manuscript.

The review process relies on reviewers and editors to assess and critique manuscripts on scientific merit as free from personal bias as possible. When requesting manuscript review, journal editors will ask the reviewers to assess themselves for any COI that could bias their review with the expectation they recuse themselves when appropriate. At this level, acknowledgement of personal and intellectual biases is extremely important. While some journals have opted for single- or double-blinded review, others have used an open process where the identity of the reviewer and author is known to each other. Each of these potential solutions has merit, but they cannot eliminate the potential for intellectual and professional conflicts which in some cases may be subconscious [47]. When opposing viewpoints exist, a potential solution for the editor is to balance the assignment of reviewers.

Editors must be held to the highest standard and should try to divest themselves of all COI prior to accepting a leadership position at a journal. They must recuse themselves from involvement in any manuscript under consideration when either a potential or actual conflict exists. The editor is also the final arbiter when, despite disclosure, a manuscript remains unpublishable due to bias from financial or nonfinancial COI.

Conclusions

The goal of every researcher is to identify and when possible mitigate the effect of bias on scientific inquiry. Conflict of interest, whether financial or nonfinancial, is one of many types of bias and must be subject to the same level of scrutiny as more traditional forms such as methodologic issues. Continued development and adoption of a comprehensive approach addressing COI requires efforts from individual researchers, societies, journals, publishers, academic institutions, and government. The solution must be multifaceted and includes universal policies and guidelines, robust self-reporting, continued research into quantifying the effect of COI, and increased use of management strategies early in the research process.

Introduction of Surgical Innovation

Innovation is critical to progress. Surgical innovation has been a constant in the history of surgery. Most surgeons are comfortable adapting when faced with a new or unanticipated problem in the operating room, which is a form of innovation, though not the main focus of this section. How one learns new techniques, acquires new skills, and/or incorporates new technologies into one's practice is where ethical issues can arise. The development of new techniques and technologies has been accelerating rapidly. For the practicing surgeon, the challenge and desire to keep pace with these changes and deliver cutting-edge care is compounded by the expectations of patients, hospital administrators, and device manufacturers. Incorporating exciting new technologies and new procedures into practice as they are developed is one of the most exciting parts of clinical practice for many colorectal surgeons. However, *how* we incorporate these novel treatments is fraught with ethical issues.

Incorporating New Techniques and New Technologies

Surgical trainees learn new procedures and techniques under the supervision of qualified mentors. This allows for graduated learning and safe implementation. However, once a surgeon begins independent practice, incorporating new techniques and technologies is far more difficult and complex.

Over the years many promising technologies have been incorporated into clinical practice in a way that resulted in less than optimal outcomes. An early example was the introduction of laparoscopic cholecystectomy and the epidemic of common bile injuries that followed. With time and experience, the risk of bile duct injury decreased to levels comparable to open surgery, only to increase following the introduction of single-port cholecystectomy [48]. In colorectal surgery, the early adoption of transanal total mesorectal excision (TaTME) was unfortunately associated with a high

number of urethral injuries [49], a complication that was virtually unknown with either an open or laparoscopic approach. Add to that the moratoriums that have been placed on TaTME in Norway and the unusual locoregional recurrences in the Netherlands, one could certainly question how well we as surgeons have introduced these technologies and techniques into our practices [50, 51].

What do laparoscopic cholecystectomy and transanal total mesorectal excision have in common? Both are surgical innovations that promise significant benefits to the recovery of patients, and both came highly touted and rapidly adopted among surgeons, frequently after only a minimal amount of "training," often consisting of a weekend course. This was followed by adoption into clinical practice often without proctorship or a means to safely introduce it to our patients and often without any institutional oversight.

As surgeons, new developments and innovations are exciting but can present an ethical dilemma. We want to offer the newest and best to our patients, we want to offer everything that other surgeons are able to offer, and we feel the need to do so with minimal interruption in our clinical practice. Jaffe et al. surveyed 150 faculty surgeons and found that 98% reported learning a new procedure or technology after their formal surgical residency training [52]. They found a large discrepancy between what surgeons actually did to acquire knowledge and learn a new skill or technology (most commonly scrubbing in for cases performed by another surgeon or self-directed study), and what these same surgeons felt would be the most effective strategy to learn a new skill or technology (performing cases under the supervision of a proctor or mentor, or doing a "mini-fellowship"). Barriers to using the most effective strategy included the need for a significant amount of time and the fact that surgeons were confident they could implement the new procedure safely without the need for more rigorous/effective training.

Additionally, while most physicians and surgeons are aware of and accepting of the need for proper IRB approval when introducing new medications or devices into surgical practice, there appears to be far less agreement as to the need for oversight when introducing new technologies or surgical techniques. In fact, a study by Reitsma and Moreno demonstrated that authors who had published on innovative procedures frequently felt that their work was research, and yet the majority did not feel that IRB approval was necessary, and only a minority mentioned the innovative nature of the procedure to the patient in their informed consent process [53].

Oversight

New medications and medical devices are typically heavily monitored and regulated in all countries by regulatory bodies—in the USA by the Food and Drug Administration (FDA). However, new techniques and procedures are mostly unregulated which has led to many advances in surgery through innovation. However, as mentioned above, not all innovations are beneficial, and thus many believe that implementation of new procedures should be regulated to ensure patient safety before widespread adoption.

In order to help surgeons with this very difficult situation, several groups have sought to provide guidance to the clinician on how best to apply surgical innovation into one's surgical practice. Two of these groups are the Society of University Surgeons and the IDEAL Collaboration.

The Society of University Surgeons published a position statement on the responsible application of surgical innovation into clinical practice in 2008 [54] This position statement provides guidance to the surgeon on what constitutes an innovation that should undergo a formal review. In short, if the innovation is planned, AND the surgeon seeks to confirm a theory about the innovation, OR the innovation differs significantly from currently accepted local practice, OR the outcomes of the innovation have not been previously described, OR the innovation entails potential risks for complication, OR specific or additional patient consent appears appropriate, THEN the innovation should be reviewed by a local surgical innovation committee (or institutional review board if there is a plan to publish results), submission to a national innovations registry should be done, and additional informed consent is required of the patient specific to the nature of the proposed innovation.

The IDEAL collaboration is an international group of surgeons and researchers whose goal is to improve the quality of research in surgery. They have proposed that there should be no innovation without study. Their recommendations couple innovation with continuous evaluation based on a five-stage description of the surgical development process [55, 56]. Stage 1 is the proof of concept (or innovation) stage, performed on very few patients by very few surgeons, and is meant to describe the innovation, typically with case reports, to include details of the technique, and outcomes, including adverse events to avoid replication of dangerous methods. Stage 2a is the development stage. A few innovators and early adopters continue with procedure development on a small number of patients, with prospective studies focusing mainly on safety and technical and procedural success. Stage 2b is the exploration stage. Additional surgeons begin to undertake the procedure, broadening the indications to include a larger number of patients. The procedure gets refined, and details on community learning evolve. Patients should be entered into a research database, and the main focus should be on safety, clinical outcomes, patient-centered outcomes, and feasibility. Stage 3 is the assessment stage. At this point many sur-

geons (the "early majority") carry out the procedure on many patients, as the indications expand. Comparison trials or randomized controlled trials (RCTs) would be ideal, and clinical outcomes, middle- and long-term outcomes, patient-centered outcomes, and cost-effectiveness should be the areas of focus. Last is Stage 4, long-term study. At this point the procedure is typically more widely available, and the focus becomes audit, regional variation, quality assurance and risk adjustment, using registry data and available databases. Rare events, long-term outcomes, and quality assurance come to light at this point. They recommend that ethics approval should be considered in stage 1 and should be mandatory for stage 2a, 2b, and 3.

Both of these groups emphasize the critical importance of surgeons taking responsibility for careful evaluation of new procedures or innovations with oversight by either a surgical innovation committee or research ethics board/institutional review board to ensure that patient safety is kept paramount.

Informed Consent

Another ethical challenge to the surgeon incorporating a new technique into their practice is obtaining appropriate informed consent. The consent process is not only a legal requirement; it also is a critical component to the establishment of trust in the surgeon-patient relationship.

Informed consent should include a description of the proposed operation, the indications, material risks and benefits to the patient, treatment alternatives, and who will be conducting the procedure. In the case of a new procedure, a description of the surgeon's training and/or experience with the procedure may be warranted.

Several issues deserve mention here. It is critical that a surgeon's enthusiasm for a new technique does not affect the way that information is conveyed to the patient. The options available to the patient, the potential benefits, AND risks of the new technique must be explained. Patients and surgeons are often under the belief that newer must also be better, which can affect one's judgment. Information must be conveyed in an unbiased, balanced, and honest manner, to allow the patient to make an educated decision regarding their desire to undergo the new procedure.

Surgeon experience with a new procedure is particularly important to consider. In one study, the majority of patients felt that surgeon experience was one of the most important determinants of whether they would want to undergo a new procedure, particularly whether it was the surgeon's first case [57]. While some surgeons feel that they have no choice but to perform a new procedure on a patient in order to gain experience, it is clear that education and appropriate training are critical for safe implementation. Visiting apprenticeships or "mini fellowships" can often be used to gain the required initial experience. Proctorship or mentorship from a more experienced colleague can help optimize the initial learning curve of the surgeon.

Ahmed et al. surveyed 244 surgeons about their knowledge, attitudes, and practice when introducing novel surgical techniques [58]. They found that surgeons often did not discuss the novelty of the procedure, the alternative options, the surgeon's experience with the procedure, or the risks of the procedure. The IDEAL Collaboration has made recommendations regarding these ethical issues across the IDEAL stages of surgical innovation [59]. In stage 1, they recommend sharing appropriate information with patients (including surgeon's expertise, experience with the innovation, and reason to recommend it) and careful attention to ensure true informed consent by providing written information, requiring repeat appointments to discuss the innovation, and taking steps to avoid the surgeon's optimism bias with the innovation.

Lastly, there is sometimes uncertainty about the true risks and benefits of new procedures. This is particularly true for relatively uncommon complications that may not become apparent to the surgical community until the procedure has been adopted more widely. A surgeon's enthusiasm for a new procedure can also subconsciously bias the discussion with the patient, emphasizing the potential benefits while downplaying the potential risks. This bias must be avoided to allow the patient to make a truly informed decision.

Outcomes

As surgeons adopt new or innovative techniques, particularly as "early adopters," they have an ethical obligation to track their outcomes to ensure their patients are not being harmed. While RCTs are considered the gold standard to assess surgical innovations, they are often not felt to be feasible to conduct for a number of reasons. There is the need to establish the learning curve for the procedure and enroll surgeons who are beyond that prior to beginning the trial, so that the study reflects the true effect of the innovation. Without knowing all outcomes and potential risks, it can be difficult to properly design and power a study to assess for those differences. Lastly, once a new technology has been out and adopted for a sufficient period of time, surgeons may lose the "clinical equipoise" needed to feel that they can ethically enroll patients into a trial.

For these reasons, other strategies may be required, including the use of prospective registries or databases to track outcomes. Whether they are personal, institutional, or national, it is critical to capture outcomes and adverse events AND to make that data available to others via publication, to ensure patient's safety.

Industry Involvement

Industry often plays a key role in developing and promoting new technologies. As a critical component of surgical innovation, they are often largely responsible for the widespread adoption of new surgical techniques through the provision of training courses and arranging apprenticeships and/or proctorships. They may also provide grants and other support to enable new technologies to be studied and evaluated. However, it is also important to be aware of the potential conflict of interest that the relationship between surgeons and industry can lead to. Some surgeons working for industry are paid consultants and thus may have conscious or unconscious biases favoring the new technology as outlined in the previous section.

Conclusions

New technologies and innovations are critical to advancing the surgical care of our patients. However, they also have the potential to cause unintended negative consequences. Appropriate training and careful roll out of new technologies is essential, as is clear and transparent communication with our patients and tracking of our results.

End-of-Life and Surgical Care

Advances in medical and surgical care have greatly increased our ability to temporarily interrupt the dying process and prolong life. While recovery to a premorbid state is usually not possible, patients may be able to maintain a quality of life that is consistent with their overall goals of care. The important question often becomes a discussion of not *can we* but *should we*, which raises a number of ethical issues in surgical end-of-life care.

Providing excellent and ethical end-of-life care requires attention to three principles: effective communication, accurate prognostication, and sound decision-making. This section will explore these three principles and related ethical issues as they pertain to the practicing surgeon.

Communication

Effective communication is the cornerstone of ethical end-of-life care. Patients, their families, and their care providers require accurate honest information delivered in an open nonjudgmental environment to enable informed and appropriate treatment decisions concordant with their goals and values. Ethical communication also includes effective listening. Understanding what is important to the patient is the hallmark of patient-centered care.

Communication should occur early, often, and when possible, prior to any acute changes in medical condition which tend to complicate discussion and decisions. When planning a meeting, consider timing, setting, content, context, and key points. Meetings should be private without outside pressure or interference, with ample time and space. As the most responsible practitioner, you should facilitate the meeting rather than run it. Probe for understanding and establish the level of shared decision-making that is expected [60]. Prognostic information must be delivered clearly and compassionately with honesty avoiding false hope. Elicit the patients' goals/values and fears/worries to ensure that treatments are aligned and that expectations are realistic and attainable. Uncertainties between family members and clinicians must be fully disclosed and resolved. When several clinicians are involved in decisions regarding care, a premeeting briefing should be arranged to ensure messaging is clear, concise, and consistent.

Poor communication confers a significant risk for harm [61]. While clarity is essential, the surgeon should be aware of how framing and context affects what the patient hears, understands, and prioritizes. Communication issues are magnified by cultural and language barriers. While it may be convenient to use a family member, the translator may insert their own values and judgments or inaccurately describe a medical situation due to a lack of understanding or verbal facility. The message may be distorted, possibly harmful, and the exact content received by the patient is unknown. When possible, a professional translating service should be used. Pictures and diagrams transcend language and effectively supplement verbal communication.

Prognostication

An understanding of the expected treatment course, potential risks, and possible outcomes is the foundation of ethical treatment decisions. Surgeons must provide accurate and honest prognostic information to patients and their families which addresses functional, cognitive, and psychosocial outcomes. Unrealistic patient expectations coupled with erroneous assumptions regarding acceptable patient outcomes are often the underlying reason behind treatment that is at odds with end-of-life goals of care [60]. The SUPPORT trial demonstrated that half of ICU patients experienced unwanted medical treatment, more than half were undertreated for pain, and many did not have their preferences for care identified or carried out by the management team [62]. Some of these issues can be ascribed to what has been termed "clinical momentum," multiple interventions which

in isolation are standard patterns of care without considering the cumulative effect on an individual's likely outcome or preferences [63].

When prognosticating, the surgeon should consider a range of outcomes and their likelihood, identifying which outcomes are acceptable to the patient and which are not. Although multiple scoring systems exist to predict short-term morbidity and mortality, they are most useful for populations and may not accurately predict functional outcomes and health-related quality of life of an individual patient. Discussion should not focus solely on survival but prognosticate the future clinical course and expected state of health [60]. Acknowledging and discussing expected functional outcomes also sets the stage for any future discussion regarding withdrawal of life support should this become necessary. Elderly patients especially those with an element of dementia require a discussion regarding the possibility of further decline in mental and physical function following surgical interventions especially when emergent.

Use of a time-limited trial is appropriate and ethical when there is prognostic uncertainty or difficulty accepting outcomes. This may include a surgical procedure with time-limited postoperative ICU support, setting specific functional and physiologic parameters to be attained within a specified time frame. Inability to attain these goals within the trial period is evidence that the specified treatment course is unlikely to benefit the patient and requires reevaluation.

Decision-Making

Decision-making is central to ethical end-of-life care. The clinician should be guided by the four primary principles of medical/surgical ethics: respect for autonomy, beneficence, non-maleficence, and justice [64]. These principles are not hierarchical and may seem at odds with one another at end of life. If a situation presents an apparent conflict between two of these principles, every attempt should be made to come to an agreeable compromise. If this is not possible, a consult should be obtained with an expert in ethics or palliative care.

Respect for Autonomy

The right of patients to determine their own goals of care and accept or decline treatments is a basic tenet of ethical end-of-life care. Yet, regardless of the amount of information they receive, it is difficult for patients to fully comprehend the expected outcomes and potential consequences of a treatment decision. Furthermore, acute and chronic effects of an illness may further inhibit reasonable discussion and thought.

Advanced directives enable a competent individual to determine and document their healthcare plan in advance of a future terminal illness or disability. These can be either instructional where a competent individual records their healthcare choices in advance or by proxy where a patient specifies their wishes to their care provider or family to carry out if and when they become incapacitated. Ideally, these documents provide some autonomy to the patient allowing them to receive end-of-life care consistent with their wishes.

Unfortunately, advanced directives are still rare with only 30% of adults having completed them, the majority of whom are over 65 years of age [65]. They are usually completed without contextual background or an understanding of the potential circumstances of a medical crisis and the consequences of many end-of-life decisions. Even when an advanced directive is completed, it may not provide guidance for a specific end-of-life situation such as when an acute potentially solvable problem is superimposed on a chronic terminal illness. A patient's end-of-life preferences may have developed in the absence of a balanced medical discussion, based on previously observed family situations or even movies and television scenarios which may not apply to the current situation. A recent study found that over 70% of surrogate decision-makers thought that survival after CPR was >75%, only 20% understood that brain damage could be present afterward, and only 2% understood that the patient could be dependent on life support [66]. Accurate and consistent communication is important to avoid unrealistic expectations such as these. Patients may also limit their interventions unnecessarily based on a fear of burdening their family in the future [67].

Patients views and expectations are not necessarily fixed and may change depending on the circumstances and disease course. When a situation becomes protracted or there is an acute change in health, it is important to revisit and reassess to ensure alignment with treatment goals. Careful communication is needed to temper unrealistic expectations and ensure that the patient/family understands how an accepted treatment may now be in opposition to previously stated goals and values. When the care provider also functions as the surrogate decision-maker, it may be difficult to perform both roles due to exhaustion and burnout. A study of surrogate decision-makers in end-of-life care found that over 75% of them wished to eliminate or limit their role in medical decision-making [68]. The surgeon must be sensitive to this possibility and rebalance the decision-making process depending on the desires and capabilities of the surrogate decision-maker and patient [69]. It also raises the question of whether the presumed autonomy that we maintain for patient-/surrogate-led decision-making is always meaningful and effective [70].

The concept of shared decision-making (SDM) ensures that the patient's viewpoint is always considered. Although SDM has become standard of care, the nature and optimal strategies for applying SDM have not been fully researched [71]. It is clear that SDM should not be limited to a discussion between a physician and patient/surrogate that is focused

solely on choosing the best treatment option from a list of potential options. From an ethical point of view, it should be a relationship where the patient/surrogate identifies and prioritizes their important goals and values while the physician identifies management options including risks, benefits, and expected functional outcomes, exploring how each option aligns with or opposes the prioritized goals and values. When done properly, the surgeon is well equipped to recognize when a patient is being overtreated or undertreated.

Decision aids are often used to help focus a patient on the issue at hand by reducing extraneous information. A Cochrane review suggested that patients and their families felt they were more knowledgeable and clearer with respect to their values and their understanding of risk and outcomes following the use of decision aids [72]. They should be simple, easy to understand, and generalizable to a number of situations. Another approach to SDM is the best case/worst case framework. Rather than focusing on treatment pathway or acute surgical problem, discussion is centered on outcome by presenting the best case, worst case, and the most likely outcome [73].

Beneficence

Doing what is best for the patient includes actions that improve a situation and those that prevent or remove potential harms. At the end of life, this includes effective symptom control and reasonable attempts at resolving surgical problems. Decisions are based on the patient's disease state, expected course, and the patient's expectations regarding a "good outcome" [70]. When the patient cannot speak for themselves, the clinician may probe family members for anecdotes and previous conversations to obtain a deeper understanding of their views.

What is typically recognized as routine and standard of care may not be appropriate or ethical at end of life. The surgeon must differentiate between ordinary "medicines, treatments and operations which offer a reasonable hope of benefit and which can be obtained and used without excessive expense, pain or other inconvenience" and extraordinary "that which cannot be obtained or used without excessive expense, pain or other inconvenience or which, if used, would not offer a reasonable hope of benefit" [74]. What is reasonable vs. unreasonable requires context, an understanding of the patient's goals and values, and careful interpretation. As the most responsible physician, understand your own biases and take steps to mitigate the effect of them on your decisions. If you feel you are too close to the patient or their problem, you may have to take a step back and ask the advice of or transfer care to an experienced colleague who is removed from the situation.

Aggressive interventions to control symptoms may lead to an inadvertent decline in the patients' overall well-being also called the double effect. For example, aggressive pain management may lead to sedation and hasten death. Provided that the primary intention is to benefit the patient (in this case alleviating suffering), these actions are justifiable and ethical.

As the population ages, increasing numbers of elderly patients require surgery near end of life. Healthy elderly patients may tolerate surgery, but a complication can be devastating due to inadequate reserve. It is important for the patient to maintain realistic expectations especially if the procedure is of limited benefit to quality or quantity of life. Communication errors may compound the problem especially in emergency situations when it may be difficult to ensure that the patient and their family understand the short- and long-term consequences and the expected outcomes [61]. The surgeon should strive to be direct and clear but not callous. While age should not be used as the sole reason for denying treatment to an elderly patient, the surgeon must ensure that any expected benefit far outweighs the risk.

Non-maleficence

To do no harm has long been associated with therapeutic intervention and is at the core of surgical care: "… that it is only the second law of therapeutics to do good, its first law being this – not to do harm" (Bartlett 1844) [75]. A procedure which may be standard of care in a more typical situation may be non-therapeutic or place the patient at significant risk when near the end of life. In complex situations where there is diagnostic or prognostic uncertainty, understanding and evaluating the risk benefit ratio becomes very difficult as the therapeutic window is often very narrow and may change as the patients' condition evolves. Initial interventions may be very reasonable and acceptable to patients and their families in the short term. Frequent reevaluation by the surgical team, the patient, and their family is important to avoid interventions that exceed what would be acceptable to the patient [61, 63].

Central to a discussion of an intervention which is potentially harmful is an understanding of the natural history of disease process given the patients' circumstances. Compounding these situations is the differing perspective of the involved healthcare providers who may submit very different opinions with regard to disease course and thus the value of a specific therapeutic intervention. As individual practitioners we are influenced by our own values, training, and practice environment [76, 77]. A difference of opinion regarding a therapeutic decision that can't be resolved may cause moral distress; the surgeon recognizes the proper course of action but feels they cannot act upon it [78]. This may include a surgical intervention or the persistence of a therapy either of which is seen by one party as potentially harmful. A second opinion from a respected expert who is removed from the situation may be required. An ethics consult may also be helpful to support these difficult decisions and preserve future working relationships within the team.

Removal of life-sustaining interventions once they have been initiated or removal of care following a therapeutic trial is ethically justifiable if one of two conditions are met:

1. The patient/surrogate recognizes that the treatment is no longer consistent with previously identified goals and values.
2. The most responsible physician recognizes that the treatment is no longer medically indicated [70].

The term "no longer medically indicated" should be used for any treatment that will not or has ceased to accomplish the intended goal or deliver the benefit for which it was intended. The term "futility" has also been used in the past, but it has proven difficult to define as it is value based and requires contextual discussion [79]. Difficulties can arise when the patient has an acute reversible issue superimposed on a terminal irreversible disease or when multiple reversible issues occur simultaneously making recovery highly unlikely. In these cases, withdrawal of care is ethically justified to prevent interference with the natural process of the disease. The patient/family and the surgeon should reach mutual agreement by exploring the lack of benefit of the treatment, the inability to change the course of the disease, and any risks of continuing with the treatment.

At times there can be differences of opinion regarding a treatment course between family members. There may also be family members who have some medical experience but not in the area in question who harbor strong opinions about a specific treatment course. These situations can be difficult to navigate and may also create moral distress [80]. Early and frequent communication is required emphasizing that the treatment course must remain consistent with the values and goals of the patient. These differences are often the result of errors in communication that have been magnified due to the stress of the situation rather than a true difference of opinion. Additional input and consultation from senior colleagues, intensivists, palliative care, and ethicists may be necessary. In some cases, the patient may need to be transferred to a colleague whom the patient or family feels has a viewpoint more consistent with their own.

Justice

Justice is a form of fairness where each patient is entitled to the fair distribution of all available medical resources, based on equality and equity. Equality means that everyone has equal access to all available treatments, while equity means that everyone gets the support they need when needed. Both of these concepts are important in end-of-life care as each situation is unique with patients having differing needs.

In every health system demand exceeds available resources. While no patient should be denied a potentially beneficial treatment, in reality access may be limited by a number of factors including available expertise and resources. Healthcare systems without universal healthcare have the potential for limiting access due to variations in private insurance, while systems with universal health coverage may have limitations on expensive treatments due to system and societal costs [81, 82]. Unfortunately, social issues such as age, social status, ethnic background, culture, sexual preference, disability, and insurance coverage also factor into access [83–86]. While many of these issues are unsolvable, the surgeon should be aware of how they may affect the provision of treatment. Any potential solutions to mitigate these effects must be explored and offered.

Many of the social factors present in marginalized communities may lead patients to late engagement and mistrust of the medical system. The surgeon should be sensitive to these issues and make every attempt to understand how they affect end-of-life decisions and acceptance of care. In some cases, cultural and ethnic differences may be an overarching consideration at end of life and may include religion, racial identity, and socioeconomic status. While the surgeon cannot expect to have a complete understanding of cultural nuance, he/she must be open to considering other viewpoints to deliver patient-centered care [87]. For example, in some cultures, end-of-life decisions are made collectively by the family or by a senior member of the family. In this situation, patients could be asked how much information they would like to receive, how involved they would like to be in decision-making, and how much they want their families involved [87]. This approach provides them some autonomy yet respects their cultural needs. Most hospitals have a liaison service which should be involved to help bridge these gaps.

Conclusions

End-of-life care presents a number of ethical issues for the practicing surgeon. The principles of effective communication, accurate prognostication, and sound decision-making are the hallmarks of ethical patient-centered end-of-life care. Central to the decision-making process are the four primary principles of medical/surgical ethics: autonomy, beneficence, non-maleficence, and justice. All decisions must uphold the patient's values and goals, and the resulting actions must be directed toward conserving the best interests of the patient.

References

1. Stokes W. The ethics of operative surgery. Dublin J Med Sci. 1894;3–16.
2. Angelos P. Orlo Clark and the rise of surgical ethics. World J Surg. 2009;33(3):372–4.

