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Management of Radiation Proctitis

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KEYWORDS

• Radiation proctitis • Radiation colitis • Sucralfate • Short-chain fatty acids
• Hyperbaric oxygen • Formalin • Endoscopic laser therapy
• Argon plasma coagulation

KEY POINTS

- Radiation proctitis is a common complication of radiation therapy but most instances of proctitis are self-limited and respond to medical management