3. Angelos P. Surgical ethics and the challenge of surgical innovation. Am J Surg. 2014;208(6):881–5.
4. Thomson DF. Understanding financial conflicts of interest. N Engl J Med. 1993;329(8):573–6.
5. Bero L. Addressing bias and conflict of interest among biomedical researchers. JAMA. 2017;317(17):1723–4.
6. Steinbrook R. Physician-industry relations—will fewer gifts make a difference? N Engl J Med. 2009;360(6):557–9.
7. Khan R, Nugent CM, Scaffidi MA, et al. Association of biologic prescribing for inflammatory bowel disease with industry payments to physicians. JAMA Intern Med. 2019;179:1424–5.
8. Rhee TG, Ross JS. Association between industry payments to physicians and gabapentinoid prescribing. JAMA Intern Med. 2019;179:1425–7.
9. Lo B, Grady D. Payments to physicians: does the amount of money make a difference? JAMA. 2017;317(17):1719–20.
10. Grande D, Frosch DL, Perkins AW, et al. Effect of exposure to small pharmaceutical promotional items on treatment preferences. Arch Intern Med. 2009;169(9):887–93.
11. Armstrong K, Freiberg AA. Challenges and opportunities in disclosing financial interests to patients. JAMA. 2017;317(17): 1743–4.
12. Wiersma M, Kerridge I, Lipworth W. Dangers of neglecting non-financial conflicts of interest in health and medicine. J Med Ethics. 2018;44:319–22.
13. Erde EL. Conflicts of interest in medicine: a philosophical and ethical morphology. In: Spece RG, Shimm DS, Buchanan AE, editors. Conflicts of interest in clinical practice and research. New York: Oxford University Press; 1996. p. 12–41.
14. Kaur S, Balan S. Towards a balanced approach to identifying conflicts of interest faced by institutional review boards. Theor Med Bioeth. 2015;36(5):341–61.
15. Bero LA, Grundy Q. Why having a (nonfinancial) interest is not a conflict of interest. PLoS Biol. 2016;14(12):e2001221.
16. Fehr E, Falk A. Psychological foundations of incentives. Eur Econ Rev. 2002;46:687–724.
17. Holte JH, Kjaer T, Abelsen B, et al. The impact of pecuniary and non-pecuniary incentives for attracting young doctors to rural general practice. Soc Sci Med. 2015;128:1–9.
18. Peterson SJ, Luthans F. The impact of financial and nonfinancial incentives on business-unit outcomes over time. J Appl Psychol. 2006;91(1):156–65.
19. Fineberg HV. Conflict of interest why does it matter? JAMA. 2017;317(17):1717–8.
20. Lo B, Ott C. What is the enemy in CME, conflicts of interest or bias? JAMA. 2013;310(10):1019–20.
21. Taylor R, Giles J. Cash interests taint drug advice. Nature. 2005;437:1070–71 paraphrased by Polk HC, et al. Conflicts of interest in contemporary surgery: toward greater transparency. Dis Colon Rectum. 2019;62:392–94.
22. Thomas K, Ornstein C. Top Sloan Kettering cancer doctor resigns after failing to disclose industry ties. New York Times. 13 Sept 2018.
23. www.icmg.org. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals updated December 2018. Accessed 1 Mar 2020.
24. Centers for Medicare & Medicaid Services. Open payments database. https://www.cms.gov/openpayments/. Accessed 14 Mar 2020.
25. ProPublica. Dollars for docs. https://projects.propublica.org/docdollars/. Accessed 14 Mar 2020.
26. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev. 2017;2:MR000033.
27. Lundh A, Bero L. The ties that bind. BMJ. 2017;356:j176.
28. Barnes DE, Bero LA. Industry-funded research and conflict of interest: an analysis of research sponsored by the tobacco industry through the Center for Indoor Air Research. J Health Polit Policy Law. 1996;21(3):515–42.
29. Kearns CE, Glantz SA, Schmidt LA. Sugar industry influence on the scientific agenda of the National Institute of Dental Research's 1971 National Caries Program: a historical analysis of internal documents. PLoS Med. 2015;12(3):e1001798.
30. Yank V, Rennie D, Bero LA. Financial ties and concordance between results and conclusions in meta-analyses: retrospective cohort study. BMJ. 2007;335(7631):1202–5.
31. Wang AT, McCoy CP, Murad MH, Montori VM. Association between industry affiliation and position on cardiovascular risk with rosiglitazone: cross sectional systematic review. BMJ. 2010;340:c1344.
32. Bobardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of celecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520–8.
33. Rosenbaum L. Reconnecting the dots- reinterpreting industry- physician relations. N Engl J Med. 2015;372(19):1860–4.
34. Cherla DV, Viso CP, OLavarria OA, et al. Impact of financial conflict of interest on surgical research: an observational study of published manuscripts. World J Surg. 2018;42:2757–62.
35. Cherla DV, Viso CP, Hollhan JL, et al. The effect of financial conflict of interest, disclosure status and relevance on medical research from the United States. J Gen Intern Med. 2019;34(3):429–34.
36. Forbes TL. Author disclosure of conflict of interest in vascular surgery journals. J Vasc Surg. 2011;54(3 Suppl):55S–8S.
37. Dunn AG, Arachi D, Hudgins J, et al. Financial conflicts of interest and conclusions about neuraminidase inhibitors for influenza: an analysis of systematic reviews. Ann Intern Med. 2014;161:513–8.
38. Bes-Rastrollo M, Schulze MB, Ruiz-Canela M, et al. Financial conflicts of interest and reporting bias regarding the association between sugar-sweetened beverages and weight gain: a systematic review of systematic reviews. PLoS Med. 2013;10:e1001578; discussion e78.
39. Ebrahim S, Bance S, Athale A, et al. Meta-analyses with industry involvement are massively published and report no caveats for antidepressants. J Clin Epidemiol. 2015;70:155–63.
40. Spithoff S, Leece P, Sullivan F, Persaud N, Belesiotis P, Steiner L. Drivers of the opioid crisis: an appraisal of financial conflicts of interest in clinical practice guideline panels at the peak of opioid prescribing. PLoS One. 2020;15(1):e0227045. https://doi.org/10.1371/journal.pone.0227045.
41. Institute of Medicine. Clinical practice guidelines we can trust. Washington, DC: National Academies Press; 2011. https://www.nationalacademies.org/hmd/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx. Accessed 10 Mar 2020.
42. Viswanathan M, Carey TS, Belinson SE, et al. A proposed approach may help systematic reviews retain needed expertise while minimizing bias from nonfinancial conflicts of interest. J Clin Epidemiol. 2014;67(11):1229–38.
43. Hakoum MB, Anouti S, Al-Gibbawi M, et al. Reporting of financial and non-financial conflicts of interest by authors of systematic reviews: a methodological survey. BMJ Open. 2016;6:e011997. https://doi.org/10.1136/bmjopen-2016-011997.
44. Cain DM, Lowenstein G, Moore DA. The dirt on coming clean: possible effects of disclosing conflict of interest. J Leg Stud. 2005;34:1–24.
45. Barnes B. Financial conflicts of interest in continuing medical education: implications and accountability. JAMA. https://doi.org/10.1001/jama.2017.2981.
46. Lenzer J. When is a point of view a conflict of interest? BMJ. 2016;355:i6194.
47. Fontanarosa P, Bauchner H. Conflict of interest and medical journals. JAMA. 2017;317(17):1768–71. https://doi.org/10.1001/jama.2017.4563.

48. Strasburg SM, et al. Single incision laparoscopic cholecystectomy and the introduction of innovative surgical procedures. Ann Surg. 2012;256:7–9.
49. Sylla P, Knoll JJ, D'Andrea AP, et al. Urethral injury and other urologic injuries during transanal total mesorectal excision: an international collaborative study. Ann Surg. 2019;10. https://doi.org/10.1097/SLA.0000000000003597.
50. Larsen SG, Faerden AE, Wasmuth HH. Author response to: comment on: transanal total mesorectal excision for rectal cancer has been abandoned in Norway. Br J Surg. 2020;107(7):121–30.
51. van Oostendorp SE, Belgers HJ, Bootsma BT, et al. Locoregional recurrences after transanal total mesorectal excision of rectal cancer during implementation. Br J Surg. 2020. https://doi.org/10.1002/bjs.11525.
52. Jaffe TA, Hasday SJ, Knol M, et al. Strategies for new skill acquisition by practicing surgeons. J Surg Educ. 2017;75:928–34.
53. Reitsma AM, Moreno JD. Ethical regulations of innovative surgery: the last frontier? J Am Coll Surg. 2002;194(6):792–801.
54. Biffl WL, Spain DA, Reitsma AM, et al. Responsible development and application of surgical innovations: a position statement of the society of university surgeons. J Am Coll Surg. 2008;206(6):1204–9.
55. McCulloch P, Altman DG, Campbell WB, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet. 2009;374(9695):1105–12.
56. Hirst A, Phillippou Y, et al. No surgical innovation without evaluation: evolution and further development of the IDEAL framework and recommendations. Ann Surg. 2019;269(2):211–20.
57. Lee Char SJ, Hills NK, Kimberly SK, et al. Informed consent for innovative surgery: a survey of patients and surgeons. Surgery. 2013;153(4):473–80.
58. Ahmed AM, Giang HTN, Ghozy S, et al. Introduction of novel surgical techniques: a survey on knowledge, attitude and practice of surgeons. Surg Innov. 2019;26(5):560–72.
59. Rogers WA, Hutchinson K, McNair A. Ethical issues across the IDEAL stages of surgical innovation. Ann Surg. 2019;269(2):229–33.
60. Berlin A. Goals of care and end of life in the ICU. Surg Clin N Am. 2017;97:1275–90.
61. Cooper Z, Courtwright A, Karlage A, Gawande A, Block S. Pitfalls in communication that lead to nonbeneficial emergency surgery in elderly patients with serious illness: description of the problem and elements of a solution. Ann Surg. 2014;260(6):949–57.
62. Connors AF, Dawson NV, Desbiens NA, et al. A controlled trial to improve care for seriously ill hospitalized patients. JAMA. 1995;274(20):1591–9.
63. Kruser JM, Cox CE, Schwarze ML. Clinical momentum in the intensive care unit a latent contributor to unwanted care. Ann Am Thorac Soc. 2017;14(3):426–31.
64. Beauchamp TL, Childress JF. Principles of biomedical ethics. 7th ed. New York: Oxford University Press; 2015.
65. Yadav KN, Gabler NB, Cooney E, Kent S, Kim J, Herbst N, et al. Approximately one in three US adults completes any type of advance directive for end-of-life care. Health Aff (Millwood). 2017;36(7):1244–51.
66. Shif Y, Doshi P, Almoosa KF. What CPR means to surrogate decision makers of ICU patients. Resuscitation. 2015;90:73–8.
67. Ornstein KA, Kelley AS, Bollens-Lund E, Wolff JL. A national profile of end-of-life caregiving in the United States. Health Aff (Millwood). 2017;36(7):1184–92.
68. Azoulay E, Pochard F, Chevret S, Adrie C, Annane D, Bleichner G, et al. Half the family members of intensive care unit patients do not want to share in the decision-making process: a study in 78 French intensive care units. Crit Care Med. 2004;32(9):1832–8.
69. Wendler D, Rid A. Systematic review: the effect on surrogates of making treatment decisions for others. Ann Intern Med. Cham: Springer Nature Switzerland; 2011;154(5):336–46.
70. Brasel K, Condron M. End of life issues. In: Ferreres ARD, editor. Surgical ethics. Cham: Springer Nature Switzerland; 2019. p. 239–56.
71. Elwyn G, Edwards A, Thompson R. Shared decision-making in health care: achieving evidence-based patient choice. 3rd ed. Oxford/New York: Oxford University Press; 2016. xxi, 309 p.
72. Stacey D, Kryworuchko J, Belkora J, Davison BJ, Durand MA, Eden KB, et al. Coaching and guidance with patient decision aids: a review of theoretical and empirical evidence. BMC Med Inform Decis Mak. 2013;13(Suppl 2):S11.
73. Taylor LJ, Nabozny MJ, Steffens NM, Tucholka JL, Brasel KJ, Johnson SK, et al. A framework to improve surgeon communication in high-stakes surgical decisions: best case/worst case. JAMA Surg. 2017;152(6):531–8.28.
74. Kelly G. The duty to preserve life. Theol Stud. 1950;11:203–20.
75. Chomel quoted in Bartlett E. An essay on the philosophy of medical science. Bull N Y Acad Med. 1973;49(7):651–2. Lea and Blanchard, Philadelphia. 1844. p. 288–9.
76. Barnato AE, Herndon MB, Anthony DL, Gallagher PM, Skinner JS, Bynum JP, et al. Are regional variations in end-of-life care intensity explained by patient preferences?: a study of the US Medicare population. Med Care. 2007;45(5):386–93.
77. Barnato AE. Challenges in understanding and respecting patients' preferences. Health Aff (Millwood). 2017;36(7):1252–7.
78. Curtis JR, Burt RA. Why are critical care clinicians so powerfully distressed by family demands for futile care? J Crit Care. 2003;18(1):22–4.
79. Kon AA, Shepard EK, Sederstrom NO, Swoboda SM, Marshall MF, Birriel B, et al. Defining futile and potentially inappropriate interventions: a policy statement from the Society of Critical Care Medicine Ethics Committee. Crit Care Med. 2016;44(9):1769–74.
80. Crippen D. Moral distress in medicine: powerlessness by any other name. J Crit Care. 2016;31(1):271–2.
81. London DM. Rationing gets official seal of approval from UK health. Lancet. 2000;355(9197):49.
82. Drummond M, Mason A. Rationing new medicines in the UK. BMJ. 2009;338:a3182.
83. Chin MH. Movement advocacy, personal relationships, and ending health care disparities. J Natl Med Assoc. 2017;109(1):33–5.
84. Chinn PL. Commentary: lesbian, gay, bisexual, and transgender health: disparities we can change. Nurse Educ. 2013;38(3):94–5.
85. Iezzoni LI. Why increasing numbers of physicians with disability could improve care for patients with disability. AMA J Ethics. 2016;18(10):1041–9.
86. Barnato AE, Chang CC, Saynina O, Garber AM. Influence of race on inpatient treatment intensity at the end of life. J Gen Intern Med. 2007;22(3):338–45.
87. Chessa F, Moreno F. Ethical and legal considerations in end of life care. Prim Care Clin Offic Pract. 2019;46:387–98.

Welcome to Litigation

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Dennis K. Ames

Key Concepts

- In litigation, preparation is the key to a successful outcome.
- Preparation should begin as soon as you become aware of an adverse outcome likely to lead to litigation.
- Don't conduct an independent investigation.
- Never appear at a deposition without consulting an attorney.
- Meet with your attorney early.
- Communicate with your attorney regularly.
- Know what you can expect of your attorney and when.
- Know what is expected of you and when.
- Do your homework, and make yourself available.

The unfortunate reality for today's physician is that he or she will almost certainly be sued for medical malpractice in his or her career. According to data published in *The New England Journal of Medicine* in 2011, general surgeons (the publication does not include a cohort for colon and rectal surgeons) face a 15.3% annual probability of facing a medical malpractice claim. Along with other "high-risk" specialties, 80% of general surgeons are projected to face a claim by the age of 45 years, and by age 65, fully 99% of those physicians in "high-risk" specialties such as general surgery are projected to face a claim [1].

The pertinent question for today's surgeon is not "What should I do *if* I get sued?"; rather, it is now "What should I do *when* I get sued?"

If there is comfort to be taken in this data, it is that while physicians, depending on specialty, face a 5–20% probability of facing a malpractice claim in a given year, the probability of any such claim leading to an indemnity payment is substantially lower.

This chapter is designed to guide the physician-defendant toward achieving the *best result* the facts of the case allow. *Best result* is not measured only in the sense of winning or losing the case. As importantly, *best result* implies minimizing the human toll the process exacts on the physician-defendant, by reducing anxiety and frustration [2].

Anxiety is reduced by education and managing expectations. This chapter is organized to provide a general outline of each of the stages of the litigation process. It will describe each stage of the process and define the role of the attorney and of the physician-defendant at each stage.

Frustration is reduced with preparation and being proactive in your defense. As a physician facing a malpractice claim, you have the right to expect your attorney to be well prepared at each stage of the litigation. As the physician-defendant, you, too, have a significant role in the preparation of your own defense. To be prepared, you must know what to expect during the course of the litigation. You must understand the litigation process. You must understand what you have the right to expect from your attorney, and finally, you must understand what your attorney has the right to expect of you.

In an effort to minimize frustration, *Teaching Points* are provided. These *Teaching Points* include a list of things which the physician-defendant can do proactively at each stage of the litigation to assure himself or herself that everything which can be done in his or her defense is being done and that his or her defense is not unwittingly being compromised.

Preparation: Key to Success

The probability of a successful defense to any claim rests first on the underlying medical facts. Though relatively rare, true, "indefensible" surgical misadventures occur. Wrong-

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site surgery is one, for example. In such cases, the relevant medical facts may not be in dispute. If a claim arises from the occurrence of a true surgical misadventure, it may be prudent to posture the matter toward settlement from the outset. But even in these situations, understanding the entirety of the process and advance preparation for it remain critical.

Even if the case involves an admitted surgical error, it remains important for the physician and the lawyer to be cognizant that the litigation process for the physician likely will not end with settlement of the claim with the patient—there is still the matter of a possible future investigation of the case by the state medical board. In such a case, the physician might appropriately ask whether or not the *best result*, when consideration is given for potential medical board investigation, wouldn't be a settlement before a formal complaint is filed or, if the complaint is already filed, before the surgeon or hospital staff is deposed. Preparation in this setting would include an early consultation with counsel to discuss the ramifications to you personally and professionally of an early settlement versus proceeding to protracted litigation.

In the great majority of cases, however, the facts are disputed. The dispute may or may not involve what happened in surgery. The disputed facts may include the indications for surgery; the consent discussion; preoperative knowledge of the patient's relevant medical history, laboratory values, medications, or other contraindications; the substance of discussions with other medical providers, referring physicians, nurses, or radiologists; the existence of alternative therapies or surgical approaches; or the patient's postoperative course.

The reality of litigation is that the "facts" of a case are what the jury says the facts are on its verdict form. Until that moment, there are no facts; there is only evidence of facts. In coming to its verdict, the jury determines the facts after balancing the evidence presented at trial, giving weight to the evidence on either side of an issue as the members of the jury, individually and in their cumulative wisdom, see fit. Experience establishes that evidence which either side believes to be clearly decisive on an issue, nevertheless, may be marginalized or discarded in whole or in part by the jurors.

Effective litigation requires effective accumulation of evidence and effective presentation of that evidence. Effective accumulation and presentation of evidence require thorough and focused preparation. That process begins at the initial meeting between the lawyer and the physician-defendant, if not sooner, and continues through the conclusion of the litigation process.

There are certainly many aspects of the process over which the physician-defendant may have little or no control, but it remains incumbent for the physician to recognize those aspects of his or her defense that he or she can affect and to do whatever is necessary to achieve the *best result*.

Stages of the Litigation Process

The litigation process can be divided into three stages:

I. Initiation of the litigation process
   A. Notice of an occurrence likely to lead to litigation
   B. Notice of events which suggests that litigation is imminent: handling requests for medical records
   C. Service of the summons and complaint: initial meeting with counsel
II. The discovery process
   A. Written discovery
   B. Your deposition
III. Trial

Initiation of the Litigation Process

Notice of an Occurrence Likely to Lead to Litigation

The litigation process may commence in a number of ways. First among them is the unexpected occurrence of something adverse to your patient.

Something happens during surgery or in the postoperative period which you believe may lead to a lawsuit. At surgery, an adjacent organ or vessel is punctured; there is profound blood loss or spillage of bowel contents resulting in significant compromise, or there is even an unexpected patient death. In the immediate postoperative period or even after discharge, the patient becomes septic and decompensates. Imaging demonstrates a previously unappreciated rent in the bowel. The patient is taken back to surgery at which time the rent is identified and repaired, but the patient has a rocky course. Or several months or even years after bowel resection surgery, you notice, for the first time, that the pathology report had identified a potentially malignant lesion for which no additional investigation was conducted.

In these instances, the litigation process may be said to be initiated by you, in anticipation of litigation. When these adverse events occur, the important thing for you to recognize is that there are preexisting protocols and procedures in place for you to access which have been established for just such events. The purposes of those protocols and procedures are twofold: (1) to accumulate and preserve the necessary evidence about the event in a timely manner and (2), as appropriate, to protect the evidence from undue disclosure to the opposition by veiling it within the cloak of one or more legal privileges.

Know the reporting procedures for significant clinical events of your hospital, your medical staff, your risk management department, and your malpractice insurance company. These will typically include voluntary or mandatory

incident reporting which are in place for purposes of quality assurance or for reporting of events which will likely lead to litigation.

Although evidentiary rules vary among state and federal jurisdictions, as a general proposition, when a hospital, medical staff, or even an insurance company has in place a preexisting procedure for reporting such events for quality assurance purposes, any statement or disclosure made in furtherance of that purpose of quality assurance is privileged from disclosure as a matter of public policy [3]. Likewise, statements made to a risk management department or to an insurance company representative in anticipation of litigation are typically protected from disclosure by the attorney work-product privilege (which is different from the attorney-client privilege).

Whether either of these "pre-litigation" privileges will apply to a physician's disclosure depends on *why* the disclosure is being made. For example, the quality assurance privilege belongs to the hospital or its medical staff. The hospital or medical staff is deemed the "holder" of the privilege. It is the hospital and medical staff's obligation to conduct periodic and incident reviews of its staff's conduct and to investigate significant or "sentinel" events. To fulfill those duties, the hospital and its medical staff have procedures in place for these events to be reported. The goal of these procedures and the attendant privileges is to promote candid disclosure and discussion, which may be adversely affected if the participants are fearful that any statement made can or will be used against them later in litigation—thus the privilege. Therefore, *if the reason* the physician discusses or reports an event is pursuant to preexisting hospital protocol to ensure that an adequate investigation of the event occurs, the physician's disclosure is deemed to be in furtherance of the quality assurance process, and generally, that disclosure will be protected from later discovery. Application of the privilege depends on the physician's mindset when the statement is made.

Teaching Points

- By knowing the hospital's or medical staff's quality assurance and reporting procedures, a physician can tailor his disclosures and, later, his deposition testimony to be consistent with those procedures. At deposition:
  - Q. "Did you discuss what happened in surgery with anyone?"
  - A. "Yes."
  - Q. "With whom?"
  - A. "I told the operating room supervisor and the chairman of the department."
  - Q. "Why them?"
  - A. "Because I understood that the hospital quality assurance department requires that these kinds of events be reported and investigated."
  - Q. "What did you tell them?"
  - By defense attorney:
  - "Objection, quality assurance or peer review privilege."

Unless the physician understands that such procedures exist and knows the reporting requirements of those procedures, the physician may not be prepared to provide the necessary foundation to invoke the privilege. The foundational question to establish the privilege is: "Why did you make the disclosure?" The foundation for the quality assurance privilege is established if the disclosure was made in furtherance of an existing and known hospital or medical staff policy.

Similarly, in anticipation of litigation, malpractice insurance organizations and risk management departments have procedures in place for the physician to report adverse occurrences so that an investigation into the matter can occur while memories are fresh and potential witnesses and other evidence are available. The purpose of these pre-litigation procedures is to accumulate reliable evidence that, if litigation does ensue, can then be produced to the assigned counsel to promote the physician's defense. The rationale of these pre-litigation reporting procedures is that it is anticipated that the physician's attorney will need, and therefore will request from his physician client, a *summary of the occurrence*. This request for a summary of the occurrence will be better served if the summary is prepared soon after the event. Memories fade. Reports made to the insurance company early, without waiting for a formal claim to be made, may be more reliable. Thus, insurance companies have established early reporting procedures in anticipation of the attorney's needs. It is recognized at law that the insurance company collects these pre-litigation reports in furtherance of the physician's defense as an ostensible agent for, and on behalf of, the attorney—even though the attorney has not yet been retained.

Because the pre-litigation reports are presumably being collected on behalf of the attorney, the collection of these reports by the insurance company is deemed to be the "work product" of the attorney. Although there are exceptions, generally, these reports are protected from disclosure by the attorney work-product privilege, much like disclosures made by the physician directly to the attorney are protected by the attorney-client privilege.

Summaries prepared by the physician on his own, outside of the medical chart, may be protected if, but only if, the summaries are being made in anticipation of a request from the malpractice insurance company, or in anticipation of a request directly from the attorney, and are kept confidential.

Teaching Points

- To avoid question as to why you are preparing a summary of the events outside the medical chart and thus to bolster your position that the summary is protected by the attorney work-product and attorney-client privileges, begin the summary with, "The following summary is being prepared in anticipation of litigation, to be provided to my attorney when litigation commences." Ask your malpractice insurance company if it has forms for you to use for such a purpose.

Caveat

- Privileges can be waived. Summaries prepared in anticipation of later disclosure to the attorney can only be protected if they are kept confidential. Disclosure of the summary to others who are not in the line of communication with the insurance company or attorney likely will waive the privilege. For example, placing the summary in the patient's hospital or office chart, where it is open to review by hospital or office staff, defeats the presumption of confidentiality. The summaries must be kept separate and apart from the chart and may not be disclosed to others.

Teaching Points

- By knowing the malpractice insurance company's procedures for collecting statements from its physician insureds, the physician can anticipate that request and prepare a summary in a timely manner. By knowing that the statement must be kept confidential, the physician can take appropriate steps to assure that the statement is not disclosed to others or placed in the patient's chart. At deposition:
  - Q. "Did you prepare a summary of the events?"
  - A. "Yes."
  - Q. "When?"
  - A. "The day after the surgery."
  - Q. "Where is the summary?"
  - A. "I gave it to my insurance company."
  - Q. "Did you keep a copy?"
  - A. "Yes."
  - Q. "Have you shown it to anyone else?"
  - A. "Yes."
  - Q. "To whom?"
  - A. "To my attorney."
  - Q. "Have you shown it to anyone else?"
  - A. "No."
  - Q. "Where is your copy?"
  - A. "It is in a locked drawer in my desk."
  - Q. "Why did you prepare the summary?"
  - A. "I was told by my insurance company that when unexpected adverse results occur, I should prepare a summary of the events and maintain it confidentially for later use by my attorney."
  - Q. "Show me a copy of the summary."
  - By defense attorney:
  - "Objection, attorney work-product and attorney-client privilege."

The work-product privilege may also apply to discussions among the physicians in a group practice, if the statements are made in furtherance of an established (and preferably written) preexisting policy of the group which provides that such events are to be reported to the president or general partner of the group, so that they can then be reported to the malpractice insurance company or the group's attorney.

Notice of Events Which Suggest that Litigation Is Imminent: Handling Requests for Medical Records

You may be placed on notice of ensuing litigation for the first time by the patient or her attorney requesting a copy of her medical records from you (as opposed to asking that a copy of the records be provided to another physician for future care) or by the patient asking that a copy of her records be sent to an attorney. These requests must be handled carefully and consistently. The response to the request should include everything that is being requested. If requested, this must include the entire record. Once litigation ensues, you will be asked again to produce your records. The record produced then will no doubt be compared to the record produced to the patient when first requested. Any difference will need to be explained. Additions or deletions to the record which are found in the later production can be devastating to your case.

The law allows the patient to obtain a copy of his medical record from his physician. This may seem to be a simple task; yet, the prevalence of electronic medical records (EMR) has made this task anything but simple. To respond to a request to produce the office patient chart from an EMR, the medical record is "created" by someone sitting at a terminal and choosing which screens to print. That person decides what is, or is not, part of the record. The terminal operator will decide whether to include clinical notes; referral, demographic, or insurance information; and data imported from outside sources (e.g., operative reports or consult notes from referring physicians or hospital consultants). The terminal

operator will decide whether to include billing information or scheduling information.

The operator will also decide whether or not to include metadata. Metadata, or "data about data," exists in the EMR at several levels. The clinical record reflects the substance of the medical record entry—a history taken or examination findings. The metadata will include an entry log for that data, including when it was entered and by whom. At another level, the metadata may include a "comment" section for the entry. Consistent production of records requires a consistent definition of what is part of the patient's "medical record," as opposed to what is merely part of the office "administration" record. The production request and/or the laws of your jurisdiction will define the scope of the request and, therefore, will define the scope of the physician's obligation to search for, create, and produce the "medical record."

In the context of litigation, a party or his custodian of records will be asked to verify under penalty of perjury that the records produced in response to the request are a true and complete copy of the entire record as requested. That verification serves the formal evidentiary purpose of certifying that this is the complete record and that it may be used as such by any party to the litigation from that point forward, up to and including at trial. You or your staff may be questioned about the production or about any perceived inconsistencies or inadequacies of the production in deposition or trial. To be an effective witness, you and your staff must be able to rely on the production. Effective preparation to be an effective witness on this issue requires that consistent procedures be in place and followed.

It is also important that there be a process in place by which the physician is notified that a patient has requested her own records or has requested that a copy of the records be provided to an attorney. In that case, the physician should acquaint himself or herself with the patient to determine, at least preliminarily, whether this patient suffered an unexpected complication that could reasonably lead to litigation. If there is concern about litigation, it is prudent for the physician to contact his insurance company or attorney and ask for direction.

Teaching Points

- Have a formal, written procedure in place which defines the scope of your medical record for purposes of responding consistently to medical record requests on a day-to-day basis. Speak with your attorney to learn exactly what you are obliged to produce in response before you respond to a medical records request made in the context of active or anticipated litigation.
- Systematically check to confirm that your policy is being followed consistently.
- Be sure that whoever verifies the response knows the office practices for "creating" the medical record and can appropriately verify that the procedures have been followed.

Service of the Summons and Complaint: Initial Meeting with Counsel

The formal civil litigation process starts when the patient files a complaint, has a summons issued, and personally serves the summons and complaint on the physician, giving the physician notice that he has been sued. The procedural requirements relating to how specific the allegations of the complaint must be vary widely depending on the state or federal jurisdiction in which it is filed. Local rules may require that the complaint be specific and detailed and that it be verified (sworn to under penalty of perjury). More often the procedural rules only require that the complaint be specific enough that it identifies who the plaintiff is, who the defendants are, the relationship among the plaintiff and defendants that creates the duty or obligations among them out of which the claim arises, the manner in which the duty was breached or the obligations unsatisfied by the defendant(s), a statement relating to the classification of injuries suffered, and a statement, or prayer, at the conclusion of the complaint outlining the categories of damages sought.

In a medical malpractice case, the plaintiffs named will include the patient and/or affected family members. The defendants will include any one or more of the healthcare providers who attended to the patient's care and typically will include the facilities where the care was provided. The healthcare providers may include the individual physicians, the physicians' corporate or partnership entities or groups, and the physicians' attendant staff, such as nurse practitioners or physician's assistants. In appropriate cases, defendants may include medical instrument manufacturers or suppliers.

The required statement of the relationship among the parties which creates the duty or obligation may be general ("The defendants and each of them undertook to provide the patient's medical care. . . ."), or it may be specific ("On or about January 1, 2015, Dr. A performed a colectomy with anastomosis. . . .").

The statement outlining the breach of that duty may also be general or specific. The statement must, however, provide the defendant with notice of the classification of wrongdoing, which the plaintiff is alleging. The classification of wrongdoing is called a *cause of action*. In most cases, the cause of action stated is medical negligence or medical malpractice.

Extraordinary causes of action may also be alleged, and there may be subtle differences among the causes of action

which are important to recognize. For example, in most jurisdictions, failure by the physician to obtain the patient's "informed" consent prior to surgery is a type or subcategory of negligence. The complaint may set out a separate cause of action for failure to obtain informed consent, but in reality, this is a specification of the allegation of negligence. The elements of the cause of action and recoverable damages mirror those of a medical negligence cause of action.

A claim for failure to obtain "informed" consent must be distinguished from an alleged failure to obtain the patient's consent to perform the surgery which was performed or a claim that the surgery that was performed was substantially different from the surgery to which the patient consented. Performance of a surgery without actual consent is battery, an unconsented-to touching. The allowable damages in a battery cause of action can be substantially different from the damages allowed in a negligence claim. Damages in a battery cause of action may include punitive damages, awarded to punish the defendant rather than to compensate the plaintiff.

In most jurisdictions, battery is considered an intentional tort. The claim of battery in the complaint may create significant insurance coverage issues, as your medical malpractice insurance contract may contain an exclusion for intentional tort claims. The laws of your jurisdiction may not allow an insurance company to indemnify you for damages awarded for battery or for any other cause of action for intentional torts.

Similar concerns arise relating to claims couched in terms of fraud, concealment, or intentional infliction of emotional distress. For example, a patient might allege that the physician fraudulently concealed from her the injury to the adjacent organ which occurred during the surgery. Is the plaintiff alleging mere medical negligence, or is she claiming fraud?

Usually, the caption of the complaint will list the causes of action which are contained within the body of the complaint, but this isn't always true.

The allegations of injury, likewise, may be specific or general, depending on the jurisdictional procedural requirements and the plaintiff's lawyer's preference. The categories of injuries suffered generally include general damages or noneconomic damages for physical or emotional injuries (e.g., pain and suffering) and special damages or economic damages for calculable injuries for past and future medical expenses and/or for past and future loss of earnings, earnings capacity, or financial support. In the appropriate case, future medical expenses may include the cost of medical monitoring, for example, when the claim is based upon a delayed diagnosis of cancer for which monitoring for recurrence is advised. Each of these categories of damages is classified as compensatory damages—damages awarded to compensate the plaintiff for actual loss.

The classification of damages is important, especially as between general/noneconomic damages, such as pain and suffering, and special/economic damages for specific, calculable economic losses (medical expenses and loss of earnings). In several jurisdictions, the classification of damages will determine whether the plaintiff's recovery is "capped" or limited to a specific maximum number as a matter of statutory law. The statutory maximums usually apply only to general, noneconomic losses. Likewise, a defendant's liability for damages may be limited to his or her proportionate fault for general, noneconomic damages, the so-called several liability, whereas each defendant who is held liable at all or in any proportion (even 1%) for the *all* of the damages awarded to the plaintiff for special, economic damages, the so-called joint liability.

When extraordinary causes of action are included in the complaint (e.g., to include claims of willful misconduct such as battery or fraud), the categories of damages requested may be expanded to include punitive damages. Like criminal penalties, punitive damages are awarded to punish the defendant financially, with the secondary effect of deterrence of similar conduct in the future. To punish or deter, the damages must "hurt." Thus, the damages awarded must be in some proportion related to the defendant's wealth. The defendant's income and total financial assets become relevant, and therefore, at some point during the trial, the court may require the defendant to disclose his personal financial information to be used by the jury to calculate just how much must be awarded in punitive damages against that defendant to serve the purposes of punishment and deterrence. Moreover, it is because punitive damages are imposed to punish and deter *the defendant* that public policy precludes an insurance company from indemnifying the defendant from such damages.

The presence of extraordinary causes of action within the complaint creates insurance coverage issues and potential personal financial exposure for the defendant physician. The physician needs to be counseled early on in the litigation about these possible ramifications, so that the issues can be managed effectively.

Once the complaint is filed, a summons is issued. The right of the court to "summon" citizens to answer charges brought against them is rooted in the procedures of English common law. A defendant is deemed "summoned" to respond after proper service of the summons and complaint. The methods of effective service and the time and manner in which the served defendant must respond are established by the state's local procedural laws. The time in which to respond begins to run once the summons and complaint have been served on the defendant.

The complaint will identify each of the defendants who are being sued, but it is the summons which identifies who, among the defendants, is being served and, therefore, who is

obliged to respond. For example, the complaint may name as defendants an individual doctor, the doctor's personal corporation, and the doctor's practice group. That's three different defendants. To effect service on each of the three defendants, the plaintiff will have issued and served three different summonses.

If you practice as an individual doctor, have established a personal corporation (e.g., Dr. Smith, Inc.), and belong as part of a group practice and you are sued in each capacity, you may be served three different times. You will receive three summonses, which may appear identical, except that on one line, which identifies "person served," the wording will be slightly different. A separate copy of the complaint will be attached to each summons. Your attorney will need to obtain copies of all three sets of documents, even though they may appear identical to you. Keep all documents with which you are served and forward each set of documents to your insurance company or attorney as soon as you receive them.

The time allowed for the defendant to file responsive pleadings is short, usually 30 days or fewer from the date of service of the summons and complaint. Before responding to the complaint, the defense attorney must analyze the complaint and the relevant facts and law to determine, among other things:

- Who has been sued?
- Have the defendants been properly identified?
- Was the complaint timely filed, or is it potentially barred by the statute of limitations?
- Has the complaint been timely and properly served, and upon whom?
- Are the causes of action adequately pleaded?
- Does the complaint raise extraordinary causes of action, which require special handling or counseling?

Based on this analysis, the defense attorney will determine whether a routine response, an answer to the complaint, is appropriate or whether a more involved pleading is necessary to challenge the scope or validity of the claims being made. This analysis and the preparation of a formal response by the attorney take time. The time allowed by law is short, so the process must begin as soon as possible. This requires that the physician notifies his attorney or insurance company of the service of the complaint as soon as possible.

Teaching Points

- You and your office need established procedures to handle legal documents and filings.
- When a summons and complaint is received, keep the envelope in which it was served.
- Make a notation of when specifically (date and time) it was received and how it was received (by mail or in person).
- Look on the summons to determine who has been served (the doctor, the doctor's corporation, or the practice).
- Notify your insurance company or attorney immediately, and provide a copy of the summons and of the complaint to them.
- Review the complaint to determine whether any extraordinary causes of action (anything besides medical negligence or wrongful death) are listed on the first page of the complaint.
- Look at the last paragraph of the complaint, the prayer, to determine which categories of damages are being requested.

If you haven't heard from an attorney within 10 days of providing a copy of the complaint to your insurance company, contact the insurance company to identify who has been retained on your behalf. Request that the attorney contact you immediately to discuss any concerns you may have about the timeliness of the complaint and the proposed response:

- Confirm with the attorney that an appropriate and timely response has been or will be made on your behalf.
- Confirm that an appointment with the attorney is made, and ask what you need to have available at that first meeting.
- Create a file separate and apart from your medical chart, and keep a copy of the complaint and any other legal correspondence in that separate file. This is also where you should keep any summaries you may have created in anticipation of litigation.
- Do not speak with anyone (including your partners or office staff) or do any independent research relating to the case, until you have received directions from your attorney.
- Do not alter or supplement your records in any way; *I repeat, do not alter or supplement your records in any way*.

The attorney's first task is to acquire a very basic understanding of the nature of the claim and to respond to the complaint. The procedural rules of the jurisdiction will dictate how specific the response or answer to the complaint must be, just as the rules define how specific the allegations of the complaint must be. The rules may require a point-by-point response admitting or denying each allegation contained in the complaint, or it may require that the defendant merely file a general denial—a summary statement denying each and every allegation of the complaint without specification. Some jurisdictions require that the defendant verify the

pleading by signing the answer under penalty of perjury, confirming that the admissions or denials contained in the answer are true.

A point-by-point response may be a time-intensive process for the attorney and the physician-defendant, as each allegation is considered in light of the then-known information. It may require more than one conference and sifting through medical records. On the other hand, if only a general denial is required, the physician may play no role whatsoever in preparation of the responsive pleadings. The pleading requirements of the jurisdiction should be part of the initial contact between the attorney and the physician, so that the physician will know what is expected of him in this process.

In general, the responsive pleadings will serve to notify the court and opposing counsel that the defendant denies any wrongdoing, that the defendant disputes that anything he has done or failed to do has caused any injury to the plaintiff, and that the nature and extent of any injury alleged to have been suffered are disputed as well. In other circumstances, the responsive pleadings may set forth a legal challenge to the form of the complaint or the adequacy of its allegations to support the cause of action alleged. It may challenge the timeliness of the claim, with a contention that the allegations within the complaint itself establish that it is barred by the statute of limitations. It may challenge the right of the plaintiff to seek extraordinary damages such as attorney's fees or punitive damages, if the complaint contains prayers for these categories of damages.

Successful initial legal challenges to the complaint are rare. The overwhelming public policy is that all factual disputes between the parties are to be decided by a jury, in a trial, after the parties have had an adequate opportunity to conduct discovery in preparation for trial. Judges don't determine what the facts are; juries do. Judges decide what the law is and apply the law to the facts as determined by the jury. Therefore, in deciding whether to sustain or overrule an initial challenge to the complaint, the judge may not adjudicate any factual dispute. The judge must accept as true what is alleged in the complaint. A defendant's legal challenge is sustained only if, "accepting everything alleged in the complaint as true," the defendant's challenge is still valid.

This legal standard is particularly frustrating to defendants when the complaint includes allegations which are patently false. The plaintiff alleges that the physician undertook the subject surgery without his informed consent, without discussing the risks, benefits, or alternatives, and alleges further that if she had been told that there was a risk of injury to an adjacent organ she never would have consented to the surgery. You recall specifically speaking to the patient about the massive adhesions you expected to encounter and the attendant risks of injury to adjacent organs. You recall discussing the relative advantages of laparoscopic versus an open laparotomy approach, specifically as regards potential injury to adjacent structures. Your office medical record for the preoperative encounter includes a detailed note in your own hand outlining your discussion of these very risks and alternatives. Your chart includes a two-page detailed consent form which you and your partners have developed over the last 15 years, outlining the specific risks and alternatives, initialed by the patient in three different places and signed and dated by the patient and an office staff member. There is a similar document signed by the patient in the hospital. Yet, your lawyer tells you, and correctly so, that you have no right to bring this evidence to court at the pleading stage to challenge the complaint. She tells you that despite all existing evidence to the contrary, because the complaint says that you didn't obtain informed consent, the judge (as opposed to the jury) must accept as true that the issue of informed consent is in dispute, and this issue cannot be decided by the judge at the pleadings stage.

Your patience will be similarly tested repeatedly throughout the litigation process. You will repeatedly inquire "What's going on?", "Why is this taking so long?", and "Why hasn't this ridiculous case been dismissed already?" You will be told "These things take time" or "It doesn't work that way" or "There's nothing else we can do for now."

You've read in the complaint that you are being sued for unspecified amounts, based on what you know, or at least perceive, to be unfounded allegations, and now your lawyer is telling you that there is nothing you can do about it "for now." Rather, you must wait until the case or any issue in it is ripe for adjudication, and this may not be until trial. You are overcome by an overwhelming since of frustration, and justifiably so.

The frustration quotient establishes:

$$\text{Frustration} = \text{Responsibility} \ / \ \text{Authority to Act}$$

To avoid frustration in any situation, it is imperative that someone who bears the responsibility for an outcome should also have the authority to act as to effect a *best result*. The king was rarely frustrated. He could simply deny responsibility for anything while maintaining complete authority over the kingdom and his subjects. Surgeons undertake great responsibility for surgical outcomes and patient well-being. Their frustration level is manageable because, generally, the surgeon has the authority to act to effect a positive surgical result. That is the circumstance to which the surgeon has become accustomed. The duty and authority to act to fix the problem is ingrained in the very being of a surgeon and is the only way to avoid intolerable frustration.

On the other hand, surgery and the healing process can be terribly frustrating for the patient, who perceives herself to be helpless and totally dependent on you for her care. To help reduce that frustration, it is incumbent on the surgeon to educate the patient to manage expectations and to maximize her chance for a favorable outcome. The patient must be told in

advance for how long she will be bedridden or unable to return to her activities of daily living and what she can do to accelerate her healing process.

In litigation, the physician-defendant's authority to act is muted by the procedural processes. Initially, the physician-defendant may feel helpless and totally dependent on his attorney. Frustration abounds.

What can you do? Just as you educate your patients so that they can manage their anxiety and frustration, you must seek to educate yourself about the litigation process and manage your expectations and efforts accordingly. This can only be accomplished with an open dialogue between attorney and client. While you may not be able to run to court and protest your innocence, you don't need to sit by idly either. Speak with your attorney. Know what your role is, learn what will be expected of you and when, ask what can you do to best prepare yourself to succeed in your role, and, as importantly, ask what you should avoid doing so as not to inadvertently undermine your case.

There *are* things for you to do to achieve your *best result*. You have the authority to prepare yourself as directed and to manage your own expectations within the parameters of the process. This can and will reduce your anxieties and frustration level.

Teaching Points

- At the initiation of litigation, learn what you can do affirmatively to achieve *your best result*.
- Speak with your attorney early. Ask whether he intends to challenge the legal adequacy of the complaint. Ask what you need to do "now." What information and records need to be assembled? This not only includes medical records but also increasingly includes fax, e-mail, and office telephone or cell phone billing records to establish the existence, date, time, and substance of communications between you and the patient or hospital staff.
- Learn how long the process is expected to take. The estimate you receive may be broad, but it will provide you with some reasonable expectation. Tell your attorney how you would prefer to be contacted: office or personal cell phone. Tell your attorney what mailing address to use: office or home. Tell your attorney whether there is someone in the office other than yourself who can be contacted regarding the case, e.g., an office manager, or if all communication should be with you only.
- Ask when it will it be necessary for you to be personally involved. Are there court hearing dates or deposition dates pending at which you must appear? Is a trial date set? If not, find out how much notice will be given to you when your personal attendance is necessary. Tell your attorney about any plans you have to be out of the area for any significant period of time for vacations or conferences. Update your attorney when new plans are made or when plans change.
- Be patient! This will take time.

The Discovery of the Process

Written Discovery

In most jurisdictions, claims for medical malpractice are resolved in a jury trial. From the time the complaint is served on the defendant until jury selection is commenced, the parties to the lawsuit and their attorneys participate in a formalized accumulation and exchange of information which ultimately will be used at trial to educate the jurors about the relevant facts of the case. This is the discovery process.

To conduct discovery, the attorneys invoke legally sanctioned discovery procedures and the authority of the court to enforce those procedures, including the court's subpoena power. Basically, the law allows a party to subpoena or formally request relevant documents, such as medical records or employment records. The law allows parties to serve written inquiries to opposing parties, usually in the form of written questions called interrogatories. Most importantly, the law allows parties to interview opposing parties or witnesses under oath by way of deposition.

The procedural law of each jurisdiction sets forth in detail the manner in which parties may conduct this discovery. What the physician-defendant needs to know is that the discovery process is to be taken seriously as it has serious consequences.

Any party to a lawsuit may request information from any other party in the form of written interrogatories. The process is controlled by local rules of procedure. Some jurisdictions have created form interrogatories approved by the judicial council of that state. The form interrogatories cover a wide range of topics, which may or may not be relevant to the specific case. The attorney who propounds the interrogatories (i.e., asks the questions) simply checks the boxes on the form relating to the questions to be answered. The rest of the questions on the form can be ignored.

Other jurisdictions do not have judicially approved interrogatories, so that the attorney propounding the interrogatories must formulate the specific questions. Jurisdictions which use judicially approved interrogatories allow the propounding attorney to supplement the judicially approved interrogatories with special interrogatories, specifically drafted by the attorney, but maintain limitations and rules of procedure to do so.

By using judicially approved form interrogatories, the propounding party avoids objections as to the form of the question (e.g., vague, ambiguous, overbroad), which streamlines the process substantially.

The scope of the inquiry allowed by interrogatories is extremely broad. It includes personal and biographical data; insurance information; factual data relating to the underlying occurrence and medical care; information relating to potential witnesses and to legal issues such as contentions of negligence, causation, or damages; or affirmative legal defenses such as the statute of limitations.

Interrogatories are directed from one party to another. Although the interrogatories are directed to a party, the interrogatories are deemed to be directed to the party's attorney as well. The responding party is obliged to include within his response non-privileged information which is known or reasonably obtainable by the party "by inquiry to other natural persons or organizations, except where the information is equally available to the propounding party" [4]. Therefore the response must include information which the responding party may obtain by a reasonable inquiry to his office staff and his attorney. The responding party and his attorney are required to make a good faith search through the medical chart, the physician's personal files, and the attorney's files.

The local rules of procedure dictate the form of the questions and the timing and form of the response. Typically, the responding party must serve the responses within 30 days of his attorney's receipt of the questions. A party may request an extension of time within which to respond. The extension can be obtained by mutual agreement of the parties or, if necessary, by the responding party's going to court and requesting a court order granting additional time by which to respond.

Within the time allotted to respond, much must be accomplished. The good faith inquiry necessary to respond should begin immediately. As the physician-client, you can expect your attorney to have in place office procedures to notify his clients immediately when interrogatories are served. That notification should include a copy of the interrogatories and clear instructions regarding the division of labor: which of the interrogatories the attorney is going to answer and for which of the interrogatories the attorney is requesting assistance from the physician-defendant.

The notification from the attorney should also include a timetable for the response. Generally, the attorney's notification will include a date by which the physician's preliminary responses are due to him. The attorney may also ask the names of key office personnel who may be the source of additional information. There should be an agreement between the attorney and physician-defendant specifying who will be in contact with these additional personnel. In each case, confidentiality must be maintained. Any person contacted must be told not to discuss the conversation or inquiry with anyone outside of the office management staff, the physician, the attorney, or the attorney's staff.

The attorney will organize the information from each of the sources and will draft formal responses to the interrogatories. These responses may include both objections to the interrogatories and answers to the questions. Once the responses are prepared, the responses will be presented to the physician-defendant for verification.

A verification is a signature by the responding party, made under oath or penalty of perjury, which, depending on local rules, may or may not need to be notarized. The signature attests to the accuracy and completeness of the information contained in the response, at least to the best of his or her knowledge.

Once verified, the responses become affirmative statements of the responding party. The other parties to the litigation may justifiably, and legally, rely on the responses as being complete and accurate. The parties may use the responses for any relevant purpose in the litigation, up to and including trial. In some cases, the response to an interrogatory may be used as an admission against that party and can be presented to the jury as such at trial.

One important purpose of interrogatories is for the propounding party to inquire about additional potential sources of information. This could include the names of potential witnesses or other sources of documents and records. The propounding party is entitled to rely on the response to include a complete list of these additional sources, to direct further discovery efforts.

Local rules of procedure provide sanctions and other consequences for a party's failure to provide timely and complete answers. For example, objections contained in the response may be deemed waived as a matter of law if the response was not served timely. Likewise, if the interrogatory has asked for the identity of witnesses (which could include office or operating room staff or assistants) and the responding party has failed to identify a specific potential witness, either out of inadvertence or because of a failure to conduct a good faith inquiry into the records, the responding party may be barred from producing that witness at trial.

It is rarely acceptable to simply respond that the requested information is equally available to the propounding party through alternative means (e.g., looking through the hospital records himself).

As with all aspects of the litigation process the interrogatory process may be time-consuming and burdensome. But it must be taken cautiously. Inadequate or inaccurate responses will be detrimental to your defense.

Teaching Points

- Expect that you will be asked to answer interrogatories.
- Expect that your responses will need to include biographical and personal data from you.
- Expect that you will be asked to include the names of witnesses to the occurrence including relevant office staff,

hospital staff, assistant surgeons, anesthesiologists, and consultants.

- You don't need to wait until you are served with interrogatories, and the time period for responses starts to run, before you begin compiling the necessary information. At your initial meeting, ask your attorney if your jurisdiction has judicially approved form interrogatories which are used by attorneys in that area or if there are other interrogatories which you likely will be asked to answer. Obtain a copy of the anticipated questions, and begin immediately to compile proposed responses. If the opposition will want this information, your attorney should have it as well, and soon.
- Obtain assurance from your attorney that you will be notified as soon as interrogatories are served and that the notification will include the date by when your preliminary responses will be expected. You also have the right to expect that your attorney will anticipate the need to respond to interrogatories and will have begun a search of the relevant data sources in advance of the interrogatories' being served. You also have the right to expect that your attorney will provide you with the proposed formal responses with sufficient time in advance of the deadline to respond so that you can go through the questions and answers with your attorney before you sign the verification.

You can expect that at deposition or trial, your responses to the interrogatories will be presented to you. You will be asked to confirm that the verification includes your signature. You will be asked about the scope of your inquiry before providing the responses and whether you read and considered the responses before verifying their accuracy under penalty of perjury. Therefore, conduct a good faith and thorough search in providing responses, and read and understand your responses before signing the verification.

There are other kinds of written discovery process as well, such as requests for admissions, requests for production of documents (e.g., insurance policies, office protocols, licenses, and certifications), or requests for authentication of documents. In each case, the procedures are similar to responding to interrogatories. Be sure that you understand the time parameters for response and the scope of inquiry which is necessary and that you have reviewed the proposed response before signing the verification.

Your Deposition

Unquestionably, the most important aspect of pretrial discovery for the physician-defendant is the deposition. Giving an effective deposition requires effective preparation, and you have the right to expect that your attorney will aid you in that preparation. It is likely that your attorney attends depositions weekly, if not more frequently. He may have represented physicians at deposition hundreds of times or more. He may be completely comfortable with the process. But this is *your* deposition.

The situation is analogous to taking a patient to surgery. As an experienced surgeon, you have taken part in hundreds, if not thousands, of surgeries before. You have a well-founded expectation concerning what you are about to undertake. However, this may be your patient's first surgery. As a surgeon, you have the responsibility of educating your patient concerning what the patient must do to prepare herself in advance to maximize the likelihood of success at surgery. You must educate the patient regarding what is likely going to occur during surgery, including the risks associated with the process, and you must provide the patient with a spectrum of potential outcomes so that the patient's expectations will be reasonable. You are the surgeon, but this is *the patient's* surgery.

The first step in preparing for a deposition is to know what a deposition is. A deposition is a recorded question and answer session during which the attorneys for all parties to the litigation, including the opposing party and all co-defendants, have the right to ask you questions. The scope of questioning is extremely broad. As a general rule, the witness may be asked questions concerning any topic which might be directly relevant to the case and concerning any topic which might be reasonably calculated to lead to the discovery of relevant evidence. In short, this is the one time that the parties are entitled to conduct a "fishing expedition." Be patient. The deposition may take hours or even days. Your performance in the last 1/2 hour is every bit as important as your testimony in the first 1 hour.

Your deposition may be a videotaped deposition. The party who schedules the deposition will give notice of whether he intends to videotape it. Be sure you know whether it will be videotaped and dress and present yourself accordingly. In your practice, you wear your lab coat, with physician designation. This may or may not be appropriate when presenting yourself for deposition. One issue you will want to discuss with your attorney in advance is what to wear.

The use of videotaped depositions is becoming more prevalent in recent years. I've never thought it necessary for a physician to wear a lab coat in deposition; however, my opinion on this is changing. Jurors are patients. Patients have an expectation of what physicians look like. The videotaping of depositions has two purposes: to intimidate the witness and to present a video record to the jury at trial. You are a doctor. You have the extensive education, experience, and license to justify your use of the title, "Doctor." Wearing your lab coat at deposition provides an ongoing reminder to the audience or jury that you have earned and maintained that status and that your testimony should be considered and

weighed, accordingly. Being a doctor doesn't necessarily make you more believable, but it should add weight to your learned observations and opinions.

It is unlikely that you will be asked to wear your lab coat at trial. The stark difference between your appearance in a lab coat at deposition and in a suit and tie at trial may make your appearance at deposition seem staged. The decision whether to wear your lab coat, or any other questions regarding your presentation and attire, should be discussed with your attorney. In all cases, you should present yourself in business attire.

A deposition is a "legal," "formal" interview. The legality of the process is established by local rules of procedure. Foremost among them is that prior to beginning testimony, the court reporter, who is a designated officer of the court for this purpose, administers the oath. The words may vary, but the upshot is that you are being asked to swear or affirm that the answers you are about to give in deposition "are the truth, the whole truth, and nothing but the truth…." (Notably, the attorneys who are asking the questions aren't under oath. However, as the deposition is in the realm of judicial proceedings, rules of professional conduct oblige attorneys not to make material misrepresentations of fact or law at deposition.)

At the conclusion of the deposition, a transcript of the deposition will be prepared by the court reporter. It will look like a script. The questioner will be identified, and a verbatim transcript of the question will appear. The question will be followed on the page with your answer. You will be provided with a copy of the transcript. Within the parameters of your jurisdiction's procedural rules, you will have the opportunity to review the transcript and to make any changes to your answers which you believe are necessary to accurately reflect your testimony. (You may not make changes to the questions, although you may note typographical or transcription errors.) Your changes may be to form or substance.

The court reporter may have misunderstood or mistranscribed a word or may have left out a word which you believe was spoken and which you believe is necessary for the transcript to accurately reflect your testimony. You may make those kinds of corrections.

You may also make substantive changes to your testimony. For example, you may have been asked at deposition whether, before proceeding to perform surgery, you took the opportunity to review the labs or consult notes. Consistent with your customary practices, you may have answered "Yes" to that question at deposition. Upon further review of the chart or upon further reflection after the deposition, it may become apparent to you that one of the consult notes didn't appear on the chart until after you began your surgery, so that, at least as to that consult note, your appropriate response should have been "No, it wasn't on the chart yet."

You may make that kind of substantive change to the testimony, but you must be cautioned that any substantive changes you make to the transcript can be commented upon by the opposing counsel at trial, and you may be asked why you gave a different answer at deposition. These kinds of changes can adversely affect your credibility at trial and may have an adverse effect on your case. For that reason, it is important that you give your best answers at deposition to minimize the need for changes later.

Because substantive changes can adversely affect your case, it is important that you consult your attorney before marking or making changes on the original transcript. A good practice is to make any proposed changes on a copy of the transcript or a different piece of paper and then to preview the proposed changes with your attorney before they are finalized.

Once you have reviewed the transcript and made any changes you deem appropriate, you are asked to sign the deposition under penalty of perjury. Your signed deposition transcript becomes your testimony, for the trial and for any other subsequent legal proceedings. (In some jurisdictions, there are provisions for use of an uncorrected or unsigned certified copy of the deposition as if it were a signed and corrected original. These provisions may apply if you or your attorney have not notified the court reporter or the parties of any proposed changes within the time limitations provided by law or if the signed original hasn't been returned to the court reporter within the time frame allotted by law.)

Because the deposition is a legal proceeding, you have the right to have counsel present. Whether you are being deposed in a case in which you are a defendant or simply as a witness, it is important that you be represented at the deposition by an attorney. If you are subpoenaed for deposition as a witness in which you are not a party, contact your attorney, risk manager, or insurance company, and ask for representation. Too often, a non-defendant witness is lulled into a false sense of security, appears at deposition without an attorney, and, without proper preparation or representation, provides potentially incriminating testimony which provokes the patient's attorney to name the witness as a new defendant in the case. Depositions are too important to be taken lightly. You need proper representation.

It is your attorney's job to prepare you for the deposition and to represent you at the deposition. Preparation is imperative, but it is important that you be guided by counsel in that preparation. As with many aspects of the case, preparation for the deposition begins with the initial meeting. It is very important that you understand what is expected of you in anticipation of your deposition. Know what your counsel wants you to review in preparation for deposition and what he doesn't want you to review. For example, the case may involve technical aspects of the patient's medical care, such as pulmonary issues or endocrine issues, which you, as a sur-

geon, may not have studied since medical school. You are familiar with the issues and general management, but not with the current state of knowledge regarding ventilation settings or esoteric thyroid stimulation medications. Before beginning a literature search on these or any issues, be sure that the attorney wants you to do so.

Typically, the attorney will want you to be familiar with the documentation which was available to you at the time of your treatment of the patient, as it would be this information which formed the basis of your differential diagnoses, and your treatment alternatives.

As discussed more fully below, the primary liability issue in a medical malpractice trial is whether the physician's care was negligent, i.e., was it below the applicable standard of care? Though language differs by jurisdiction, basically, the standard of care requires the surgeon to act as other duly competent and careful surgeons would act *under the same or similar circumstances.*

Though seemingly tautological, it remains true that *you* acted as you did under the circumstances which then existed. Presuming that you are a reasonable and competent surgeon and accepting that you acted as you did and intended to act, then your conduct under the circumstances that then existed is, by definition, within the standard of care: You, a competent and careful surgeon, acted as you did, under the circumstances as they actually existed at the time.

It is your job at deposition to fill in the facts necessary for your lawyer to make this argument. You must be prepared to testify to your qualifications and experience, as to establish that you are a reasonable, competent, and careful surgeon. You must also be prepared to testify regarding your knowledge of the facts that existed at the time of your treatment of the patient.

The single most effective way to cross-examine a physician-defendant (or an expert) is to establish that the facts which the physician-defendant believed to be true at the time of his surgery, and which formed the basis of his actions or opinions, were not the facts as they truly existed. In that case, the physician was acting under the facts and circumstances as he *thought* them to exist, not as they, in fact, existed. In that case, the physician loses the value of the tautological argument. Knowledge of new or different facts may not have changed the conduct, but it infuses doubt.

The relevant facts would include the patient's recent and distant medical and surgical history; the existence of any peculiar risk factors, comorbidities, or contraindications; recent lab values, imaging studies, or consults; or even something as simple as whether blood had been typed and cross-matched before surgery and was therefore available immediately, if needed.

By the time the deposition takes place, it is probable that you will have forgotten these details. With your attorney's assistance, refresh yourself, so that when questioned at deposition you can recount your knowledge of the relevant facts as they existed at the time, consistently and accurately. Ask your attorney to provide you with copies of the relevant records prior to the deposition so that you have the time and opportunity to refresh your recollection. But don't access additional records unless and until you are instructed to do so by your attorney. There are specific, strategic reasons for this advice.

In most instances, the deposition of the physician-defendant occurs relatively early in the litigation process. The physician-defendant is being deposed as a percipient witness to the occurrences which form the basis of the case. As a percipient witness, the scope of inquiry generally includes exploration of all percipient observations. In the litigation process, perception goes beyond the primary senses. In addition to what the doctor saw, heard, felt, smelled, or tasted, the physician is in the unique position of knowing and, therefore, to testify to *what he was thinking at the time of the events*.

Typically, inquiry into the physician's contemporaneous thoughts is fair game for deposition. Thus, not only he can be questioned regarding what he saw or read before surgery; he can also be questioned regarding his decision-making and thought processes. This would normally include any percipient opinions, opinions *which he came to at the time of his care of the patient* concerning what may have caused or contributed to the patient's adverse outcome.

Opinions which are developed based upon supplemented or retrospective analysis of the facts are expert opinions. They differ from contemporaneous or percipient opinions. While inquiry into *contemporaneously developed* thoughts or opinions is considered appropriate during the physician's deposition as a percipient witness, opinions reached since the litigation ensued, or made retrospectively in reconsideration of the circumstances in anticipation of litigation or in furtherance of the defense, may be handled differently. Again, this is dependent upon procedural differences among the various jurisdictions, but as a general rule, where a physician-defendant processes information in anticipation of litigation, which may include information obtained from the physician's attorney, the conclusions and opinions which are the product of those processes remain the work-product of the attorney, unless and until the physician's status as a witness changes from percipient witness to expert witness. This change in status usually changes in one of the two ways: (1) at the deposition, the attorney for the witness declares his intention to proffer the witness as an expert witness at trial, or (2) during the exchange of expert designations among the parties, the attorney for the physician formally discloses his intention to call his client as an expert. In that case, the plaintiff may have the right to depose the physician-defendant a second time to explore his expert opinions and the bases for those opinions.

Assuming, however, that it is not your attorney's intention to elicit expert testimony from you (or at least he is not in a position to declare his intention to do so on the day of your deposition), then the scope of your deposition will be limited to opinions you came to at the time of your care. In preparing for your deposition, understand the difference between percipient and expert opinions and whether either or both are subject to inquiry at your upcoming deposition.

At deposition, you will be asked questions concerning your recollection of facts and occurrences. The party asking the questions is entitled to your best current recollection of those facts, even if that recollection is cloudy, vague, or nonspecific. In addition, generally, the questioner is entitled to know what documents, if any, you have accessed or reviewed to refresh your recollection. And he is entitled to question you regarding those documents. For example, you may be asked what the estimated blood loss was during the procedure. You may recall that there was nothing significant about the blood loss, but otherwise you can't provide a reasonable answer. Or you may have recently reviewed the operative report in preparation for the deposition and noted that the stated blood loss was actually substantial and estimated to be 500 ml. Reading and being reminded by this note spark a memory, and you now actually recall that there was an estimated blood loss of 500 ml.

Arguably, your present testimony of the facts is dependent upon what the operative note says. You may, therefore, also be asked, "If the note had referenced an estimated blood loss of 800 ml, would that have been your testimony?" In other words, did the entry in the chart actually spark a memory from which you are now testifying, or are you merely accepting as true and accurate what is written in the chart? Are you testifying, or is the chart testifying?

If you are testifying from refreshed memory, you may be asked a series of questions about what it is about this entry that has sparked the memory. If you testify that you are merely accepting what is written in the chart, the follow-up questions may relate to how and when the document was prepared and stored, in an attempt to call into question the accuracy of the document, as opposed to the accuracy of your memory.

For these reasons, the questioner will almost certainly ask you to list all documents reviewed in preparation for the deposition or documents reviewed to help refresh your recollection of the events. Your attorney is going to want to know in advance of the deposition what you are intending to review or have reviewed; he is going to want to control the universe of information to which you have had access in preparing for the deposition. By doing so, he will have some control over the scope of allowable inquiry.

For example, you may want to brush up on your infectious disease medicine before the deposition, out of fear that you will be asked something in that area of medicine. If you do so, you may be questioned about what you reviewed and why. The implication may be that if you *now* believe that this information is important for you to know, why didn't you do your homework before the surgery? Don't conduct independent research before the deposition unless you are directed to do so by your attorney or without first consulting your attorney.

Similarly, it may be that your attorney has provided you with a summary of the records or of the deposition testimony of other witnesses. As a general rule, that information from your attorney is privileged. It was provided to you in furtherance of your defense, not to prepare you for deposition. Know in advance whether you are to review your attorney's correspondence before the deposition, and tell your attorney that you have done so, so that he can be prepared with appropriate legal authorities to support and to invoke the attorney-client privilege in a timely manner.

At deposition, the questioner is entitled to your best estimate of anything that can be quantified. How many surgeries do you do in a year? How long does it typically take you to get to the hospital from your home? How many lap sponges did you use in this case? How long did it take to perform this aspect of the case or that aspect of the case?

The questioner is not entitled to your speculation or to ask you to guess. Often the line between an estimate and a guess is difficult to define. Ultimately, at trial the judge is the arbiter of what information does or does not go to the jury. The first step toward admissibility is for the judge to determine whether the information is reliable. Speculation and guesses typically do not go to the jury because they aren't reliable. Therefore, fundamentally, the difference between an estimate and a guess is whether you have a reasonably reliable basis or evidentiary foundation for your answer. The foundation may include your observations and memory of the case; or it can be based on your customary practices.

To demonstrate the distinction, a lawyer may ask you to estimate the length of the table in front of you. You don't have a tape measure, but based on your ability to observe the table and your presumed fundamental knowledge of units of length, you can give an estimate. Your ability to see the table is the foundation necessary to provide your estimate. If you are then asked to estimate the length of the table in the attorney's private office, where you have never been, you lack the fundamental foundation to provide such an estimate. You may have knowledge about how long office tables usually are, but that is not the question. The question is: "How long is the table in this attorney's office?" You don't even know if there is a table in his office. Any answer you might give to that kind of question is pure speculation, and should not be offered. In that case, your answer should be a direct "I don't know."

This same principle would apply to any question posed to you relating to events or conversations you did not witness.

Likewise, you would rarely have a reliable answer to any question relating to the thought processes of other individuals. You may have knowledge of how nurses usually go about taking a history from a patient in the preop holding area. However, if asked whether a specific nurse asked a specific patient a specific question in this case, and you weren't there, the answer to that question is "I don't know, I wasn't there." It is not "Usually the nurse does ask that question." Let the nurse testify regarding what happened.

Similarly, you may have an understanding as to why a prior surgeon may have decided to do a direct repair of the colon rather than performing a diverting colostomy. Don't guess or presume what he was thinking; let him testify to his rationale. This will minimize the chance of inadvertent conflicts in testimony that could call into question the credibility of both witnesses.

The questions asked at deposition must be fair. To be fair, they must be relatively intelligible and unambiguous. You have the right to understand the question and to ask the questioner to rephrase a question if you don't understand it. Exercise that right. If you don't understand a question, ask for it to be rephrased until you do understand it. If you answer a question, the presumption at deposition and at trial will be that you understood it before answering.

Ambiguous questions are troublesome. The trouble is that certain words are inherently ambiguous, such that they may have different meanings in ordinary speech as opposed to how they are used in medicine. One such word is "emergency." In ordinary parlance, "emergency" is used to describe a potentially dangerous situation for the patient which may require immediate (another word fraught with ambiguity) action. In surgical scheduling parlance, however, an emergency surgery is any surgery not otherwise scheduled as an elective surgery.

You may be asked whether the surgery you performed was an "emergency" surgery. In fact, the surgery was performed in the early evening after all scheduled surgeries were performed that day. It was performed after all appropriate preoperative testing was performed as to confirm the diagnosis and indications for surgery. It was performed by the operating room staff who were regularly on duty at that time. No one was called in. All typical time and care were taken in preparation of the patient for surgery. In anticipation of the potential need for the surgery, the patient was kept NPO since the prior evening. From the standpoint of the surgeon, this was not an emergent situation, and it was not an emergency surgery.

Yet, there on the intraoperative nursing records and on the anesthesia record, the surgery is identified as "emergency surgery." Their designations are based not on patient acuity, but because it was not a scheduled surgery. However, if you answer the question "Was this an emergency surgery?" with an emphatic "No," the plaintiff's attorney will no doubt challenge you at trial with the records prepared by the other practitioners who said it *was* an emergency surgery. This could lead to uncomfortable explanations, contradictions, and perceived back-pedaling.

There are two ways to avoid this kind of situation. In my experience, one is much preferred. The first way to avoid this ambiguity is for the deponent (the person being deposed) to ask the questioner, "What do you mean by 'emergency?'" This kind of response may escalate the situation. The questioner responds, "Doctor, do you know what an emergency is?" To which the physician answers, "I know what an emergency is, but I'm not sure that you do…." This kind of dialogue is rarely productive and may be affirmatively destructive if the jury believes the physician is being obstreperous or evasive.

The second way to handle the situation, and in my opinion the far better way, is for the deponent to answer the question as asked, but to include in that answer his or her definition of the potentially ambiguous word or phrase to clarify his or her answer. This avoids the ambiguity, the dialogue, and any suggestion that the physician is trying to avoid answering the question:

Q. "Doctor, was this an emergency surgery?"
A. "If, by emergency, you mean a surgery which needed to be performed that hour or before thorough preparation could be made, no."

Or

Q. "Doctor, was this an emergency surgery?"
A. "If, by emergency, you mean a surgery which was not a surgery on the operating room's regular schedule, yes."

If the questioner wishes to reconstruct the question to define the word differently, he can do so, and you can answer the new question accordingly.

Adjectives and adverbs used by the questioner must always be considered for their potentially ambiguous usage. The usage may be innocent, but the usage of such words must be tempered with a thoughtful response.

The potential significance of the deposition process cannot be overstated. Once the deposition is completed and signed, it is your testimony. It can be used affirmatively by the opposition at trial to establish facts stated. It can be used by the opposition to contradict the testimony given at trial.

In most jurisdictions, the trial court will actually instruct the jury concerning the effect and significance of deposition testimony. The jury will be instructed in substance, as follows:

> The deposition is the testimony of a person taken before trial. At a deposition the person is sworn to tell the truth and is questioned by the attorneys. You must consider the deposition testimony that was presented to you in the same way as you consider testimony given in court [5].

The opposing party may, therefore, literally begin his case against the physician-defendant by showing a videotape of portions of the deposition. The jury must consider that deposition presentation as if the same testimony was given by you live in court. The most common use of the deposition at trial is to emphasize possible contradictions or inconsistencies in your testimony as impeachment.

In addition, your deposition testimony can be used against you in virtually any future proceedings whether those proceedings relate to the same case or if you are giving potentially conflicting testimony in some future case. For example, if there is an investigation of the occurrence by the state licensing board, they will typically request copies of any depositions taken in the case. Or, in the future, you may be retained as an expert in other cases. It is not uncommon for parties to a case to seek and obtain copies of past depositions given by the experts. Therefore, you could well be cross-examined concerning the testimony you are giving as an expert based upon the deposition testimony you gave in a case 5 years ago.

The deposition process is a "formal" interview. The process proceeds with question, answer, question, answer. The court reporter is obliged to report and transcribe the statements made at a deposition verbatim, in the exact order in which the statements are made. Thus, for example, if, in answering a question, you anticipate the end of the question and begin answering it before the questioner has completed the question, that is exactly how the transcript will read. This leads to broken, and potentially ineffective, testimony.

In addition, your attorney has a job to do at the deposition. That job is to assure that the questions asked are appropriate as to form (relatively clear, unambiguous, and not argumentative). The attorney must also assure that the question does not call for the disclosure of privileged information which would be subject to objection. The attorney cannot do his job if you do not allow some interval after the question is asked before you begin your response.

Wait until the questioner has completed his question. Think before answering. Respond to the question directly and succinctly.

Answer the question which is asked. This would seem to be a simple instruction, easy to follow. In my experience, however, it is the instruction which my clients find most difficult to follow. The deposition process is in the form of an interrogation. It is not a conversation. In conversation, people often answer the question which they assume is being asked rather than literally answering the question which is asked. That is not the process of a deposition.

In conversation, you are asked, "Do you know what time it is?" In response, you look at your watch or your cell phone, note the time, and respond, "About 2:30." A perfectly appropriate course in conversation but a perfectly inappropriate course in deposition. The question was, "*Do you know* what time it is?" The answer to that question is "Yes" or "No." By answering the question in a conversational manner, you have not only not answered the question which was asked; you have potentially provided the questioner with invaluable information to which he was not entitled by asking the question he asked.

You have demonstrated that you use a watch as your timepiece or that you have a smart phone. Demonstrating that you have a smart phone could lead to a series of conversations concerning to what additional sources of information the smart phone is tied. Do you receive texts on the smart phone? Do you receive e-mails otherwise addressed to your office on the smart phone? Do you use the smart phone for your pages? This then could lead to additional discovery concerning your smart phone records, especially if the timing or duration of telephone calls ultimately becomes an issue.

This is not to say that the same information might not otherwise be gleaned if and when the appropriate questions are asked. It is to say that the opposition is not entitled to open that door by simply asking, "Do you know what time it is?" Don't invite him in.

Invariably, when cases go to trial, the physician-defendant reviews his deposition critically. As invariably, when reviewing the deposition, the physician will note several potentially harmful answers which could have been avoided if he or she had simply answered the question asked.

The doctor is asked, "Did you examine the patient's abdomen?" The physician responds "I don't recall, but I usually do, and note my findings in the chart." A quick review of the chart by opposing counsel reflects no examination. Rightfully or wrongfully, the implication based on your expanded answer is that since no examination was recorded, no examination of the abdomen was made—all because the physician failed to restrict his answer to the question asked.

This is not to say that every answer should be "Yes" or "No." In fact, from time to time, it may well be appropriate to provide a more comprehensive response to the question. For example, the question is, "Did you examine the patient's abdomen?" The physician responds, "I don't recall." The next question is: "When you examine the abdomen, do you chart your findings in the records?" The response is, "Sometimes I do; sometimes I don't." The physician would like to expand the answer to indicate that whether or not he charts his examination may be dependent upon his findings. He would chart any abnormal findings but would not necessarily chart the absence of significant findings. The proper way for a witness to expand his answer is not to simply continue to talk. A better way to expand the answer is to remark, "May I explain?" If the questioner responds "Yes," the physician has the opportunity to expand his answer with notice of his intention to do so to his attorney. If the questioner says "No," thus restricting the doctor's opportunity to explain his answer, that can certainly be noted at trial by your attorney.

Finally, thanks to hours of television police shows, we all know the basic Miranda warning, "You have the right to remain silent, anything you say can and will be used *against* you in a court of law." These Miranda rights relate to criminal proceedings. In a civil proceeding, such as a claim for medical malpractice, you don't have a right to remain silent, so you must appear and respond to questions at deposition. It remains appropriate, however, to know that everything you say at deposition can be used *against* you at trial. The deposition is a tool for your opposition; rarely can it be used by your attorney. Every word spoken is potentially an arrow going straight from your mouth to the opponent's quiver, to be loaded in his bow and shot back at you if and when he sees fit to do so.

The foregoing is in no way intended to suggest that you should unduly limit or manipulate your answers. It is important that you answer the question which is asked, and not expand your answers unnecessarily. Yet, in all respects, you must feel free to answer all questions truthfully and, as necessary, to include within your response all information which you believe is required to give a thoughtful, complete, and meaningful response.

Teaching Points

- Always consult with counsel before a deposition, and be represented by an attorney at a deposition, whether you are or you are not a party to the litigation.
- Consult with your attorney sufficiently in advance of your deposition so that if additional record review or preparation is necessary you have the opportunity to do it.
- Know what your attorney wants you to review prior to the deposition and what she doesn't want you to review or access.
- In every case, you should be familiar with the details of your own care, including the substance of all records, consults, or notes which you had available to you at the time of your management of the patient, so that you can reiterate at deposition the basis of your management decisions.
- Understand the difference between giving testimony based upon your memory being refreshed by review of documents and giving testimony based strictly on your acceptance of what the document states. Are you testifying, or is the document testifying?
- Understand in advance whether your attorney intends on your giving expert testimony based on a retrospective analysis or whether you are giving testimony only as a percipient witness, in which case you will testify only regarding thoughts, conclusions, and opinions you actually came to while treating the patient.
- Understand the difference between an estimate and a guess.
- Don't give answers relating to conduct of others which you did not witness or the rationale for the conduct of another, unless that person told you why he did what he did. Knowing *why someone mig*ht do something is not the same *as knowing why this person did* what they did on this occasion.
- Have available at your deposition a list of the documents you reviewed in preparation for the deposition or to refresh your memory, and provide that list to your attorney in advance of the deposition.
- Understand the question before you answer it. If a word used in the question is inherently ambiguous, define the word in your answer to clarify your response.
- Wait until the questioner has completed his question. Think before answering. Respond to the question directly and succinctly.
- Know if your deposition is going to be videotaped, and discuss your attire, accordingly.
- Be prepared to give your best and most complete answers at the deposition so as to avoid the need to make substantive corrections when reviewing the transcript.
- List proposed changes to your deposition on a separate piece of paper, and discuss the proposed changes with your attorney before correcting the original transcript.

The Trial

As the process moves toward trial, your role in many respects changes. Up to the time of your deposition, you have acted primarily as a relatively silent party to the process. After the deposition and as you move toward trial, however, you can become the most valuable and effective asset your team has. It is unlikely that any expert that your attorney retains will have as much knowledge of the situation which you encountered than you do. Often, you will be as well-educated and well-experienced as your expert. Frankly, there will be no one who is more invested in investigating and sorting out the pertinent records and testimony than you are. No one will have more at stake.

While the practices of attorneys vary, I believe that after the deposition and as we proceed toward trial, it is important to provide my physician clients with everything which has been compiled during discovery. This includes the depositions of all of the parties and all of the experts. It includes all of the records and literature.

At trial, the defense has one distinct advantage. Present at counsel table throughout the trial, defense counsel has a built-in expert, knowledgeable of the facts and of the medicine, and fully invested in the defense of the case: you. It is

my opinion that the defense lawyer should leverage the situation to his best advantage, by providing you with all relevant information.

In doing so, the attorney has the right to assume that you will read and analyze the information provided to you. This will be time-consuming. Often, the information fills two or three banker's boxes.

To facilitate this exercise, it is best for the information to be provided to the physician-client as it is accumulated, rather than delivering all the boxes to the doctor's doorstep the night before trial. Communicate with your lawyer. Know what he intends your role to be at trial. Know what he intends to provide to you, and ask that it be sent to you sooner rather than later.

You must make yourself available to meet with your attorney to prepare for trial. This may take as much as a day or two or longer. It will mean time away from your practice and your family. But the work must be done.

It is very important that you be present at trial preferably throughout the trial, but certainly as often as you possibly can be.

The plaintiff will be there. The jury will quickly understand that the plaintiff believes in her case and that she considers the proceedings important enough to her that she has placed all other aspects of her life aside to be present in the courtroom.

The jury is ordered to be in the courtroom. They are told they must arrive on time, they must be present everyday, and they must be attentive throughout the day.

They will expect no less from you. If you are not present, your absence will be noticed. Even if it is assumed that you are literally in surgery saving lives, the jury will nevertheless resent the fact that their lives and the important things that they do have been ordered to be put on hold, while you apparently are free to conduct your personal and professional life. That is not the image the defense wishes to portray. It is far preferred to portray to the jury from the outset that these proceedings, the jury's time and attention, and the outcome of this case are as important to you as it is to the plaintiff.

During the course of the trial day, the jurors will be watching everything which occurs in the courtroom. Do not be disruptive or inattentive. Keep your cell phone turned off or at least on vibrate. Do not answer texts in the courtroom. If it is absolutely necessary, alert your attorney to the situation, excuse yourself from the courtroom (assuming this is permitted by the court), conduct the necessary business, and return to the courtroom.

The trial itself will proceed pursuant to the local rules of the jurisdiction, including any particular courtroom rules of your particular judge. Trial schedules vary significantly. Rarely will a trial judge devote his entire courtroom day or week to a pending trial. There is other business to which the court must attend. Rarely will trials proceed all day, Monday through Friday.

More often, the trial court will not be in session for trial on one or more days during the week. The court's trial schedule will be made known at the outset. Most courts provide attorneys with advance notice of their trial schedules. Ask your attorney on what days the trial will be in session, when you are expected to be present, and on what days there will be no trial (days on which the court is "dark"). This will help you plan your schedule as well.

Alert your attorney as soon as possible to any vacations or schedule conflicts that might impede your ability to be present during the trial. The attorney may be able to have the trial schedule altered to accommodate your schedule, but the likelihood of her being able to do so will be greatly diminished without advance notice.

Although practices vary, trials are typically scheduled to begin on Mondays. Your attorney will appear at trial at the appointed date and time. Often, the court will have scheduled more than one trial to begin on the same day. Most cases don't go to trial; they settle or are otherwise disposed of. Still, the court may have two or more cases ready to begin on the same day, or his courtroom may be occupied with an ongoing trial. Ask your attorney what the likelihood is of your case actually starting on the date assigned, so that you can attempt to accommodate your professional schedule.

Once your case is assigned to a specific courtroom, the attorneys and judge typically proceed with pretrial procedural matters. This may take a small portion of the day, or it may take the entire day. Your attorney should be able to provide you with some preview of whether your personal attendance will be necessary in the morning of the first day of trial, in the afternoon of the first day of trial, or not until the following day.

Once the preliminary matters are completed, the judge will typically call up a panel of jurors who will then be interviewed by the judge and the attorneys to determine their suitability for your trial.

The jury selection process, called *voir dire*, is often time-consuming. Nevertheless, your attendance during jury selection is extremely important.

First, it is within the jury selection process that the prospective jurors make their first impression of the case. You don't want the jury's first impression to be that you are absent from the courtroom.

Likewise, jury selection is the first opportunity you will have to form your first impressions concerning each of the jurors. Observe the jurors. Observe their mannerisms and their willingness to make eye contact. Listen to their comments. Listen to their concerns about their own experiences with the medical profession. Your "gut feeling" about the jurors is important.

In most jurisdictions, your attorney will have the opportunity to excuse jurors without specifying a reason. These peremptory challenges are exercised based as much on *gestalt* as on any science. Your ability to evaluate the perspective jurors' response to the parties, the attorneys, the court, and the process is likely just as valuable as your attorney's. At the appropriate time, share your observations and thoughts. They might be important to the attorney.

Once the jury is selected and this could take an entire day or longer, the attorneys for each party are invited to make an opening statement. The opening statement is not an argument. Rather, it is merely a summation of what the attorney believes the evidence will establish. Some attorneys use a broad approach. Other attorneys provide a detailed analysis of what they believe the evidence will show.

Listen to the opening statements. The plaintiff's attorney may well expose his intentions, which may provide you with additional information concerning what aspects of your testimony need to be better prepared. Do not comment or gesture or react to the statements. To do so is inappropriate and disruptive, and you likely will be admonished by the court.

Your attorney's opening statement will include what she expects the evidence to prove. Implicitly, she is telling the jury what she expects you to tell them when you testify. Listen to what she says. If there have been mistakes made by your attorney about the facts or the medicine, point it out *after* she completes her opening statement so that the errors won't be perpetuated.

The parties then begin presentation of the evidence. The plaintiff has the burden of proof and therefore goes first. The plaintiff's attorney may or may not call you in his case in chief (i.e., the legal term for the initial portion of the trial in which the plaintiff puts on his case).

If you are called to testify by the opposing attorney, he will be questioning you as an adverse witness. This will entitle him to ask you leading questions. Be respectful of the process. Answer the question which is asked. Do not insist on attempting to expand or explain your answers, except, as in deposition, by asking, "May I explain?" Direct your comments to the questioner, not to the judge. By asking the questioner if you can explain, you have once again placed him on the horns of a dilemma. If he answers "Yes," he's inviting a narrative which will no doubt be adverse to his case. If he answers "No," the jury will infer that the lawyer is trying to hide the true facts from them.

The most common derogatory comment made by jurors about any witness is that the witness was evasive, argumentative, and nonresponsive. Don't be.

If your attorney believes that additional testimony from you is necessary on any topic, she will be prepared to ask you those questions herself. Trust her to do so.

During the course of the questioning, the opposing counsel may read from your deposition. Do not try to object to this; it is his right to do so. Do not comment about the passage read by saying that it was taken out of context, etc. Rather, patiently and confidently await your opportunity to explain the answers when asked to do so by your attorney.

During the course of the testimony, always direct your answers to the questioner, unless asked to do otherwise. Unduly directing your comments to the jury may appear patronizing and unduly solicitous. Looking to your own counsel during your answer may appear to be a sign of weakness, as if you are looking for help.

There are other specifics concerning how to present yourself as the best possible witness, which you should discuss with your attorney.

While other witnesses are testifying, be respectful of them as well. Do not gesture as if in disbelief. Do not be dramatic. Present yourself always as the respectful professional that you are. Ultimately, most cases are greatly influenced by the testimony of the physician-defendant. Direct, confident, and responsive answers are always appreciated.

The roles of the judge and jury in a trial are different. It is the jury's duty to determine the facts of the case. The judge determines the law of the case. The jury hears the relevant evidence, deliberates among themselves, and then responds collectively to the questions on the verdict form. Although the questions on the verdict form may have several variations or subparts, there are really three inquiries:

1. Was the defendant negligent in the medical diagnosis or treatment of the plaintiff?
2. If so, was the negligence of the physician a legal cause of injury to the plaintiff?
3. If so, what dollar amount of damages do you award to compensate the plaintiff for the injuries, which you have determined were caused by the defendant's negligence?

Most often, the case turns on question No. 1:

Was the doctor negligent in the diagnosis or treatment of the patient?

The plaintiff has the burden of proof with respect to each of these questions. Generally, this means that in order to prevail, the plaintiff must persuade the jury, by the evidence presented in court, that what he or she is required to prove is "more likely to be true than not true." The jury will also be instructed that "if, after weighing all of the evidence, … you cannot decide that something is more likely to be true than not true, you *must* conclude that the party did not prove it." (Emphasis added.) If the plaintiff has not proven that you were negligent (if, for example, the jury determines that the evidence on this issue is evenly balanced), the jury must decide the issue of negligence in the favor of the defendant [6].

How then can jurors, who are not doctors, decide whether a doctor was or was not negligent?

The jury will be given jury instructions by the judge, which outlines their task and how they are to go about satisfying that task.

The court will instruct the jury on the doctor's duty to conduct himself or herself in accordance with the standard of care and on what evidence the jury should consider in coming to this conclusion.

The basic standard may be expressed as follows:

> A surgeon is negligent if he or she fails to use the level of skill, knowledge, and care in diagnosis and treatment that other reasonably careful surgeons would use in similar circumstances. This . . . is sometimes referred to as "the standard of care" [7].

In directing the jury as to what evidence the jurors may consider when deciding whether the doctor did or did not act as other reasonably careful doctors would act under similar circumstances, a basic instruction is as follows:

> You must determine the level of skill, knowledge, and care that other reasonably careful surgeons would use in the same or similar circumstances, based *only* on the testimony of the expert witnesses [including the defendant] who have testified in this case. (Emphasis added) [7].

In most circumstances, the standard of care is defined as a standard of conduct, not a standard of result. The fact that a patient has suffered an unexpected or unintended adverse consequence is not, in and of itself, evidence of negligence. Again, while the verbiage of any instruction on this issue to the jury may vary depending on the jurisdiction, a basic statement of the applicable standards is as follows:

> A surgeon is not necessarily negligent just because his efforts are unsuccessful or he makes an error that was reasonable under the circumstances. A surgeon is negligent only if he was not as skillful, knowledgeable, or careful as other reasonable surgeons would have been in similar circumstances [8].

The jury typically also will be instructed that simply because the experts on either side differ on what their personal preference is concerning proper management of the situation or that reasonable alternative methods for diagnosis or treatment were available does not necessarily mean that the physician's choice of one approved method over another, even if the defendant's choice, in retrospect, proved to be the wrong choice, was negligent. This tenet of the law can be expressed as follows:

> A surgeon is not necessarily negligent just because he chooses one medically accepted method of treatment or diagnosis and it turns out that another medically accepted method would have been a better choice [9].

"A difference of medical opinion concerning the desirability of one particular medical procedure over another does not… establish that the determination to use one of the procedures was negligent" [10]. Likewise, "[m]edicine is not a field of absolutes. There is not ordinarily one correct route to be followed at any given time. There is always the need for professional judgment as to what course of conduct would be most appropriate with regard to the patient's condition" [11].

It is important for the physician-defendant to understand these various legal propositions and the significance of each of them.

In deciding whether or not the physician-defendant was negligent, the jury is to consider only the testimony of the experts. Ultimately, the jury's decision will come down to which party's experts were more persuasive. The court may also instruct the jury concerning how they might go about weighing the conflicting testimony of the experts. One such instruction is as follows:

> . . . [I]t is up to you to decide whether you believe the experts' testimony and choose to use it as a basis for your decision. You may believe all, part, or none of an expert's testimony. In deciding whether to believe an expert's testimony, you should consider:
>
> (1) the expert's training and experience;
> (2) the facts the expert relied on; and
> (3) the reasons for the expert's opinion [12].

Additionally:

> If the expert witnesses disagreed with one another, you should weigh each opinion against the others. You should examine the reasons given for each opinion and the facts or other matters that each witness relied on. You may also compare the experts' qualifications [13].

In short, the weight to be given an expert's opinion is to be determined not only by the qualification of the experts but also more specifically by considering the reasons given for each opinion and the facts or other matters relied on.

The fundamental question is whether the physician-defendant acted reasonably under the established circumstances. The fundamental method used to invalidate an expert's opinion is to establish that the facts stated as the basis for the opinion are inaccurate or incomplete. An opinion is of no greater value than the facts upon which it is based. An opinion without proper factual foundation must, necessarily, collapse.

In preparation for trial, therefore, as your own advocate in the case, you should be well acquainted with the identities and opinions of the experts on either side. You must likewise be acquainted with the factual basis for each of those opinions. And you should be prepared to guide your attorney to the records which you believe discredits the factual basis of the opinions of your opposing expert and to the records which confirm and support the factual basis of the opinions of your own experts.

In addition, you should be prepared to tailor your own testimony, mindful of the value of testimony you give which

contradicts the factual basis of the opposing expert and supports the basis of your own expert. Knowing the bases of the opinions of the experts on both sides, and tailoring your efforts and testimony to contradict the plaintiff's expert and to support your own expert, is the best way that you can contribute toward a successful defense of your case.

In the proper situation, as noted above, it is not fatal to your case to recognize that alternative methods and diagnosis also existed. In fact, it may be beneficial for you to explain that you were aware of these alternative methods, and considered them, but ultimately selected your method for reasons on which you are prepared to elaborate. By being prepared to discuss (both in deposition and trial) your knowledge of alternative treatments and the rationale for choosing the course you chose after discussing the options with your patient, you are potentially providing your defense with the factual foundation necessary to promote the "alternative methods of treatment" defense.

Familiarize yourselves with the applicable legal standards and instructions used in your local jurisdiction. Doing so immediately before trial, and at trial, is valuable. Doing so at the commencement of the case, as early as your first meeting with your counsel, is far more valuable.

At the conclusion of the evidence, the attorneys will proceed with their summation of the case or final argument. Because the plaintiff bears the burden of proof, traditionally the plaintiff goes first, the defense attorney then makes his argument, and the plaintiff's attorney makes the rebuttal and final comments to the jury. It is within the court's discretion to instruct the jury either before or after final argument.

Once the evidence has been completed and the jury has received the final arguments of counsel and instructions from the court, the jurors will then proceed into the jury deliberation room. The documentary evidence will be delivered to them for their consideration.

During the course of deliberation, the jury may ask questions which will be considered by the court and counsel and responded to. The jury may also request that the testimony of one or more witnesses be read back to them. In that case, depending on the jurisdiction, either the jury will be brought into the courtroom, at which time the court reporter will recite the testimony, or the court reporter will proceed into the jury deliberation room and read the requested passages to them.

Some jurisdictions require that the jury decide the cases unanimously. Other jurisdictions require a so-called super majority; typically 3/4 of the jurors must agree to decide any single question. Once the requisite number of jurors has come to a conclusion, the jury is then returned into the courtroom, and their verdict is announced.

Based on the factual findings, or verdict, by the jury, the judge then will enter judgment in favor of one side or the other. The jury decides the fact of whether or not the physician-defendant was negligent and records that decision on the verdict. With that factual question answered, the judge then decides the legal effect of that answer (decides who wins) and incorporates that decision into his decision in the form of a judgment.

After the jury returns its verdict, either party to the case may ask that the jury be "polled." In that case, each individual juror will be asked his or her response to each of the questions. In this way, it will be confirmed that the requisite number of jurors have responded and agreed on the answer to each question so that it is a competent verdict.

Even if the case is won at trial, it will undoubtedly exact a huge toll on you personally and professionally. Jury trials are extremely expensive in terms of time, effort, and money. The jury system is not perfect, but in my experience, far more often than not, the jury gets it right.

Teaching Points

- At trial, you are your attorney's best technical asset.
- In preparation for trial, obtain copies of all relevant records and depositions, especially your deposition and all expert depositions.
- Analyze the data with a focus on knowing the circumstances as they existed when you treated the patient; point out where the plaintiff's expert is wrong in his assumption of the facts, and be prepared to support the factual basis of your expert's opinion.
- Know the basic legal standards that will be applied to define "medical negligence," so that you can tailor your testimony to meet that standard.
- Understand the significance of "alternative methods" of treatment.
- Alert your attorney to any schedule conflicts as soon as possible.
- Consult your attorney regarding when exactly the trial is set to begin and when your personal presence is necessary.
- Be present at trial, including jury selection.
- Be cognizant of the opening statements of both sides; it will provide you with valuable insights relating to the proposed testimony.
- Do not react to testimony with gestures or speech. Don't be disruptive of the proceedings or of your attorney's efforts.
- When testifying, direct your responses to the questioner, not to the jury, the judge, or your own counsel.
- Do not expand your answers beyond the question asked, unless you have asked to do so, e.g., "May I explain?"
- Recognize that preparation at each stage requires knowledge of the process and the respective roles of attorney

and client and that preparation is the key to achieving your personal *best result*.

Concluding Remarks

It has been the goal of this work to provide a primer for those not acquainted with the litigation process. It is intended as a guide to facilitate timely and effective communication between physician-defendants and their attorneys. It is further hoped that by affording the physician-defendants a better understanding of the process, they can come to a better understanding of what is expected of them as clients, of what they can expect from their attorneys, and of how the attorney and client can work together toward managing expectations, minimizing anxiety and frustration, and formulating a strategy to achieve the *best result* available under the circumstances.

Communication is the key. Meet early. Discuss the case regularly. Know what is expected of you and when. Know when your personal presence is likely to be necessary. Do your homework, and make yourself available.

If you prepare to succeed, the likelihood of achieving your *best result* will improve exponentially.

References

1. Jena AB, Seabury S, Lakdawalla D, Chandra A. Malpractice risk according to physician specialty. N Engl J Med. 2011;365:629–36.
2. This is not a law review article. It is intended to be of general application to clinicians. Citations to relevant laws are kept to a minimum, as the letter of the law varies from jurisdiction to jurisdiction. I practice in California. The citations included are to California legal authorities, and may not be specifically applicable in your jurisdiction. Consult your attorney for a more detailed discussion of the law as it applies to your case.
3. See, e.g., Cal. Evid. Code section 1157, et seq.
4. See, e.g., Cal. Code of Civ. Proc. section 2030.220 (c).
5. Judicial Council of California, *Civil Jury Instructions*, Instruction 208.
6. Judicial Council of California, *Civil Jury Instructions*, Instruction 200.
7. Judicial Council of California, *Civil Jury Instructions*, Instruction 501.
8. Judicial Council of California, *Civil Jury Instructions*, Instruction 505.
9. Judicial Council of California, *Civil Jury Instructions*, Instruction 506.
10. *Clemens v. Regents of Univ. of Cal.* (1970) 8 Cal.App.3d 1, 13.
11. *Barton v. Owen* (1977) 71 Cal.App.3d 484, 501-502.
12. Judicial Council of California, Civil Jury Instructions, Instruction 219.
13. Judicial Council of California, Civil Jury Instructions, Instruction 221.

Quality

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Elizabeth C. Wick and David A. Etzioni

Key Concepts

- The Donabedian structure/process/outcomes model is a useful paradigm for categorizing and conceptualizing different approaches to measuring quality.
- Process measures are preferable to outcome measures when there is clear evidence supporting a particular clinical activity and when there is a related gap in care delivery.
- Outcome measures are highly valid, but often do not generate a clear path for quality improvement; they are most useful in situations of high complexity where clear standards are not well established.
- Administrative data and registry data can yield very different measurements of quality, and leaders in surgical quality should be familiar with the strengths and weaknesses of these two types of data.
- A broad range of nontraditional measurements of quality are on the horizon, including patient-reported outcomes, patient satisfaction, and return to health.
- Accreditation programs such as the National Accreditation Program for Rectal Cancer (NAPRC) have an important potential role in improving quality of care by improving the structure of care delivery throughout the country.

Introduction: What Is Quality?

The discussion of quality in surgery is pertinent to every aspect the work performed by surgeons, day in and day out, from the clinic to the hospital and beyond. In this chapter we will offer the reader a framework for approaching quality and offer insights about how quality can be measured, analyzed, interpreted, and improved. Toward this goal we will review a broad range of current topics and paradigms that are relevant to the pursuit of quality in colon and rectal surgery.

The National Academy of Medicine has defined quality as the "degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge." The report "Crossing the Quality Chasm" outlined six principle domains of quality [1]:

1. Patient safety: avoidance of harm to the patients during care delivery
2. Patient-centeredness: providing care that respects patient preferences
3. Effectiveness: the use of services that have a basis in evidence
4. Efficiency: healthcare delivery that avoids waste of resources
5. Timeliness: delivery of prompt care to avoid delays that may result in harm
6. Equity: optimizing an optimal level of care for all patients

It is important to consider this definition and the associated domains of quality when reflecting on surgical care and in developing processes for continuous improvement that encompasses all of the areas. For surgeons interested in quality improvement, some of the domains within this definition are more applicable than others.

Measuring Quality

Efforts to improve quality of care in the field of surgery necessarily begin with an organized approach to measuring quality. The measurement of surgical quality is challenging, however. This fact is clear when reviewing the methods used by the wide range of federal and private sector organizations that have sought to analyze and report surgical quality [2–5].

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There is no single approach to quality measurement that is best suited to *all* circumstances.

One of the most common approaches to organizing thinking around quality measurement in medicine was described by Avedis Donabedian in 1966 [6]. In his paper he categorizes methods for assessing quality of care into three main domains: outcomes, process, and structure. *Structure* refers to the context in which care is delivered – this includes the facility and services, workforce, and payment structure. Structural measures ask, "Are the appropriate services, equipment, incentives, and people available?" *Process* is the application of these tools, equipment, and policies/procedures to patients (good practices and evidence-based medicine). Process measures ask, "Are the right tools, policies, and equipment being used for all patients?" *Outcome* is the result on patients. Outcome measures ask, "How often do patients achieve the desired result of surgery?" or "How often are patients harmed during the course of their perioperative care?" In the Donabedian model, structure (how care is organized) plus process (what we do) influences patient outcomes (the results achieved).

As one considers the approaches to quality measurement outlined in more detail below, it is important to remember the forums where the metrics can be used – internal quality improvement, informational external reporting (patients and payors), and financial incentives or penalties for hospitals/providers.

Outcomes

For surgeons, the measurement of outcomes as a representation of quality carries important face validity. A broad range of outcomes are commonly used as targets for quality assessment, including complications such as surgical site infection, urinary tract infection or venous thromboembolism, mortality, and readmission. Anything that occurred to a patient in the course of their care that impacts quality of life can be considered an outcome worthy of measurement. Outcomes are therefore a tangible way of assessing the patient's perspective of their treatment and frequently are the most meaningful to surgeons.

Virtually anything significant that happens to a patient as a result of their surgical care is documented in the medical record and translated into a digital format. The wealth of data that arises from the digitization of medical care is widely used as the basis for monitoring quality, through several different surveillance systems. Within the United States, there has been an increasing movement to make these data available to parties interested in using these data for quality reports [7]. This movement has focused largely on postoperative complications, although many other types of outcomes are possible foci of quality improvement (e.g., quality of life, return to work, etc.).

Outcome-oriented approaches to quality measurement are powerful and widely accepted as important metrics. Their appropriate use should encompass a careful evaluation of their underlying accuracy and validity. Also, it is important to note that outcome-oriented approaches to quality of care do not guide interested parties onto a clear path toward quality improvement [8, 9]. These approaches should be viewed as tools to focus and direct other efforts that support quality improvement.

Process

Process-oriented approaches to quality measurement depend on a preexisting body of evidence that informs clinicians regarding what the *right thing* to do for patients is. Armed with this knowledge, it is possible to assess the frequency with which a specified population of patients receives this element of care.

The best example of this in colorectal surgery is the Surgical Care Improvement Project (SCIP) [10, 11]. These measures were developed to guide hospital-based efforts to reduce rates of surgical site infections (SSI). Multiple parties took part in the construction of these measures including the Joint Commission and the Centers for Medicare and Medicaid Services (CMS) with mandatory participation. Ultimately, compliance with the SCP measures was publically reported through CMS' Hospital Compare website and tied to hospital payment. SCIP measures important for the practicing colorectal surgeon were those related to timing, selection, and discontinuation of antibiotics for surgical prophylaxis (surgical site infection [SSI]) prevention, maintenance of normothermia in the operating room (SSI prevention), use of venous thromboembolic event (VTE) chemoprophylaxis, and removal of the Foley catheter by postoperative day.

There is widespread agreement that the SCIP measures were effective in guiding hospitals toward the uptake of evidence-based practice regarding SSI prevention. At the time of the introduction of SCIP measures, less than 60% of patients were receiving antibiotics preoperatively, and many patients were recovering on inpatient units with urinary catheters in place long after they were needed. Despite the clear evidence basis supporting a link between process and outcome, studies linking hospital performance on SCIP measures with complication rates were lacking, however [12, 13]. The SCIP measures were officially retired in December 2014 with a commitment by CMS to move to more outcome-based measures over the next couple of years.

A process-oriented approach to quality measurement can be very effective, especially when there is a clear standard

regarding what should be done for patients with a certain condition. A common example in colorectal surgery is time to initiation of postoperative adjuvant therapy in patients with stage 3 colon cancer. It is established that initiating chemotherapy within 3 months of surgery is associated with improved survival; therefore, it is reasonable to both *measure and improve compliance* with this evidence-based practice. The greatest challenges to a process-oriented approach are faced when the evidence regarding a specific practice is unclear or when the use of evidence-based methods is already near 100%.

Structure

The structure perspective into quality measurement is the vaguest and the most challenging for clinicians to directly impact. According to Donabedian, structure assessment pertains not to the care provided itself, but instead "…the settings in which it takes place and the instrumentalities of which it is the product...." Areas of quality in healthcare that could be described as being related to structure include a wide range of factors, including hospital cleanliness, the availability of CT scanners, and certification/licensure.

The importance of these types of structural factors on quality of care is highly intuitive but challenging to quantify. A significant body of research has focused on several aspects of the relationship between structure and outcomes. Two of the most important domains of research include work demonstrating the importance of nurse staffing ratios and higher patient volumes in determining postoperative outcomes. Not all elements of structure can be easily studied, however. There are no studies examining postoperative mortality in the hands of physicians who are licensed to practice vs. not.

Quality Measurement: Making the Right Choices

A thoughtful approach to quality improvement necessarily includes some strategic decisions regarding the measurement of quality. Each institution, patient population, and clinical practice has factors that need to be considered in order to arrive at a sensible approach. In this section several important "forks in the road" in choosing how to measure quality are presented and discussed.

Process Versus Outcome Measures

The decision to pursue a process-oriented vs an outcome-oriented metric to monitor quality is one of the most important initial aspects of any quality improvement effort. Which types of efforts are best served by one approach over the other? As alluded to earlier, the most important two prerequisites for a process-oriented approach to quality improvement is consensus regarding optimal practice(s) and a significant gap between optimal and current practice. Without meeting these two criteria, a process-oriented approach is infeasible.

In general, situations where rates of undesired outcomes/complications are higher are better suited to an outcome-oriented approach [14]. An outcome-oriented approach assumes that there are multiple processes (known and/or unknown) that play an important role in determining process. The emphasis on quality improvement that arises from an outcome-oriented approach needs to acknowledge this and allow for an approach that is not necessarily grounded in strong evidence for process change. An outcome-oriented approach may form the basis for generating evidence to inform subsequent process-oriented quality improvement.

Registry Versus Administrative Data

The data that are analyzed for quality measurement come from one of the two types of sources. *Administrative* data are those that are captured in the normal course of healthcare delivery. These data are often termed "claims data" as they are the basis for reimbursement to clinicians and hospitals for clinical services. *Registry* data differ from administrative data in that the data are abstracted in a way that is purpose-specific and separate from the financial mechanisms of the hospital. In general, the processes that generate registry date are held to a higher standard for accuracy but engender a significantly higher cost for abstraction.

Administrative Data

Administrative data are derived entirely from the medical record; therefore, only what is documented can be measured. Clinical phenomena are translated into diagnostic and procedure codes most often using the International Classification of Diseases, 10th Clinical Modification (ICD-10 CM). These codes can then be reported through any one of a number of different surveillance systems. The main benefit of administrative data is that they are generated by healthcare facilities as part of the normal way of "doing business." A common criticism of these data, however, is that they are often abstracted by staff with no clinical background and therefore are inaccurate and misleading.

Registry Data

Registry data represent an effort to address the shortcomings of administrative data. In situations where administrative data are either incomplete or inaccurate, a registry becomes a natural solution. Through the use of more highly trained

staff using tightly controlled program definitions, a registry is generally able to abstract data that is of better quality. The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) is the registry most relevant to colorectal surgery. Hospitals that participate in the ACS NSQIP receive risk-adjusted outcomes data regarding their performance on a wide range of complications. The data accuracy is considered superior to administrative data, but come at a significant cost.

Which Is Better, Administrative or Registry Data?

The decision to use administrative vs. registry data to monitor quality is critically important to the success of any quality effort, as different systems yield different pictures regarding quality [15, 16]. Why do these systems give such different measurements, even when analyzing the same outcome? Existing research highlights that systems can differ significantly in terms of the definitions that they use, as well as in the accuracy with which their own definitions are applied [17]. In general, the decision to use administrative data or registry data is a question of tradeoff between data quality and cost. With registries, interested parties can exert more control over the mechanisms of data abstraction, but this control comes with a significant additional cost.

Evaluative Versus Transactional Data

Quality data can also be categorized as being *evaluative* or *transactional*. *Evaluative* data refer to those types of data that represent a judgment that was applied. Many complications fit into this category, and an excellent example of this is SSI. The occurrence of a SSI can be determined according to any of a number of different schemes, but each occurrence needs to be identified by a particular person(s) using a particular set of criteria. Each of these occurrences requires an evaluation, and therefore there is an intrinsic possibility of measurement error – false-positive *or* false-negative.

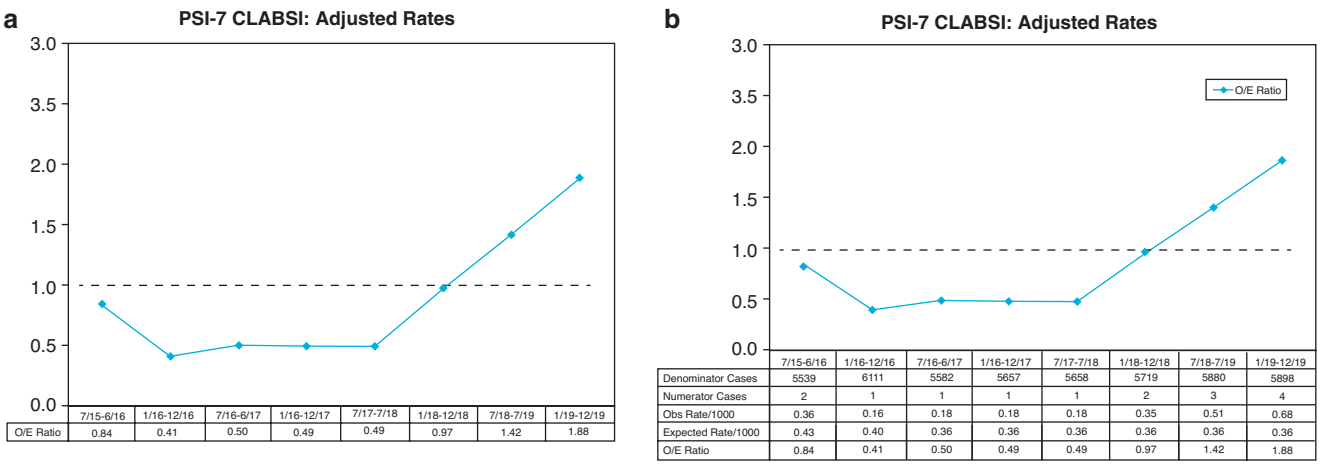
Transactional data refer to those types of data which are generated without any specific judgment. Some examples of outcomes of this type include reoperation, readmission, and length of hospitalization. While different systems may have different definitions for each of these outcomes, the documentation of these types of occurrence happens automatically.

Making the right choice between using evaluative vs transactional data depends on several factors. The US News and World Report methodology is an example of developing a rich outcomes monitoring system without using any evaluative outcomes data [5]. This is a relatively unusual approach and certainly differs from that used by the NSQIP or by CMS in their online reports [2, 18]. There are many more possible outcomes that can be monitored if evaluative data are used. In using evaluative data, however, it needs to be considered that hospitals/institutions may differ in their systems for evaluation and that this may result in biased reports.

Composite Versus Single Outcomes

Fortunately, most postoperative complications are relatively rare. The rarity of complications, however, poses a challenge to parties interested in following outcomes over time. What does it mean if during one measurement period the rate of pressure ulcers increases from 0.1% to 0.3%? Does a tripling of this rate represent a quality gap or statistical noise? An example of this is shown in Fig. 71.1a, with a potentially disturbing increase in the observed/expected (O:E) ratio of central line-associated blood stream infections (CLABSIs).

While the trend in Fig. 71.1a carries some weight because the reported figures are risk-adjusted, there is a serious flaw in how the information is presented. Without knowing the



	7/15-6/16	1/16-12/16	7/16-6/17	1/16-12/17	7/17-7/18	1/18-12/18	7/18-7/19	1/19-12/19
O/E Ratio	0.84	0.41	0.50	0.49	0.49	0.97	1.42	1.88

	7/15-6/16	1/16-12/16	7/16-6/17	1/16-12/17	7/17-7/18	1/18-12/18	7/18-7/19	1/19-12/19
Denominator Cases	5539	6111	5582	5657	5658	5719	5880	5898
Numerator Cases	2	1	1	1	1	2	3	4
Obs Rate/1000	0.36	0.16	0.18	0.18	0.18	0.35	0.51	0.68
Expected Rate/1000	0.43	0.40	0.36	0.36	0.36	0.36	0.36	0.36
O/E Ratio	0.84	0.41	0.50	0.49	0.49	0.97	1.42	1.88

Fig. 71.1 (**a**, **b**) Composite vs. single outcomes. Observed/expected (O:E) ratio; central line-associated blood stream infections (CLABSIs)

actual number of cases at risk (denominators) and actual observed events (numerators), the importance of the noted trend is difficult to understand. A better version of the same graph is shown in Fig. 71.1b, where these important elements of information are included. The problem of limited sample sizes is *almost always* a serious challenge to the accurate interpretation of outcomes. When occurrences are rare, even systems that accurately assess thousands of patients can yield measurements that are plagued by uncertainty.

There are several approaches that can be taken to overcome issues with sample size. Outcomes can be aggregated over a longer period of time. Figure 71.1a, b utilizes this approach but does so informally by placing all the data over a 3.5 year period onto a single visualization. Another valid approach is to aggregate multiple outcomes into a composite outcomes (e.g., death or serious morbidity).

The composite outcome approach is popular with agencies interested in evaluating global quality of care across large numbers of institutions. For example, CMS relies on the Patient Safety Indicator-90 (PSI-90) measure as part of its Value-Based Purchasing Program. The PSI-90 quality measure examines whether a patient had any one of ten different events while hospitalized for any one of a broad range of conditions (Table 71.1) [19].

There are benefits and problems associated with using a composite measure (relative to a single outcome). A composite measure may be more sensitive to detecting *global* issues with quality. For parties interested in improving quality, however, a composite measure will likely not give useful insights regarding specific areas for quality improvement.

Unadjusted Versus Risk-Adjusted Outcomes

Postoperative complications occur at higher rates in patients undergoing more complex operations and especially in those patients with higher degrees of preexisting medical comorbidity. The science of risk adjustment is designed to allow for appropriate comparisons – between institutions – that accounts for the varying levels of risk that are present in patient populations. Risk-adjusted outcomes are widely accepted as a standard for certain types of outcomes reports. Virtually all of the federal and third-party sites that report hospital outcomes use some type of risk adjustment.

If adjustment is not done well, surgeons or hospitals that care for patients with more complex underlying medical comorbidities or surgical diseases may appear worse than surgeons or hospitals that shy away from these cases. The preferability of a risk-adjusted approach over unadjusted outcomes is not always a foregone conclusion. This is particularly true in situations where an outcome is directly/causally linked to an underlying process failure (e.g., specimen labeling errors, iatrogenic pneumothorax). In these situations, the additional burden of data acquisition and analysis may not add any significant additional insight.

Table 71.1 Patient Safety Indicator 90 (PSI-90) conditions

PSI 03 Pressure Ulcer Rate
PSI 06 Iatrogenic Pneumothorax Rate
PSI 08 In-Hospital Fall with Hip Fracture Rate
PSI 09 Perioperative Hemorrhage or Hematoma Rate
PSI 10 Post-Operative Acute Kidney Injury Requiring Dialysis Rate
PSI 11 Postoperative Respiratory Failure Rate
PSI 12 Perioperative Pulmonary Embolism or Deep Vein Thrombosis Rate
PSI 13 Postoperative Sepsis Rate
PSI 14 Postoperative Wound Dehiscence Rate
PSI 15 Unrecognized Accidental Puncture or Laceration Rate

Final Words on Quality Measurement

Surgeons have a good level of comfort with existing/traditional quality metrics (e.g., complication rates, mortality, readmissions, lengths of stay). Looking into the future, there is a broad spectrum of newer quality metrics on the horizon, including patient-reported outcomes, ability to return to health, and patient satisfaction.

There is no perfect metric. Each quality metric has specific strengths and weaknesses in different contexts and may be suitable or unsuitable depending on the situation. In the absence of a perfect metric, leaders in quality have to focus on using/designing quality metrics that best suit their framework. More important than selecting a perfect metric, however, is working to ensure that measurement and data collection are translated into meaningful quality improvement.

Quality Improvement

The ultimate goal of quality, as defined by the National Academy of Medicine is to "increase the likelihood of desired health outcomes and are consistent with current professional knowledge." With this goal in mind, the path to improved quality requires a particular skillset that is not a formal part of standard training in either medical school or surgical residency. Success in quality improvement involves developing an infrastructure that is primed to act on data and drive change.

In the field of surgery, there is an increasing understanding that quality improvement needs to include the entire continuum of care, starting from the decision to operate and not ending until the patient successfully transitions home and recovers fully. This vision of quality naturally requires work-

ing through an effective multidisciplinary team; furthermore, that these teams must be led and resourced for success. Effective leaders in quality find the right ways to align quality improvement efforts with institutional leadership.

Finally, and perhaps most importantly, quality improvement leaders need to employ a scientific approach to design interventions and assess impact. There is no single approach that is useful in all situations. Several resources are specifically designed to help leaders develop an organized, methodical approach to translate concepts into practice. In the final portion of this chapter, we review several important areas of work in the area of surgical quality that are directly relevant to surgeons seeking to lead in quality.

Organizational Culture and Quality and Safety

Culture is to an organization what personality is to an individual – a hidden, yet unifying theme that provides meaning, direction, and mobilization [20]. One way to think about it is that one person's opinion is an attitude while everyone's opinion is a reflection of the culture. Organizations with effective safety cultures share a constant commitment to safety as a top-level priority that permeates the entire organization.

Traditional surgical culture stands have the potential to work in opposition to the values upheld by organizations with effective safety cultures for several reasons. Surgeons have been hesitant to discuss errors as mistakes have been equated to incompetence. Surgeons also tend to minimize the effects of stress on their ability to make decisions. The surgical culture, especially in the operating room, is extremely hierarchical with the surgeon at the leader [21]. Ultimately, while there needs to be clear role clarity, hierarchy can prevent nurses and other OR staff from pointing out potential errors or mistakes made by the team resulting in potentially preventable adverse events.

These cultural barriers to quality are not limited to surgeons or to the operating room. Medicine strongly values professional autonomy, which frequently promotes individualism over cooperation, often to the detriment of patient care [22]. Finally, patient safety, although often viewed as important, is seldom promoted from an organizational priority to an organizational value. Organizations often do not feel the need to devote resources to overhauling their patient safety systems as long as they perceive their existing processes to be adequate.

Alternative Payment Models

Traditionally healthcare providers are reimbursed solely on the basis of services provided. Over the past decade, payers are shifting to a model where payment is linked to high-value care through "value-based payment models." This approach is taking root in both commercial and government contracts. At the federal level, CMS has sent clear messaging that alternative payment models are part of their long-term strategy [23].

Although most of the federal efforts are directed at primary care and population management (accountable care organizations), episode-based alternative payment models (APMs) are being deployed in surgical areas including colorectal surgery. APMs hold both providers and hospitals accountable for both quality of care delivered and the total costs.

An approach that uses APMs to drive quality (and reduce costs) is fundamentally an outcome-oriented strategy. Given that it is easier to evaluate cost than it is to measure quality of care, most of the programs focus on using cost as a proxy for quality. When hospitals and providers engage in APMs, they have the potential to receive additional payments that may arise from cost savings, as well as the risk incurred as a result of excessive costs ("down side risk").

The initial approach of CMS to APMs is through voluntary participation, but over time participation may become mandatory. An example of this evolution is seen in the Bundle Care Program Initiative (BCPI). The BCPI APM looks at 90-day episode costs after select procedures (Fig. 71.2). Within the BCPI program, the greatest experience is seen in total joint arthroplasty, with participation now mandatory in 67 markets around the country [24].

A similar program for patients undergoing major bowel surgery, including colorectal surgery, is in development. Concerns are raised regarding appropriate accounting for the heterogeneity of patient populations and the limited options available to control costs. There is also the possibility that the program could have unintended consequences if the hospital or providers are not adequately supported to transform care to higher quality and value. It is essential that colorectal surgeons partner with their delivery systems to test and evaluate these models so meaningful feedback can be shared with CMS.

National Accreditation Program for Rectal Cancer

Accreditation programs are formal approaches to evaluate and support structural- and process-oriented approaches to improving quality of care. Within the area of surgery, the most mature example of the accreditation process is within the specialty of bariatric surgery. Through a joint venture of the American College of Surgeons and the American Society for Metabolic and Bariatric Surgery, the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP) sets hospital standards. These standards cover a broad range of targets for quality assessment/

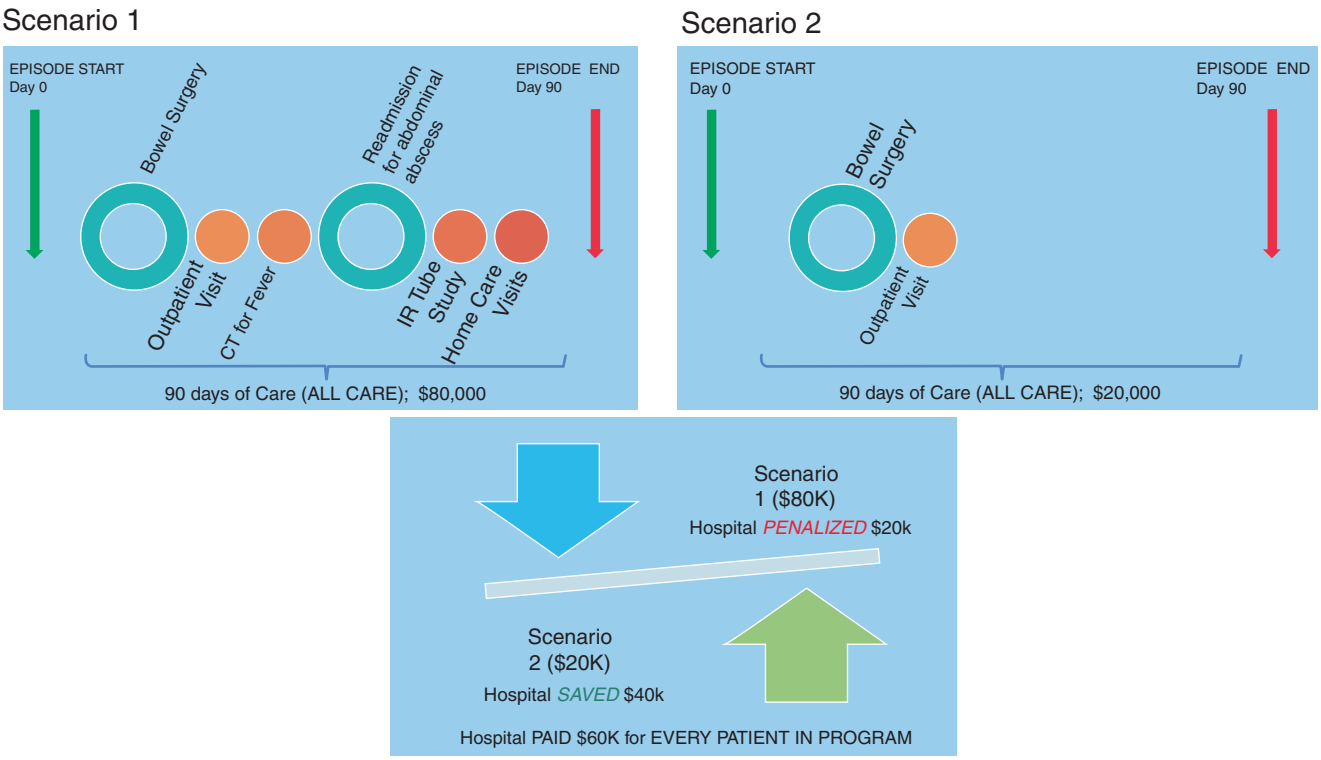


Fig. 71.2 Bundled payments for bowel surgery

improvement, including key physical, and human resources, and practice standards for bariatric surgery. Program compliance is monitored with regular site visits, and all centers are required to monitor and report their surgical outcomes to the MBSAQIP database [25–27].

Despite the intuitive appeal of accreditation, the relationship between accreditation and improved outcomes is unclear. CMS originally endorsed accreditation for bariatric surgery programs and mandated that all Medicare patients undergoing bariatric surgery must be treated in an accredited center [28]. Although procedures done in centers of excellence were associated with superior quality by many measures, this was not reflected in a Medicare analysis, and CMS endorsement of the program was discontinued in 2013 [29].

Within the area of colorectal surgery, the ACS Commission on Cancer (CoC) has worked to develop an accreditation program that is specific to rectal cancer treatment. The structure of this program was initially developed through the Consortium for Optimizing the Treatment of Rectal Cancer (OSTRiCh), a multidisciplinary group including all medical and surgical specialties engaged in rectal cancer treatment. The National Accreditation Program for Rectal Cancer (NAPRC) was developed in 2018 by the ACS-CoC in collaboration with OSTRiCh.

Since its launch, the NAPRC has worked to develop and support standards regarding the optimal care of the patient with rectal cancer. Hospitals review the standards and implement structural changes to ensure that the standards are followed. Effectiveness of the implementation is then verified by site surveyors. Accreditation through the NAPRC is based on the ability of hospitals to comply with 22 standards, covering a broad range of areas related to program quality [30]. To date, 12 hospitals have been verified, and 5 are in the process.

In its current state, the NAPRC accreditation focuses on a broad spectrum of areas regarding the ability of rectal cancer treatment programs to deliver high-quality care [31]. An important focus of the program is a focus on ensuring the presence of dedicated/highly trained surgeons, pathologists, medical oncologists, and radiation oncologists. There is also the requirement for a structured, documented multidisciplinary tumor board where patients with rectal cancer are formally reviewed throughout their care. Additionally, ongoing monitoring of quality metrics and quality improvement activities are requirements for accreditation. Further study will be needed to demonstrate the short- and long-term impact of the NAPRC on rectal cancer care in the United States.

National Surgical Quality Improvement Program

In the field of surgery, the National Surgical Quality Improvement Program (NSQIP) is considered the "best in class" registry for the assessment, analysis, and reporting of

surgical outcomes. The leadership has prioritized data validity, and all data is collected by a trained abstractor, and the data integrity is periodically audited. The program was originally developed in the Veterans Affairs Health System (National Veterans Administration Risk Study) in the 1990s as a means to benchmark 30-day outcomes for VA hospitals. Risk adjustment was a key focus of the program as the Veterans Affairs Hospital population was notably different than other health systems with a preponderance of older, male patients with multiple comorbidities [32].

The VA program became a model for continuous process improvement. In 2001, with support from the Agency for Healthcare Research and Quality (AHRQ), the American College of Surgeons (ACS) began offering the NSQIP to non-VA hospitals [33, 34]. Colorectal surgery has been a key area of focus for the program with special colectomy and proctectomy disease-specific variables developed within the program.

Recognizing that data alone is not sufficient for quality improvement, ACS-NSQIP has worked to develop a community of surgeons who are committed to improvement and provides opportunities to participate in including the Annual American College of Surgeons Quality and Safety Meeting. The meeting has many interactive sessions and draws participants from a broad range of areas including hospital leadership, surgeons, trainees, and data abstractors. Both during and outside of this annual meeting, the ACS-NSQIP provides opportunities to participate in regional collaborative and pilot programs.

Most recently, related to colorectal surgery, the ACS-NSQIP joined forces with the Johns Hopkins Armstrong Institute for Patient Safety to launch the Improving Surgical Care and Recovery Program [35]. This program aims to form a collaborative to accelerate adoption of enhanced recovery programs for colorectal surgery (as well as other surgical areas). To date, over 300 hospitals have participated and benefited from tools, coaching, and shared learnings around enhanced recovery. Early results from participating programs are encouraging, with notable reductions in length of stay, decreased rates of complications, and faster return of bowel function.

Conclusion

The need for surgeons to be actively engaged in quality improvement is increasingly clear. The surgical perspective on quality is critical, and surgeons need to commit to learning how to translate concepts and data into continuous quality improvement. Surgeons finishing training today are far more facile in this type of work than in the past, but ongoing growth in this important area will ask more of future generations of leaders in surgery.

References

1. Crossing the quality chasm: a new health system for the 21st century. Washington, DC: National Academy Press; 2001.
2. https://www.medicare.gov/hospitalcompare/search.html. Accessed 4 Mar 2020.
3. https://projects.propublica.org/surgeons/. Accessed 4 Mar 2020.
4. http://www.checkbook.org/surgeonratings/. Accessed 4 Mar 2020.
5. https://media.beam.usnews.com/da/5b/7646c0e744aea61f55e5aa816870/190709-bh-procedures-conditions-methodology-2019.pdf. Accessed 4 Mar 2020.
6. Donabedian A. Evaluating the quality of medical care. Milbank Mem Fund Q. 1966;44:166–206.
7. Brennan N, Conway PH, Tavenner M. The Medicare physician-data release--context and rationale. N Engl J Med. 2014;371(2):99–101.
8. Etzioni DA, Wasif N, Dueck AC, Cima RR, Hohmann SF, Naessens JM, et al. Association of hospital participation in a surgical outcomes monitoring program with inpatient complications and mortality. JAMA. 2015;313(5):505–11.
9. Osborne NH, Nicholas LH, Ryan AM, Thumma JR, Dimick JB. Association of hospital participation in a quality reporting program with surgical outcomes and expenditures for Medicare beneficiaries. JAMA. 2015;313(5):496–504.
10. Fry DE. Prevention of infection at the surgical site. Surg Infect. 2017;18(4):377–8.
11. Munday GS, Deveaux P, Roberts H, Fry DE, Polk HC. Impact of implementation of the surgical care improvement project and future strategies for improving quality in surgery. Am J Surg. 2014;208(5):835–40.
12. Hawn MT, Vick CC, Richman J, Holman W, Deierhoi RJ, Graham LA, et al. Surgical site infection prevention: time to move beyond the surgical care improvement program. Ann Surg. 2011;254(3):494–9; discussion 9–501.
13. Stulberg JJ, Delaney CP, Neuhauser DV, Aron DC, Fu P, Koroukian SM. Adherence to surgical care improvement project measures and the association with postoperative infections. JAMA. 2010;303(24):2479–85.
14. Birkmeyer JD, Dimick JB, Birkmeyer NJ. Measuring the quality of surgical care: structure, process, or outcomes? J Am Coll Surg. 2004;198(4):626–32.
15. Lawson EH, Louie R, Zingmond DS, Brook RH, Hall BL, Han L, et al. A comparison of clinical registry versus administrative claims data for reporting of 30-day surgical complications. Ann Surg. 2012;256(6):973–81.
16. Lawson EH, Zingmond DS, Hall BL, Louie R, Brook RH, Ko CY. Comparison between clinical registry and medicare claims data on the classification of hospital quality of surgical care. Ann Surg. 2015;261(2):290–6.
17. Etzioni DA, Lessow CL, Lucas HD, Merchea A, Madura JA, Mahabir R, et al. Infectious surgical complications are not dichotomous: characterizing discordance between administrative data and registry data. Ann Surg. 2018;267(1):81–7.
18. https://data.medicare.gov/Hospital-Compare/NSQIP-HOSPITAL-COMPARE-DATA/c635-s3cy. Accessed 10 Mar 2020.
19. https://innovation.cms.gov/Files/fact-sheet/bpciadvanced-fs-psi90.pdf. Accessed 2 Mar 2020.
20. Ruchlin HS, Dubbs NL, Callahan MA. The role of leadership in instilling a culture of safety: lessons from the literature. J Healthc Manag. 2004;49(1):47–58; discussion -9.
21. Sexton JB, Thomas EJ, Helmreich RL. Error, stress, and teamwork in medicine and aviation: cross sectional surveys. BMJ. 2000;320(7237):745–9.
22. Amalberti R, Auroy Y, Berwick D, Barach P. Five system barriers to achieving ultrasafe health care. Ann Intern Med. 2005;142(9):756–64.

23. https://innovation.cms.gov/innovation-models/bpci-advanced. Accessed 4 May 2020.
24. Liao JM, Pauly MV, Navathe AS. When should medicare mandate participation in alternative payment models? Health Aff (Millwood). 2020;39(2):305–9.
25. El Chaar M, Claros L, Ezeji GC, Miletics M, Stoltzfus J. Improving outcome of bariatric surgery: best practices in an accredited surgical center. Obes Surg. 2014;24(7):1057–63.
26. Morton JM, Garg T, Nguyen N. Does hospital accreditation impact bariatric surgery safety? Ann Surg. 2014;260(3):504–8; discussion 8–9.
27. Young MT, Jafari MD, Gebhart A, Phelan MJ, Nguyen NT. A decade analysis of trends and outcomes of bariatric surgery in Medicare beneficiaries. J Am Coll Surg. 2014;219(3):480–8.
28. https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/ncd103c1_Part2.pdf. Accessed 5 May 2020.
29. Dimick JB, Nicholas LH, Ryan AM, Thumma JR, Birkmeyer JD. Bariatric surgery complications before vs after implementation of a national policy restricting coverage to centers of excellence. JAMA. 2013;309(8):792–9.
30. https://www.facs.org/quality-programs/cancer/naprc. Accessed 4 May 2020.
31. https://www.facs.org/-/media/files/quality-programs/cancer/naprc/naprc-standards-manual.ashx. Accessed 5 May 2020.
32. Khuri SF, Daley J, Henderson W, Hur K, Demakis J, Aust JB, et al. The Department of Veterans Affairs' NSQIP: the first national, validated, outcome-based, risk-adjusted, and peer-controlled program for the measurement and enhancement of the quality of surgical care. National VA Surgical Quality Improvement Program. Ann Surg. 1998;228(4):491–507.
33. Fink AS, Campbell DA Jr, Mentzer RM Jr, Henderson WG, Daley J, Bannister J, et al. The national surgical quality improvement program in non-veterans administration hospitals: initial demonstration of feasibility. Ann Surg. 2002;236(3):344–53; discussion 53–4.
34. Khuri SF, Henderson WG, Daley J, Jonasson O, Jones RS, Campbell DA Jr, et al. Successful implementation of the Department of Veterans Affairs' national surgical quality improvement program in the private sector: the patient safety in surgery study. Ann Surg. 2008;248(2):329–36.
35. https://bulletin.facs.org/2018/12/ahrq-safety-program-for-iscr-expands-scope-in-2019/. Accessed 3 May 2020.

Practice Management

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Jennifer D. Rea and Jeffrey L. Cohen

Key Concepts

- Building a successful practice starts with providing excellent patient care first and foremost.
- Attempt to achieve the quadruple aim of providing improved patient/customer experience with increased quality and cost efficiency while also focusing on provider health and wellness.
- The basic premise behind salaries is that they should correlate to the work performed by the surgeon and align incentives with the goals of the individual and the practice.
- Developing a practice involves incorporating the four A's of a successful surgeon—availability, affability, ability, and accountability.

Introduction

Being successful in medicine starts with taking excellent care of your patients. Education, training, and board certification launch you into the subspecialty career of your dreams. Establishing a rewarding practice so that you can focus on taking excellent care of your patients does not come with such a clear-cut pathway to success. While there are a lot of resources on these topics in print and in organized web-based or weekend courses, it is often the conversations among physicians in casual settings that offer the most real-world advice about successes and failures in the realm of managing a medical practice. The healthcare environment is rapidly changing, so it would be impossible to predict what policy changes may come about after this publication. It is the authors' goal to provide guidance in maximizing your position to address the opportunities and challenges that will most certainly come your way throughout your practice.

In this chapter, we set out to address some of the most challenging issues facing physicians and practices today outside of patient care in an ever-changing healthcare environment, for instance, understanding the culture in the type of practice model you choose and recognizing the internal and external pressures of each model. When choosing a particular practice setting, you will also be choosing your challenges, as every model will have them. Knowing yourself, how you make decisions and work your best with others should lead you to the right path.

Practice finances bore most physicians. We like anatomy, pathology, and procedures. Profit and loss statements and revenue cycles are for accountants, right? While it is crucial to choose talented, well-vetted advisors, knowing the basics about how your practice finances work are critical. If you are in private practice, these data mean everything to your take-home pay. If you are an employed model, knowledge of the finances of your group means power when negotiating your position.

While some practice models are becoming more popular than others, there are still examples of successful practices in all models. Whether you are employed or private, strategies for building a referral base and running an efficient clinic are similar and are outlined in more detail below. As more healthcare systems form and smaller practices are acquired by larger entities, understanding how that process works will help you to adapt to what is happening in your community, your region, and on a national level. Identifying where your practice fits into this dynamic will help you make decisions about how you are positioned and allow for a well-informed approach to questions such as the following: Should I leave my current health system? Should we merge with another private group? Should we sell our practice to the health system we partner with? Should we consider private equity

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investors in our group practice? If you are not thinking about these questions, it is time to ask yourself how serious you are about taking control of your future.

From the perspective of a chief clinical operating officer of a large health system and a full-time clinical surgeon in a multispecialty private group practice, we will outline the highlights of successful practice management applicable to any practice environment.

Practice Models

Independent Practices

Single Specialty

For many decades, the most common type of independent group practice was that of a single specialty. This was true for colorectal surgery as well, with a single specialty group structure being the predominant model until the last decade. A single specialty practice allows for a successful culture to be built on a common focus and interest of the physicians, as well as the staff. There is a singular orientation toward the specialty, with an expert knowledge possessed by all the partners, allowing for the development of a cohesive practice management plan. This also allows for standardization of patient care delivery by the staff and a consistency across multiple sites of service. Furthermore, consensus can be easily achieved with respect to new initiatives, as all the physicians can be involved in both the development and the execution of the emerging opportunity.

Oftentimes, the recruitment of new physicians occurs through the network created either locally or nationally by the specialty society. This furthers the fostering of a cohesive group practice environment and culture, essential to the ultimate success of the independent group practice. Since there are no competing clinical interests from other specialties, a single specialty practice is more easily able to drive a unifying vision. The attractiveness of this model is obvious, not only for newly trained physicians who see a practice like their fellowship training environment but also to well-established physicians who value consistency and clarity within their practice.

While a single specialty practice can enjoy financial security if it is critical to the community it serves, there are risks to this structure should significant competition emerge. Without the diversification of a multispecialty practice (see below), or the support of a health system, the practice may not be able to support the number of clinicians in the practice. This is especially true if the group practice has not been able to develop ancillary services, such as imaging, lab, or surgery centers. In fact, one of the major benefits of single specialty practices is the ability to invest in these ancillary sources of revenue to support the overhead of the practice and allow for an enhanced patient experience commensurate with what large, integrated healthcare systems can deliver. If the single specialty practice is unable to leverage itself with these ancillary revenue streams, then it is likely to face financial pressures to its ultimate viability.

Multispecialty

Over the past two decades, there has been a significant growth in forming multispecialty group practices [1]. This has occurred both as a strategy to deliver integrated care to patients, as well as a response to external pressures on small independent physician practices. From the positive standpoint, coalescing like-minded physicians under a unifying vision can facilitate growth opportunities and initiatives that small group practices and single specialty practices may struggle to achieve. For example, a digestive health division within a multispecialty group practice can bring together gastroenterologists, colorectal surgeons, nutritionists, and therapists to provide an integrated clinical care experience for the patient. This can also be replicated across many service lines, which patients as consumers of healthcare are looking for and coming to expect from their healthcare experience. In addition, having many specialties available to support the development of ancillary services can lead to a higher success rate and ultimate profitability of the endeavor, which is especially true for the ability to support lab and imaging services. As for ambulatory surgery centers, some single-specialty-focused centers, such as orthopedics and ophthalmology, are able to achieve higher returns on investment than multispecialty centers, but having a critical mass of volume from multiple specialties within a group practice can also create a successful investment opportunity. Furthermore, by having the practice own the surgery center, the group's overall practice philosophy can be easily extended to the management of the center.

While there are many positive benefits to the development of a multispecialty group practice as outlined above, there is also a defensive strategy associated with joining a large group practice. With the growth of integrated healthcare systems and the consolidation of commercial payer models across the country, remaining part of an independent practice model has become more challenging. Large systems that are relatively well capitalized can offer an integrated patient care experience comparable to private practices should they orient their care model to achieve that goal. Therefore, creating large multispecialty independent group practices oftentimes is the only way to remain competitive in the rapidly consolidating healthcare environment. Not only is it essential to create a unifying vision that adds value to the patient experience, as well as to the physician partners, but it is just as important to develop cohesive specialties and service lines that cannot be easily replicated by competing organizations. Furthermore, exploring opportunities to partner with either the local

healthcare system or one or more of the payers in the community can create protections from being commoditized, jeopardizing the financial solvency of the group practice.

One of the challenges of multispecialty group practices is that different specialties may have growth imperatives or strategies that are not consistent with the rest of the practice. There can be requirements for capital investment in one service line that requires the rest of the group practice to divert away from other areas and lead to disharmony within the practice. As multispecialty group practices become larger and more diverse, these types of decisions become commonplace and place significant demands on the practice management and culture. It is imperative that a strong governance model be in place that the physician partners are committed to offset the inevitable disagreements that are precipitated by competing interests within the various service lines. Anyone wishing to join a multispecialty group practice should have a clear understanding not only of the practice vision and culture but also of the governance model, the financial strength/challenges of the organization, the pathway to partnership, and the obligations of the shareholders to the organization and their fellow partners.

External Investment (Private Equity, Venture Capitalists)

As healthcare has increased in complexity and with it the requirement for access to capital to remain viable as an independent practice with growth potential, there has been a resurgence in a practice model which proved unsuccessful in the 1990s. Practice management companies, in the form of private equity investment, has returned as a vehicle to support private practices in their goal to remain independent [2]. Given that most states have laws preventing nonphysicians from owning medical practices, private equity companies establish management services organizations (MSO) which take over the business functions of the practice. The practice pays the MSO a management fee, generally either a flat fee or a percentage of the practice's revenue. Care must be taken in the latter arrangement to avoid any structuring which might suggest a fee splitting arrangement. In return for the practice entering into this arrangement, the private equity investor assumes a majority share in the MSO, paying the physician partners a large upfront cash payment. This is generally calculated on the practice's EBITDA (earnings before interest, taxes, depreciation, and amortization) and can range between a 5 and 15 times multiple. In order for this investment to be attractive to private equity, the physician partners agree to accept a reduction in salary for a period of time, as well as contribute their ancillary services to the MSO.

The ultimate payout for the private equity investment comes several years later, when it looks to sell its position in the MSO to another entity, which presents a risk to the practice as it will have a new partner to work with. The majority of the private equity deals over the past decade have taken place in dermatology, as this specialty provides investors with access to a large self-referral base, significant retail options, and other ancillary services, a growing demand for the services supplied by dermatologists, as well as a highly fragmented delivery model. However, over the past several years, this model has expanded to other specialties, in particular, gastroenterology, where some of the same benefits attributed to dermatology also exist. To the degree that a colorectal surgery practice possesses a significant ancillary revenue stream through an ambulatory surgery center and lab services, it can be a desirable target for private equity investment. The cautionary tale is that the ultimate goal for the investment company is to increase profits so as to create a liquidity event and sell their stake at a significant return on investment. This results in the physician group losing control of their destiny at some point in the future even if the initial arrangement was working well.

Employed Models

For the first time since the metric has been tracked, more physicians are working in an employed model than in an independent practice. Last year, the American Medical Association reported that 47.4% of practicing physicians were employed while 45.9% owned their own practices [3]. To further highlight the dramatic trend taking place over the past decade, there has been a 70% increase in the percentage of hospital-based physicians from 2012 to 2018, as well as a concomitant increase in the number of hospital-acquired practices during the same time period. While the trend varies from region to region, every part of the country saw a steady increase in physician employment and practice acquisition during this time frame. And in the Midwest region, fully 55% of physicians are now in an employed arrangement, up from 34% in 2012.

To understand the reasons for the shift from an overwhelming private practice model to one of employment, it is worthwhile to examine the changing healthcare environment, as well as the motivation and goals of those choosing a career in medicine. From a business standpoint, a long-standing trend of flat or declining reimbursement for professional services, while medical inflation has driven up overhead costs, has led to pressure on profits and, therefore, compensation. At the same time, hospitals and healthcare systems are able to recognize the downstream contribution margins of an employed practice model and are willing to increase compensation so as to attract top-flight candidates from residency and fellowship programs. As noted in the previous section, the important offset for this is access to a significant ancillary revenue stream, which is not always available to an independent practice, especially one that does not have a ready source of capital to invest.

Other challenges to the private practice model include the rise of consumerism and retail clinics, insurance and billing changes with the shift to value based care, continual technology investments in an electronic health record and subsequent upgrades to include the integration of big data and artificial intelligence, and, lastly, investments needed to create a full service integrated patient care experience. When added to these factors the diminishing entrepreneurial spirit of those physicians entering practice at the present time, who are oftentimes saddled with a large debt burden, it is not surprising to see the trends in physician employment that have been outlined above.

While traditional employment by hospitals did not tend to address a lot of the issues important to physician engagement and job satisfaction, this is an area that is evolving as well. When physicians were directly employed by hospitals, they were overseen by hospital administrators who generally had little to no experience in practice management. This led to inefficiencies resulting in financial losses and poor patient experience, not to mention diminished staff and clinician satisfaction. Given this scenario, it is somewhat surprising that the trend toward physician employment occurred to the degree that it did, which only serves to emphasize the degree to which the changing healthcare environment played such a central role.

Over the last decade, there has been a recognition by growing healthcare systems that a robust employed clinician enterprise is essential to the ultimate success of the organization and, furthermore, that the business of practice management needs to be separated from that of running hospitals and placed in the hands of experts in this field. When optimized, the governance and operational structure of employed medical groups develop into a dyad model, with healthcare management experts partnering with physician executive leaders, not unlike that seen in successful private group practices. Fortunately, this model has existed for many decades in organizations as diverse as Kaiser Permanente, Mayo, Cleveland Clinics, and Henry Ford Medical Group. They and many others have successfully addressed the issues of perceived loss of autonomy by physicians while preserving clinician and staff engagement. And as physician burnout has become a significant issue facing healthcare, the preservation of some degree of autonomy and governance by physicians, coupled with the robust support mechanisms supplied by large, health-system-employed practices, can be a recipe to offset this disturbing trend [4].

In deciding which type of employed practice model to join, it is important to understand some of the fundamental differences that exist in the varied settings. First and foremost, the underlying mission of the organization should dictate which direction to go in. For example, if research and education are what is most important, then employment by an academic medical center makes the most sense. While other types of organizations may value the contribution that research makes to the enterprise, academic medical centers are constructed to support the mission directly and will supply the resources that are likely to contribute to the individual's success in that environment. Conversely, if the goal is to create the best patient experience while performing cutting edge, innovative surgery, then a large, integrated healthcare system which states those goals as its mission will be a better fit. And in the ultimate, completely vertically integrated healthcare system such as Kaiser Permanente, one can achieve complete clarity of mission and vision with little ambiguity.

A relatively new type of employed physician model has emerged over the past several years that promises to disrupt the existing healthcare ecosystem. Healthcare insurance companies, as well as other nontraditional entities, are entering the physician practice employment model, either for the benefit of their own employees or as an alternative to the perceived lack of consumer responsiveness in the environment today. With the entry of companies such as Amazon, Apple, and Walmart now employing healthcare clinicians, another alternative for physicians interested in employment can be driven by innovation as their mission. And the largest employer of physicians in the United States, OptumHealth, with 50,000 employed or affiliated physicians, is owned by the largest healthcare insurer in the United States, UnitedHealthcare [5]. These resource- and capital-rich organizations provide new opportunities for physician employment and development that for the most part did not exist a decade ago.

Acquisition of an Independent Practice

With the rapidly changing healthcare environment, independent practices need to continually assess not only their continuing viability but also whether they are positioned to effectively deliver on their vision and goals. In particular, if the ability of the practice to experience sustained growth and a differentiating patient experience is limited, then consideration should be given to forging partnerships or becoming acquired by another entity. Should an opportunity materialize whereby there is alignment of the practice's vision and goals with its local healthcare system, the partners may determine that merging into the healthcare system is in their best interests for long-term viability and sustainability.

Independent practices that are considering proceeding through the acquisition process first must build consensus among its partners and, if possible, involve the employed physicians as well. An effective method to achieve this goal is through a series of strategic retreats, which can be facilitated by an outside healthcare consultant. Clarity surrounding the motivation to leave private practice and become acquired is critical to the ultimate success of the merger. In addition, prioritization of objectives to be realized through

the acquisition process should be an outcome of the consensus building process.

As negotiations proceed with the acquiring healthcare entity, the key objectives of each side should be clearly articulated and referenced so as to ensure alignment of goals and reduce the likelihood of post-acquisition disagreements. A prudent investment by the practice is the early engagement of a consultant experienced in the area of healthcare mergers, as well as the ongoing involvement of the practice's accounting and legal teams. At regular intervals during the negotiation phase, the physician leadership team should meet with all of the shareholders to disseminate information and receive feedback. Ultimately, agreement between the parties will have to occur on not just the purchase price for the hard assets of the corporation (an asset purchase agreement) but also on the length of the initial contracts; the compensation model, including salary guarantees and performance as well as productivity incentives; governance within the new entity; staffing models and ratios; stipends for new roles that the physicians may need/want to take on in the employed medical group; and many other details related to decision-making rights within the new entity. The time to reach agreement on all of these issues is before executing the contracts, as all the leverage accrues to the acquiring entity afterward.

It should be noted that there are significant federal statutes and regulations governing the acquisition of independent medical practices by healthcare systems, especially when they are not for profit. The most important concepts relate to fair market value and commercial reasonableness, so as to insure that health systems are not buying referrals as the motivation to acquire a practice. And while physicians tend to think in terms of the downstream revenues that a hospital and health systems enjoy from the work that they perform, compensation cannot be in any way tied to this relationship. Given the risks associated with the acquisition of an independent practice by a healthcare system, it is imperative that each entity be well represented by legal expertise, preferentially with a healthcare background.

Finance

Effective practice management requires a strong understanding of the financial underpinnings of the business. Given the lack of expertise in this area of most physicians not only entering practice, but even those who are well established, generally medical groups will employ a finance team to handle revenue cycle, billing and coding, and compliance. Whether a shareholder in a private practice model or employed by a healthcare entity, it is still recommended that the physician become educated in at least the basics of healthcare practice finance. By partnering with your finance and revenue cycle experts, higher efficiencies and profitability are likely to occur.

Regardless of the practice model, the fundamental principle remains the same. That is, revenue minus expenses determines the ultimate financial success of the practice. While the sources of revenue can be similar for independent practices or an employed model group practice, more opportunities exist for revenue enhancement in the latter structure. Professional fees are either regulated by the federal government through the Center for Medicare and Medicaid Services (CMS) or negotiated with commercial payers, with variation related to the local competitive environment. In general, large organizations such as integrated healthcare systems can command higher reimbursement rates from commercial payers, oftentimes partly related to their obligation to treat all patients regardless of whether they are underinsured or completely uninsured. While all practice models can generate revenue from ancillary services, smaller group practices generally are limited in their ability to do so. Conversely, large healthcare entities are structured to realize significant revenue streams from diverse sources such as ambulatory surgery centers, imaging centers, and lab services and from contracting in value-based models of care.

A key decision for a private practice medical group is whether to outsource revenue cycle functions or develop the expertise internally. While it might be advantageous to fully align incentives by having the revenue cycle team employed by the practice, consideration needs to be given to the size of the group practice and whether it can afford the expertise required to insure best in practice outcomes. For many small- to medium-size practices, it makes more sense to identify a revenue cycle company that is willing to be incentivized by the success they achieve in maximizing the efficiency of the practice's billing and collections processes.

A critical component of revenue cycle is the accurate coding of the provider-patient encounter. Whether the service is outsourced or integrated into the practice, extensive education should take place for all providers. As this knowledge base is not typically acquired during residency or fellowship training, it is essential that billing and coding training takes place as part of the orientation process when entering practice. Furthermore, numerous courses and workshops are available to supplement the training process for colorectal surgeons entering practice and can be quite valuable regardless of in-house expertise. To ensure compliance and reduce the risk of fraudulent billing, in addition to documentation of educational programs, best practice also incorporates routine auditing of the surgeon's billing practices. Certified coders are employed to not only oversee this process but also to partner with the providers in insuring proactively that the correct billing codes are applied for the work that is being done. This includes education and coaching on accurate and complete documentation of the patient encounter, whether in

the ambulatory setting or procedure based. It is incumbent upon the provider to submit timely and complete billing and coding so as to maximize the revenue cycle process and eliminate rework, which not only adds to the cost of the process but can also lead to denials by payers of care and treatment that has been provided.

While an in-depth comprehension of the coding process is beyond the scope of this chapter, the key components can be readily understood. Every encounter requires both a diagnosis code and a procedure code tied to it when one is performed for a medical provider to be reimbursed for services rendered. The catalogue of diagnosis codes is referred to as the International Classification of Diseases (ICD-10), which underwent extensive revision in 2015. It is a medical coding system designed by the World Health Organization (WHO) to catalogue health conditions by categories of similar diseases [6]. The objectives of the system are to measure the safety and efficacy of patient care, determine the health status and risk factors of defined populations, improve and monitor providers' performances, assess healthcare costs, and investigate and prevent coding and billing abuses. Current procedural terminology (CPT) codes reflect the services rendered to the patient and can be in the form of evaluation and management (E/M) codes and/or procedure codes [7]. In the past, the coding would be entered into a paper "superbill," which would be submitted to the payers for reimbursement. With the advent of electronic medical records, all of the billing and coding information can be entered in to the medical chart prior to closing the encounter, which can then facilitate a complete review of the chart for appropriate documentation by the coding department prior to sending out the bill. Ultimately, an explanation of benefits (EOB) will be generated by the insurance company and communicated to the patient and the practice. It will document the allowable contractual reimbursement with adjustments and denials, as well as the patient's responsibility for any portion of the bill.

Compensation

While there are many different compensation formulas, the basic premise is the same. Salaries should correlate to the work performed by the surgeon and align incentives with the goals of the individual and the practice. Needless to say, it also must be competitive relative to the geographic location and the training and degree of specialization of the provider. When evaluating a compensation model, an understanding of the entire benefit package, including expectation of work hours and call responsibilities, is essential to avoid surprises and misunderstanding later.

Since the underpinning of a medical practice is its profitability, the most straightforward calculation relates to a revenue minus expense model. When appropriately applied to an individual surgeon, it has clarity with respect to the financial contribution of the clinical effort. However, there is tremendous variation in how the expenses are applied to an individual contributor, since there are both fixed and variable components involved. Furthermore, startup costs for the new surgeon can be considerable if related to an expansion of services or minimal in the case of a replacement for a retirement. A straight calculation of profitability to determine salary can undermine the value of non-remunerative contributions of the individual to the group practice culture, as well as foster a culture of an "eat what you treat" mentality which discourages the synergy of a group culture. Some of these issues can be overcome by designing a compensation model that pools excess revenue over expenses at the specialty or group level and then distributes it in a predetermined sharing formula that attempts to align the distribution with the practice's goals.

Implementation of a relative value unit (RVU)-based model of compensation allows for more flexibility and is almost essential in multispecialty group practices that employs a variety of specialties. An RVU represents an attempt to standardize physician work into numerical units [8]. They account for the time it takes to perform a specific service, the skill needed to complete the service, the judgement and experience required of the provider, and the liability risk associated with the service being performed. There are three individual components to the RVU calculation which determine the clinical activity of the service: the work effort, the practice expense, and the malpractice expense, and this can be adjusted for geographical differences. The Center for Medicare and Medicaid Services determines the value for RVUs related to CPT codes, and there are committees that incorporate physician and medical society feedback to recommend adjustments to the assigned values as new procedures are developed and implemented.

It is the ability to value a provider's services across specialties that enhances the value of the RVU methodology in a multispecialty group practice when creating a compensation model. Furthermore, the RVU is "payer blind," as the value does not vary according to insurance, an important consideration in not-for-profit care models whose mission may be to treat all patients regardless of their ability to pay for the care they receive. In addition, compensation is decoupled from the revenue cycle, with the exception of the accurate tracking of RVUs. This creates an environment where the surgeon is not beholden to the performance of the revenue cycle team, although care must be taken to engage and create accountability for the timely and accurate submission of bills by the provider.

When creating a compensation model based on RVU productivity, consideration should be given to nonclinical activity and how that is incorporated into overall income that the

surgeon receives. Examples of nonclinical activity might be serving or chairing committees in the practice or larger organization, development of new service lines, mentoring or peer support, or community-based activities. These valuable contributions to the practice can be recognized through stipends or reduced thresholds to earn productivity incentives. Alternatively, the individual who is valued to perform these services may be allowed to earn a full-time salary yet have protected time to attend to these activities.

In fact, this is now the preferred methodology for academic medical practices, who generally have the dual mission of clinical activities while focusing on education and research. A determination is made as to the percentage of time that the surgeon devotes to each area, and the research/education component is protected by time and guaranteed salary. The clinical responsibilities can be rewarded by a compensation model that is RVU based, so as to align income with clinical effort.

Separate from compensation based upon productivity or nonclinical activities is the potential for earning additional income through the generation of ancillary revenues. As discussed earlier, the opportunity to invest in and realize income from ancillary sources is generally proportional to the size of the practice and its ability to access capital for the initial investment. While seen most commonly in large, independent medical practices, some employed models also allow its providers to invest in activities such as ambulatory surgery centers or real estate investments. Regardless of the employment arrangement, the one guardrail is that it is illegal to tie income of any type to the volume of referrals to that healthcare entity.

Distribution of ancillary revenues within the practice is most commonly through equal distribution to all shareholders if in private practice or to all employed physicians that contribute to the activity. This is also the methodology for distributing revenue from value-based contracts, although incentives can be aligned for an individual's successful achievement of the metrics specified in the value contract. Segregating these activities and utilizing a sharing model fosters the goal of aligning a group practice culture, which is important to achieving the benefits of driving patient-centered care through teamwork and care coordination.

Developing a Referral Base

We have all been taught the three A's of a successful surgeon—availability, affability, and ability. More recently accountability has been added as a fourth value of utmost importance to the successful surgeon. Certainly, these hold true regardless of practice type. Saying yes to consults and helping other physicians when called upon is not just essential for new surgeons, it is vital to maintain an outstanding reputation throughout your career. You want referring doctors to say that everyone in your group takes care of their patients, answers phone calls promptly, and makes it easy for them to take care of patients with you and your partners. This is especially relevant in markets with competing colorectal specialty groups. Furthermore, taking advantage of the wealth of knowledge and experience of senior members of the practice should not be overlooked. Seeking out their opinions and advice can be invaluable. A culture of mentorship is prevalent among colorectal practices. Oftentimes, a senior surgeon will pass his or her practice on to a younger partner. This group of patients will feel most comfortable knowing that their new designated physician has been oriented to their long-time provider's practice philosophy and methods. While passing the baton is an important part of transitioning retiring surgeons out of the practice, retiring surgeons should maintain standard of care in their practice if they continue to participate in clinical activities, especially surgery, as the group's reputation can be as powerful as the individual reputation.

According to an American Osteopathic Association survey, the top five resources adults utilize when selecting a physician for themselves or a loved one are [9]:

- Word of mouth, i.e., family, friends, and coworkers (65.9%)
- Insurance provider directory (51.9%)
- Physician rating websites, i.e., Vitals, Healthgrades (22.8%)
- Hospital website (10.8%)
- Consumer review websites, i.e., Yelp (10.5%)

The first take-home message from these statistics—be kind, be affable. If you are kind, you will rapidly engender respect in the community, and your practice will grow. It is easy to become frustrated with a slow schedule at the beginning of your career. After all, you just finished residency or fellowship where every day brought new experiences and a wealth of opportunities to care for patients. It can feel like an abrupt slamming of the breaks on a career that has been defined by clinical volume and intense activity. Instead of focusing on the slow schedule, use this time to develop relationships. Relationships aren't important—they're everything, whether in our business, in our homes, or among friends. They are the threads that weave through the fabric of our entire being [10]. This is a gift of time. In order to have patients find you by "word of mouth," other patients have to have something nice to say. Spend extra time in consultation and get to know your patients. If you are in a new city, have them show you where they are from on a map. Take extra time with family members in the waiting room after surgery. The patient and family interactions are invaluable to your success, but do not underestimate your interactions with

everyone else from the unit clerk to the janitor to the CEO of the hospital. Every time someone mentions your name, you want people to say, "Dr. New is so nice." Of course, this behavior should be delivered in a genuine way. And remember, even when you are tired and frustrated, be kind. There's never a good time to be unkind.

You may be employed in a system where there is a well-defined referral network and there is less energy to be spent on securing referral sources to fill the schedule. However, in these models, the relationships you form with your employed colleagues will not only bring satisfaction to you personally but also help drive the culture of the organization. Furthermore, in many organizations you will likely be evaluated on collegiality, and your contract renewal may factor in these considerations.

Spending time meeting referring providers in person at the beginning of your career will be time well spent. Now that hospitalists have taken over inpatient care of the medical wards, the days of meeting primary care providers in the doctor's lounge is over. However, these settings are still fruitful for networking. You will invariably encounter oncologists, radiologists, and other specialists that create your multidisciplinary shortlist of go-to providers of inpatient services. In addition, you are likely to encounter representatives from hospital administration. This is a good time to talk with them about new projects, as well as inquire how you can help achieve their goals and that of the health system. Phone calls can be a way to facilitate relationships in the absence of face-to-face time. If you have a patient in your office with a particularly difficult situation or a new cancer, a quick call to introduce yourself and discuss the case shows dedication to quality care. There are more and more concierge medical practices opening, and these providers are paid fees by their patients for personalized care coordination. Reaching out by phone to these providers is not only appreciated, but often expected to be part of their referral network.

When you can schedule face-to-face time with referring providers, be mindful of their busy schedules. Be prepared to have a very brief period of their time. Scheduling breakfast or lunch in their office can make your meeting easier on their schedule. As a rule, bring food for the whole office and inquire about dietary restrictions/preference. This is a good time to highlight services you provide and also letting them know about new techniques you might be adding to the practice such as transanal minimally invasive surgery, robotics, fecal transplant, etc.

Highlighting new services your practice is offering gives a reason to reach out to new referring providers, as well as remind regular referring providers why you are the colorectal surgeon of choice. You might put together a short video of an operation and the cosmetic outcome for patient. It is always important to understand established referral patterns of your partners prior to determining your strategy. It is unlikely to sit well with your partner and likely to confuse the referring provider if you schedule a visit with someone who is committed to sending patients to one of your partners. These types of meetings should be supported by the entire practice, and communication about the strategy should be determined by the group.

When meeting with referring providers, try to figure out how you can make their lives easier. If the provider says everything is going well and they are getting your notes and letters and patients are happy, talk to the office staff/scheduling coordinators. They may prefer fax referral forms to free up their staff from the telephone. A laminated original may help them to be able to make copies easier (Fig. 72.1). Offering same-day appointments for diagnoses such as acute rectal pain, abscesses, and fissures can help their patients avoid ER visits. Practices participating in accountable care organizations are motivated to keep their overall cost of care down, so this may be very attractive to them. Being able to offer same-day or next-day diagnostic colonoscopy for patients that might have otherwise gone to the hospital is a valuable option, and referring providers need to know this is possible and available. Given that there are so many challenges in healthcare today, when meeting with referring groups, ask about their biggest challenges. Maybe you can share a practice problem and can work on a solution together which can create loyalty through collaboration. This could cover anything from IT support to health insurance to staffing. These visits are also a good time to inquire how they are marketing their practice and what they have had success with while learning what has failed.

One strategy for identifying potential referring providers is to find providers that are like you in some way, such as race, ethnicity, or gender. As a female, gynecologists and urogynecologists may be an untapped source of referrals, especially if you are joining an all-male group. As a minority, networking with other minority providers can be powerful as minority patients tend to choose providers of their own race [11]. If you speak a language other than English, network with other providers in your area that do as well as you are able to offer a unique resource to inpatients whose primary language may not be English.

One way to help strengthen a relationship is to change the environment [10]. Setting up a fun community event for referring providers and even their families can create an atmosphere of collegiality that is not possible in the office or hospital settings. A sports arena dinner with a famous guest speaker and an exclusive tour of a thoroughbred farm or distillery could be venues to consider. Not only referring providers but their staff as well can be advocates for your practice. Doing special things for referral coordinators, the people who often have a lot of power over where the referrals get sent, can be money well spent. This could range from

Fig. 72.1 Example of a fax referral form to provide to referring practices

CSGA
Colorectal Surgical & Gastroenterology Associates

CONSULTATION FORM

Colorectal Dept: Drs. David Svetich, Charles Papp, John Dvorak, Bruce Belin & Jennifer Rea
Gastroenterology Dept: Drs. Stephen Schindler, Nathan Massey & Thomas Knopp
2620 Wilhite Drive, Lexington, KY 40503 859-278-6031 (CR) & 859-278-8486 (GI)

Colorectal: FAX 859-277-7015

☐ NO PREFERENCE
☐ SVETICH ☐ DVORAK
☐ PAPP ☐ BELIN
☐ REA ☐ DANVILLE OFFICE

Gastroenterology: FAX 859-278-8488

☐ NO PREFERENCE
☐ SCHINDLER
☐ MASSEY
☐ KNOPP
☐ DANVILLE OFFICE

DATE: _____

Pt. Full Name _____ DOB _____

Address _____

City_____ State_____ Zip_____

Phone #s (_____)_____ **&** (_____)_____

Social Security Number_____ Patient E-Mail _____

PRIMARY Insurance _____

ID# _____GROUP #_____

SECONDARY Insurance _____

ID# _____GROUP # _____

Consulting Physician_____

Procedure or Appointment Requested: ☐ Office Visit ☐ Colonoscopy ☐ EGD

Consulted to evaluate/treat the DIAGNOSIS(s) of _____ _____

****Please send copy of Insurance Cards,**

And, if applicable, please send chart notes, test results, patient's history and medication list

(For CSGA Staff use in faxing back appt. information back to consulting office)

CONSULTING OFFICE FAX # and CONTACT NAME _____

Appointment Date and Time _____

flowers at Valentine's day, Starbucks cards, or even a night out at a local pub. In these clerical positions, they may not be receiving the type of positive feedback that the clinical providers do in the practice and a little appreciation can go a long way with this group.

Getting involved in the community, outside of the healthcare setting, can be an effective way to meet people and increase your visibility. Local medical societies, hospital committees, coaching youth sports, parent-teacher organizations, and church groups are just a few of the opportunities for not only networking, but learning more about unmet needs in your area. If you have a significant other, they can also get involved and tastefully get the word out about you and your practice to others. For several reasons outside of building your practice, community service and involvement can be very rewarding.

Although you might be achieving the three A's and offering the best that colorectal surgery has to offer, there might be external forces affecting referral patterns that you are not able to control. Hopefully, you were aware of these prior to taking the job. With changes in the healthcare environment, new challenges with referral pattern challenges may come up, even after you have been in practice for some time. You may experience your established referring doctors leaving independent practice to go to work for a health system or switching systems. There is often considerable pressure on providers to keep patients within a health system. Some clinic models are organized such that there are financial

incentives for referring providers to keep patients within the system. While there can be incentives for in-network utilization as long as there is evidence that there is value being provided by the coordination of care, contracts for employed physicians must include a provision specifying that patient choice will be respected.

Although patients may be restricted in their choice of provider if they have enrolled in a narrow network health insurance plan, it is still possible that they may choose someone outside of the integrated healthcare system if there is some flexibility.

Healthcare systems have focused on "leakage" of patients. The electronic medical record which tracks every referral a physician makes provides this data to physicians as well as practice managers. Relationships with healthcare systems are more important than ever for independent groups. Demonstrating quality and the value that you provide for their organization is crucial. If you are only viewed as leakage and an outsider, there could be significant challenges to practice viability. For example, a local healthcare system that competes with our group for outpatient endoscopy services implemented a new EMR that linked their outpatient and inpatient sites of service. Our independent practice, even though affiliated with this system with all of our physicians having full credentials, was left off of the EMR dropdown list of providers for 6 months until we were able with a tremendous amount of time and effort to get back on the list. The workflow remains set up so that those providers must make extra effort and clicks to get patients to us versus their hired physicians. If you are in private practice, tracking practice volume and referrals is essential to analyze the stability and future of the practice in an environment of mergers and acquisitions of practices by health systems.

Although these systems have tremendous resources and creating fully integrated care models with more narrow networks, the future of well-run independent practices remains bright in our current healthcare climate focused on quality and value. By partnering with your healthcare system in meaningful ways that create synergies for enhancing care delivery models, not only can independent practices remain viable, they can actually thrive. For instance, you could probably easily list several obvious areas of waste in the operating room at the hospital. Independent physician run groups and facilities are typically a tight run ship when it comes to expenses and have the discipline to focus on areas of inefficiency to improve the hospital environment. There is demand for high-quality, low-cost sites of service whether or not the health system is also the insurer. Often cost-efficient physician-owned practices and facilities have advantages when negotiating with insurers especially where and when they can deliver similar medical services at a lower price point. Payers are likely to have access to this information, and it is important to leverage this to your practice's advantage while making sure that you collect and monitor your own data to ensure its accuracy.

For employed physicians, even though there might be an established network of referring providers, understanding the stability of the referral base is equally as important. There may be quite a few gastroenterologists in the system, but are they happy? Are they planning on leaving because of dissatisfaction with the "system"? If they leave, what does that mean for your practice? Investing in creating and enhancing referral relationships, as well as working to support and grow the organization's culture, can not only mitigate a perception of loss of control of your practice but can actually replicate the physician-led group practice governance and management seen in independent practices.

Marketing

If your group's reputation is excellent and in network with the most common insurers in your area, then patients will choose you if they know you exist.

As internet marketing has dominated current strategies for most practices, the cost has come down on some of the most effective ways to reach patients with your message. You may choose to hire someone full time or part time with a marketing background and hire consultants from time to time to do project work such as getting your website up and running or cleaning up social media profiles. You may also hire a firm to have continual management of the marketing side of the practice. No matter what the strategy, metrics on effectiveness of marketing projects are key to determine what is working and what is not.

Digital marketing has largely replaced traditional marketing strategies such as print and billboards. Billboards, mailers, putting up signs at the baseball field, pin ups at the gym, etc. can certainly reach a small audience and enhance brand recognition, but these strategies should not be the center of the marketing plan. Digital platforms are not just for millennials. Adults ages 50–64, who spend the most overall time across all platforms of any age group, spend 51% of their time watching TV and TV-connected devices and 31% on digital platforms (Fig. 72.2) [12]. Facebook Ads has become the digital billboard. In addition to a broad reach to consumers, this platform also allows the ability to target a specific audience by a variety of parameters such as age, location, gender, education, and interests. By creating a custom audience, marketers can target the exact population their services are aimed toward without wasting money on persons outside of their target audience. Facebook Ads allows you to see the reach, engagement, and impressions of each ad and post so that you can know what type of content works and does not work for your audience such as in Fig. 72.3. A call-to-action on most posts is needed to drive your audience from just

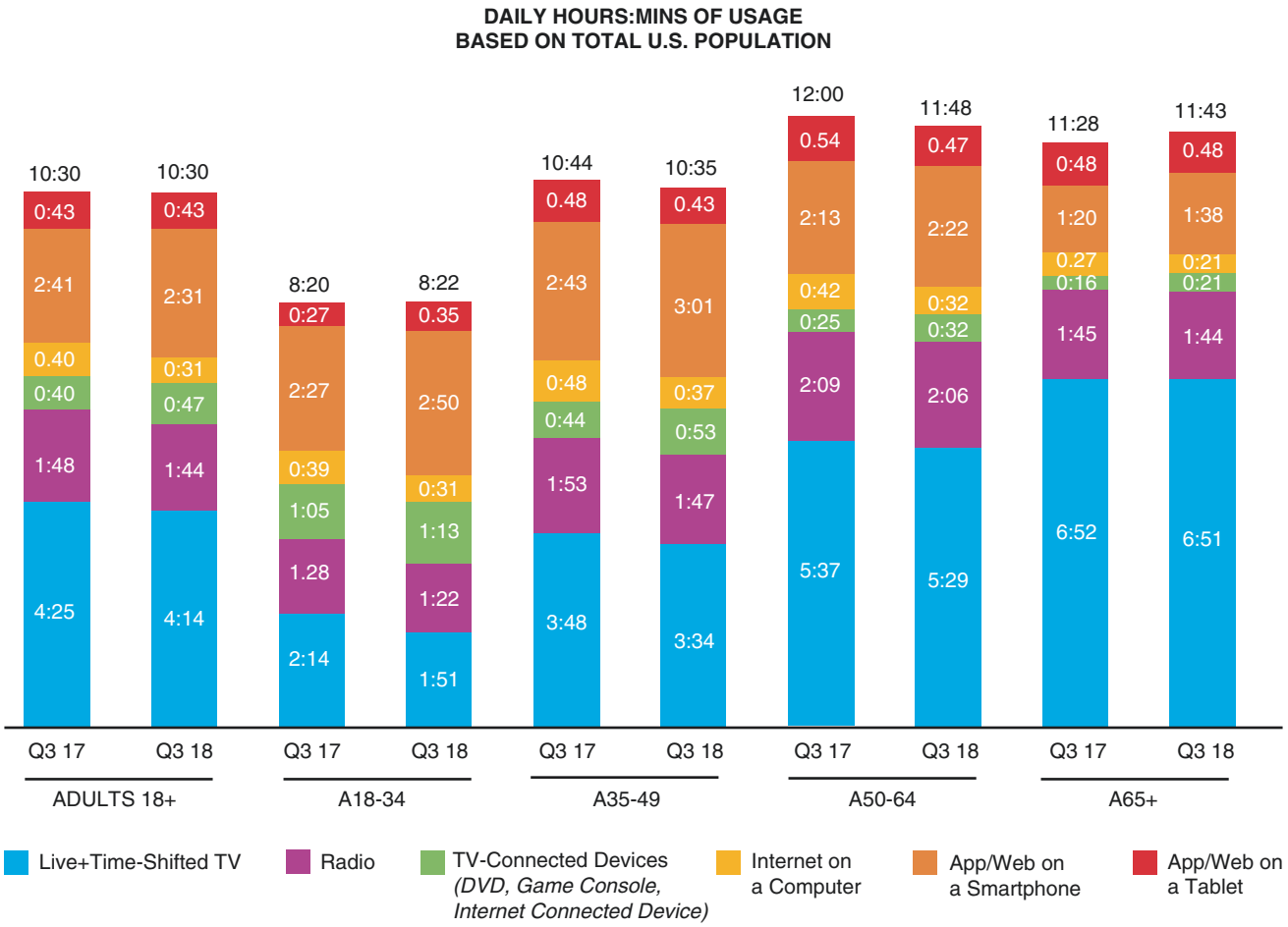

Fig. 72.2 Media time by demographic. Adults 50–64 spend more time on media than any other group

looking at your content to acting, such as scheduling an appointment.

The key to marketing a medical practice is to gain the trust of your audience. Unlike marketing tactics for a retailer or other service, marketing for a medical practice involves a higher degree of connection with your audience. Since the person's health is involved, their choice of which doctor or facility to select for their care is taken more seriously, and additional research is involved. Potential patients need to feel a sense of trust in the doctor and practice before they schedule an appointment. Healthgrades.com and Vitals.com are the first step for most patients when researching a doctor. With roughly 100 million people searching Healthgrades.com per year, keeping track of the reviews of the doctors in your practice is crucial. The same is true of Vitals.com. One major difference in these two websites is that Vitals.com allows ads on their website so practices can market directly to those patients who are using Vitals. Managing the reputation of the providers and the practice on social media should be done regularly. Reviews on Healthgrades and Vitals cannot be deleted, but they are listed in order of the date the review was written. One strategy to decrease the visibility of negative reviews is to encourage satisfied patients to leave good reviews. Another strategy is to leave a reply to negative reviews, which may demonstrate to others that you care and/or there might be other details relevant to the complaints. This could also be an opportunity for others to see that you are making efforts to remedy perceived wrongfulness and that you care. Responding to positive reviews with gratitude is also encouraged.

Content that engages your audience such as videos on healthcare-related topics or getting to know the physician and photos usually perform the best in terms of reach and engagement. A medical practice's social media accounts should always be professional, but at the same time, social media accounts should be inviting and personal. For example, your Facebook page should have a personality that matches the brand, tone, and voice of the practice. Facebook Insights allows administrators to see how each post performs and follower behavior which relates to the best time and day to post.

Aside from social media marketing, other forms of digital include over-the-top marketing (OTT) which is ads shown to a target audience through streaming services and most cable

Fig. 72.3 Example of feedback from Facebook ads regarding the results of online marketing efforts

providers and search engine marketing (SEO) which adds tags so that Google and other search engines show your page in the results of internet searches and an up-to-date website with easy to find information. YouTube channels and the era of "celebrity surgeons" is upon us. Now is the time when a patient can scan a QR code and watch a video of their surgeon performing the operation that they are about to undergo. These channels can be used for operative videos but also perioperative instructions, information about the physicians, topical discussions, etc.

As you can see, the social network environment has become extremely complicated and requires a high level of expertise to succeed in. While a physician well versed in social media can help guide a group practice's digital footprint, it is advised if at all possible for a professional to be hired either internally or as a consultant to continually manage the process. As health systems get larger and reap the benefits of scale, this has become a true focus and area of expertise for employed physicians within the network. Oftentimes, there is an entire marketing and planning department that supports this enterprise. While there are laws governing how a health system can market an independent individual or group practice in its community, there are opportunities for co-branding that can benefit each entity and the patients they care for.

Community involvement is also a good way for practices to brand themselves. Health fairs, festivals, and sponsorships of local community events such as youth sports and concerts are all high visibility opportunities to showcase the practice's logo as well as create a casual atmosphere for the public to get to know the providers and staff of the practice. There are other creative ways to market, including by reaching out to local service clubs, such as Kiwanis, the Lion's Club, or the Rotary Club to see if you can come and give a brief talk. Take business cards and handouts about the services in the practice. You may also bring a staff member who can schedule appointments right at the event. Becoming engaged with your local AORN and other nursing groups will have a far

reach. They have regular dinner meetings and conferences and need speakers. Local news stations may also have opportunities for exposure, such as a colon cancer awareness month piece on the morning show during March [13].

It should not be overlooked that some insurers will reach out to their customers with incentives to patients for utilizing certain facilities for their healthcare needs. It is essential that you know where your practice falls on these lists with the insurance company you hold contracts with. For instance, a patient may receive $100 check directly from the insurance company if they schedule their colonoscopy with a different facility which might change their decision to come see you. You want to be able to influence the variables that are in your control. Some insurers even engage in narrow network contracts where the policy covers certain healthcare services with only one provider. These are uncommon but exist and might be an option for your practice.

Setting Up Your Office

Most often you will be joining a practice that already has a system in place for seeing patients in the office setting. The office is most efficient and profitable with attention to having staff practice at the top of their license. Data entry can be done by medical assistants which are the least expensive staff to employ. Whether it be medical students, residents, or medical assistants, data entry into the EMR for medical histories, allergies and medication lists, etc., by other staff will free you up to focus on HPI, exam, assessment, and plan. At the beginning of your career, you will need less help. However, eventually, this type of staff support will be essential for you to accomplish the clinical work you have. Attention to this in your contract is imperative. Stories of surgeons being let go for poor productivity performance exist when, in reality, the employer did not provide the staffing in the office to achieve sustainable revenues or its surrogate, RVU's, for the surgeon. For example, on a day when there are 30 patients in clinic for one surgeon, a successful strategy might be having one person checking patients in and another person checking patients out. With three medical assistants in the clinic, one person chaperones in the room and two others are rooming patients and entering data into EMR. Two-three exam rooms to work in can facilitate the patient flow, while having a separate procedure room can be ideal.

Office-Based Procedures

As colorectal surgeons, the office serves as not only our primary location for consultation but also an ideal location for many simple procedures. Office-based procedures, when executed effectively, help facilitate efficient care of our patients. They also can contribute significantly to the revenue stream from the office. Anoscopy, rigid proctoscopy, flexible sigmoidoscopy, incision, and drainage of perirectal abscess among others are well-suited for the office setting. A list of common office procedures with their respective CPT code, global period if applicable, and Medicare allowable can be found in Table 72.1. The reimbursement for these procedures with private insurers will be specific to individual physician contracts. Office procedures can be done with the patient in either the prone jackknife position or left lateral position depending on the type of table available and surgeon preference. An assistant is essential. A general list of necessary supplies for the clinic is listed in Table 72.2. While not exhaustive, this should cover the majority of what you would need to perform in most office-based procedures in our specialty. There are several vendors on the national and local levels that can be used to obtain the necessary supplies and equipment for the office. A couple of the equipment vendors for items such as anoscopes, proctoscopes, and fistula probes typically visit the annual ASCRS meeting. This is a great

Table 72.1 Common colorectal office procedures with associated CPT code, global period, and Medicare reimbursement

CPT	Procedure	Global period	Medicare reimbursement
45330	Flexible Sigmoidoscopy	0	$160.70
45331	Flexible sigmoidoscopy with biopsy	0	$251.92
45338	Flexible sigmoidoscopy with snare polypectomy	0	$263.39
45300	Rigid sigmoidoscopy	0	$114.46
45305	Rigid sigmoidoscopy with biopsy	0	$150.92
45309	Rigid sigmoidoscopy with polypectomy	0	$177.02
46600	Anoscopy	0	$95.07
46606	Anoscopy with biopsy	0	$235.68
46614	Anoscopy with control of bleeding	0	$137.06
46900	Acid treatment-warts	10	$221.73
46930	Infrared coagulation	90	$199.96
46221	Internal hemorrhoid banding	10	$257.43
46230	Excision anal skin tags or papillae	10	$276.97
46320	Excision of thrombosed hemorrhoid	10	$185.16
46050	Incision and drainage of perirectal abscess	10	$202.95
10080	Incision and drainage of pilonidal abscess	10	$194.14
44385	Pouchoscopy	0	$185.29
44386	Pouchoscopy with biopsy	0	$275.86
57452	Vaginoscopy (not payable when combined with any other scope under Medicare)	0	$115.20

Table 72.2 Supplies for the colorectal clinic

Supplies		Medications
Disposable	*Reusable*	
Abdominal pads	Anoscope	Local anesthetic with and without epinephrine
Adhesive gauze roll	Autoclave	Local anesthetic cream or ointment
Alcohol swabs	Banders with forceps	Monsel solution
Band-Aid	Biopsy forceps	Depo-Medrol
Betadine	Blade holder	Gentian Violet 5%
Bleach	Fistula probe	Podophyllum Resin Salicylic Acid
Cotton swabs	Flexible sigmoidoscope	Silver Nitrate 20% Solution
Culture swabs	Forceps	Dichloroacetic Acid
Foley catheters	Hagar dilators	
Gauze	Hemostat	
Gloves	Hyfrecator	
Iodoform packing strip	IRC machine	
IRC sheaths	Light cord	
Lubricating jelly	Light source	
Mushroom catheters	Needle driver	
Needles	Oxygen tank	
Bands for ligatiors	Scissors	
Paper tape	Staple remover	
Peroxide	Suction pump	
Proctoscopes	Suction wand	
Rubbing alcohol		
Sani-Cloths		
Silver nitrate sticks		
Sterilization pouches		
Suction tubing		
Surgical blades 10, 11, 15		
Suture		
Syringes		
Table paper		
Tape		
Tissues		
Underwear/pads		

opportunity to talk with them as well as have them demonstrate their available options.

While sterilization of anoscopes and proctoscopes in the office can be easily managed with simple processes, the processing and maintenance of flexible scopes adds a layer of complexity you may or may not want to entertain. A description of this can be found at https://www.cdc.gov/hicpac/flexible-endoscope-reprocessing.html. A small autoclave and Cidex solution can be used for essentially all equipment. These processes should not take up too much space, as seen Fig. 72.4. Having enough staff in the clinic must be a consideration when setting up your clinic design. There are several vendors that now offer disposable anoscopes and proctoscopes if the staff time for processing instruments is unavailable.

Ancillary Services

Ancillary services in healthcare include a range of services that support physicians, such as laboratory tests, medical equipment, and rehabilitation programs. Ancillary services are typically classified into three categories: diagnostic (radiology, diagnostic imaging, etc.), therapeutic (physical and occupational therapy, massage, nutritional counseling, etc.), and custodial (hospice care, nursing facilities, and urgent care). Offering ancillary services as part of the practice meets several needs for patients and physicians. Services such as a pelvic floor center with anorectal manometry, physical therapy, ambulatory surgery center, and a pathology lab may be well-suited for a colorectal practice. A practice that is diversified in their revenue streams is more likely to adapt to further decline in physician compensation and rising costs of running a practice. However, embarking on projects to solely increase revenues should be avoided. Declining or delayed reimbursements, insurance claim hassles, increasing costs, growing regulatory pressures, patient demand, and patient satisfaction are good reasons to diversify the revenue stream. By adding ancillary services, physicians may be able to provide more convenient care, improve clinical outcomes, control the operation and quality of services, increase access to care, provide efficient and effective care, and offer additional services within their practice. Improved outcomes result in increased patient, physician, and payer satisfaction and decreased viability [14]. What's more, providing in-house services makes it more likely for patients to comply with physician instructions [15].

There are risks in adding ancillary services to your practice which include losing money, violating Stark laws, damaging relationships with referring physician practices or hospitals, causing harm, losing the trust of your patients, damaging one's reputation, and performing more tests/procedures than medically indicated and lawsuits [14]. Ancillary services cannot violate Stark, federal self-referral and anti-kickback laws, anti-markup rules, location oversight requirements, federal/state statutes, license and certification, OSHA, clinical laboratory improvement amendments (CLIA) certification, and insurance liability. The best advice before you make an investment or participate in ancillary income is to contact a healthcare attorney who is knowledgeable about the nuances of the Stark and other laws [14]. CMS.gov-Section 1877 of the Social Security Act (the Act) (42 U.S.C. 1395nn), also known as the physician self-referral law and commonly referred to as the "Stark Law" [16]:

Fig. 72.4 Colorectal clinic sterilization space and equipment

1. Prohibits a physician from making referrals for certain designated health services (DHS) payable by Medicare to an entity with which he or she (or an immediate family member) has a financial relationship (ownership, investment, or compensation), unless an exception applies
2. Prohibits the entity from presenting or causing to be presented claims to Medicare (or billing another individual, entity, or third-party payer) for those referred services
3. Establishes a number of specific exceptions and grants the Secretary the authority to create regulatory exceptions for financial relationships that do not pose a risk of program or patient abuse

The following items or services are DHS:

1. Clinical laboratory services
2. Physical therapy services
3. Occupational therapy services
4. Outpatient speech-language pathology services
5. Radiology and certain other imaging services
6. Radiation therapy services and supplies
7. Durable medical equipment and supplies
8. Parenteral and enteral nutrients, equipment, and supplies
9. Prosthetics, orthotics, and prosthetic devices and supplies
10. Home health services
11. Outpatient prescription drugs
12. Inpatient and outpatient hospital services

By law, physicians cannot be compensated according to the value or volume of their referrals or by the income they generate. The regulations do eliminate certain forms of self-referral, but do not ban self-referrals to specialty hospitals, ASCs, or office-based surgical or imaging procedures [17]. Ancillary services development requires a dynamic interpretation of multiple elements including cost, changing regulations, and altered reimbursement that will impact income projections and often extend the time to a positive cash flow. This is especially true for projects that require a high upfront

capitalization. Physician financial commitment to ancillary service development needs to be carefully assessed and measured in a healthcare environment that is placing increased emphasis on cost containment and value.

Ambulatory Surgery Centers

For the outpatient procedures requiring more time, equipment, and personnel than the clinic can handle, the ambulatory surgery center (ASC) is an ideal location. Most successful ambulatory surgery centers pride themselves on efficiency and decreased cost compared to inpatient operating rooms. Often, there will be restrictions on the types of patients that can be scheduled there based on factors such as BMI and ASA class. However, all but the sickest, largest patients are typically well-suited for colorectal procedures in an ASC.

Credentialing at an ambulatory surgery center should be a straightforward process. Typically, independent ambulatory surgery centers are more than happy to accommodate block time for a new surgeon to increase the procedure volume of the facility. The ambulatory surgery center generates revenue predominantly based upon facility fees that are charged on a per procedure basis. In the ASC, volume is the critical driver for profitability. Ambulatory surgery centers go through JCHO accreditation similar to hospital facilities [18]. State licensure often requires JCHO accreditation. Often, insurance companies will require state licensure for the surgery center to charge facility fees for outpatient surgical procedures. There are certain states where a certificate of need (CON) is required to open and operate an ambulatory surgery center. In those states, an option to contract with insurance companies for office-based procedures can be accomplished and may be an option for practices that have not acquired a CON. While Medicare and Medicaid require state licensure to bill facility fees for procedures, commercial insurers may be more flexible and provide contracts with similar reimbursement to the facility as if it were state licensed. In-depth understanding of your state's laws regarding ambulatory surgery centers is essential if you are considering becoming an owner or shareholder of an ASC. Counsel with specific experience in CON laws in the state is essential to the process. Currently, 36 states and Washington, D.C., operate a CON program with wide variation state-to-state [19].

Owning and operating an ASC can be extremely rewarding in many ways. Not only will it increase revenue streams to the practice if properly managed, but it gives the surgeons and patients control over cost and scheduling. With high deductible plans, patient have the potential to save money on their healthcare procedures when done in the outpatient setting. We have seen differences in patient's bills from an inpatient facility and an ASC of thousands of dollars for the same procedure. For the surgeon, control over scheduling, personnel, workflow, and equipment can be a welcome change of pace from the often slower more cumbersome inpatient care facilities. The win-win for the patient and the surgeon makes the ASC an ideal part of the colorectal practice.

Other Ancillary Services

To decide on ancillary services to add to your practice, start by doing a thorough economic analysis of the services you're currently sending out. You may also look at your community to see if there is an unmet need for the type of service you are thinking of adding. A practice's patient panel can be an important consideration in choosing an ancillary service that has the most potential to improve care [13, 15]. Some of the data required to evaluate the potential of a new ancillary service might include how often the practice currently refers out the service; total investment costs, including staff and training; and the amount of reimbursement expected. Practices should also know in advance what qualifications their payer contracts specify, such as Clinical Laboratory Improvement Amendments certification, which may be required for lab services. Upfront costs for equipment can range from just a few hundred dollars to tens of thousands. However, practices might size up the return on investment in terms of patient volume. Anorectal manometry equipment used to be a physically large machine and very expensive. Now, technology has much improved and the equipment is small, portable, easier to use, and more affordable. This is a test that most colorectal surgeons use to make clinical decisions. It is also a test that does not take that very long to complete but often requires an additional appointment at another healthcare institution for a patient who is already in your office. Therefore, adding anorectal manometry as an ancillary service to your colorectal practice would be an ideal type of service to consider. A manometry machine, for example, might cost $20,000, while the reimbursement for the procedure is $700. Disposable equipment costs $115 per procedure, which results in collected revenue to $585. It does not take long before the practice will see a return on investment. Other providers, such as gastroenterologists, may also be interested in referring these exams to you and would also provide an opportunity for networking if they are not already offering this service as part of their practice. It could also serve as an opportunity to let the gastroenterologist know what types of treatment options that you are providing to patients with chronic constipation. Consideration for additional physician and staff training must also be part of the business plan, the creation of which is an essential part of the process for this ancillary service or any other that you are contemplating.

Billing and coding for ancillary services cannot be an afterthought. Covered diagnosis codes for the services you provide are important to understand so that when the test is

submitted to insurance for billing, reliable reimbursement is expected. This includes some wariness about the Medicare Access and CHIP reauthorization Act's (MACRA) impact on ancillary services as payment moves from fee-for-service to quality-based reimbursement. Physicians should review the specific requirements of modifier −25 as they relate to each payer in a practice's mix. Some payers may deny a modifier −25 code (separately identifiable evaluation and management service by the same physician on the same day of a procedure or other service), potentially resulting in nonpayment for ancillary services [20]. Many payers, including Medicaid, do not recognize the modifier. It is also vital to market and promote the ancillary services that your practice provides. If patients are not aware of the services you are providing, they will not use them. Put posters in the waiting and exam rooms. Include details on the practice's website. Include information about these services when the practice holds community events and visits referring provider's offices.

Leadership Roles

While we all share the common goal of taking excellent care of the colorectal surgical patient, other career goals among us vary greatly. Some aspire to lead international surgical societies, while some focus on their clinical work with their patients, and others dive deep into research pursuits or cutting edge minimally invasive techniques. When done well, involvement in local, regional, and national leadership activities are the path to bigger and more important roles. If these are your goals and the path to success is not clear to you, seek out mentorship. There are now formal mentorship programs developed in surgical societies, including the ASCRS. Committee work at the local level might not seem like it should matter very much to the career of a researcher or busy robotic surgeon. However, participation is a great way to build relationships for collaborators and referring providers. If unfortunate events such as credentialing issues come about for you or one of your partners, it is crucial to have representation on medical executive committees and peer review, so you or your group have influence in making decisions about privileges. Local medical society offices can lead to state medical society appointments and even national appointments. These roles help build your personal CV but can also help your practice stay in the know on legislation affecting surgical practices such as tort reform, changes in fee schedules, certificate of need, Medicaid expansions, etc.

There may be a time in your career when you would like to transition out of direct patient care. If your nonclinical activities and interests are robust, you will likely have more opportunities for jobs and projects as this stage presents itself. An advantage of being part of a large healthcare system is that there are a myriad of career paths available to consider. This can be tied to clinical activities, such as managing a service line or leadership of the employed group practice. This is especially important if the goal of the health system is to create a physician-led culture, at least for the clinical activities. With the trend toward physician leadership of the entire healthcare system enterprise, nontraditional physician roles including operational leadership all the way to the C-suite have now become commonplace.

Sometimes, these transitions may be a conscious choice, or unfortunately it may be out of the surgeon's control. At times, due to medical illness, advanced age, or loss of privileges, a surgeon may have to give up clinical activities, including operating. Obtaining professional advice, including counseling if the transition is particularly challenging, is highly recommended as part of the process. Ultimately, a diversified approach to your skill set, just like diversification in a retirement plan, can offer a safety net in these circumstances.

Conclusions

Healthcare is rapidly changing and can be overwhelming at times. Given the magnitude of growth of the industry and its impact not only on the patients we treat but also the US economy, it is no surprise that disruption is taking place on a daily basis. Rather than resist the inevitable changes taking place, it is far more productive and healthy to both adapt, as well as lead the journey to achieve the quadruple aim (improved patient/customer experience with increased quality and cost efficiency, while also focusing on provider health and wellness). The ASCRS recognizes its role in supporting the journey for its members and there are resources available to the practicing colorectal surgeon as presented in this chapter and through the ASCRS to navigate these challenges. Topics relevant to practice management are now highlighted in a formal symposium at the ASCRS national meeting. The Healthcare Economics Committee remains dedicated to representing the needs of colorectal surgeons to lawmakers. In addition, there is now a formal mentoring program through the ASCRS. More information can be found at https://fascrs.org/my-ascrs/career-center/mentoring-program.

References

1. Kash B, Tan D. Physician group practice trends: a comprehensive review. J Hosp Med Manag. 2016;2:1(3). https://doi.org/10.4172/2471-9781.10008. Available online at: https://hospital-medical-management.imedpub.com/physician-group-practice-trends-a-comprehensive-review.pdf.
2. AMA Policy research perspectives, updated data on physician practice arrangements: for the first time, fewer physicians are

owners than employees. Available online at: https://www.ama-assn.org/system/files/2019-07/prp-fewer-owners-benchmark-survey-2018.pdf.
3. Zhu JM, Hua LM, Polsky D. Private equity acquisitions of physician medical groups across specialties, 2013–2016. JAMA. 2020;323(7):663–5.
4. West CP, Dyrbye LN, Shanafelt TD. Physician burnout: contributors, consequences and solutions. J Intern Med. 2018;283(6):516–29.
5. With 8k more physicians than Kaiser, Optum is 'scaring the crap out of hospitals'. Available online at: https://www.beckershospitalreview.com/payer-issues/with-8k-more-physicians-than-kaiser-optum-is-scaring-the-crap-out-of-hospitals.html.
6. International Classification of Diseases (ICD) Information Sheet. Available online at: https://www.who.int/classifications/icd/factsheet/en/.
7. Centers for Medicare and Medicaid Services. Evaluation and management services guide. Available online at: https://www.cms.gov/Regulations-and-Guidance/Regulations-and-Guidance.
8. Calafell J, Cohen JL. What the heck are RVUs? A guide to productivity based compensation. Semin Colon Rectal Surg. 2020;31(1).
9. 6 of 10 People choose a doctor based on a convenient location. https://healthcaresuccess.com/blog/hospital-marketing/6-10-people-choose-doctor-based-convenient-location.html. Referenced 22 Feb 2020.
10. Sobel A, Panas J. Power relationships: 26 irrefutable laws for building extraordinary relationships. 1st edn. Wiley; New Jersey. 2014.
11. Saha S, Taggart SH, Komaromy M, Bindman AB. Do patients choose physicians of their own race? Health Aff. 2000;19(4):76–83.
12. The Nielsen total audience report Q3 2018. https://www.nielsen.com/wp-content/uploads/sites/3/2019/04/q3-2018-total-audience-report.pdf. Referenced 24 Feb 2020.
13. Making the most of your practice's ancillary medical services. https://www.phreesia.com/2018/01/22/blog-making-most-of-your-ancillary-services/. Referenced 16 Feb 2020.
14. Baum N, Bonds RG, Crawford T, et al., editors. The complete business guide for a successful medical practice. New York: Springer; 2015.
15. Why surgical practices are bringing ancillary services in-house. https://www.surgimate.com/blog/surgical_practices_bring_ancillary_services_in_house/. Accessed 19 Jan 2020.
16. Physician Self Referral. https://www.cms.gov/Medicare/Fraud-and-Abuse/PhysicianSelfReferral/index?redirect=/physicianselfreferral/. Accessed 19 Jan 2020.
17. Casalino LP. Physician self-referral and physician-owned specialty facilities. The Synthesis Project. Robert Wood Johnson Foundation, Research Synthesis Report No. 15. 2008.
18. Ambulatory care accreditation and certification options. https://www.jointcommission.org/accreditation-and-certification/health-care-settings/ambulatory-health-care/learn/accreditation-options-certifications/. The Joint Commission Ambulatory Surgery Center Accreditation. Referenced 19 Jan 2020.
19. CON-Certificate of need state laws. https://www.ncsl.org/research/health/con-certificate-of-need-state-laws.aspx. Referenced 19 Jan 2020.
20. Grow your practice with ancillary services. https://www.medicaleconomics.com/business/grow-your-practice-ancillary-services Referenced 19 Jan 2020.

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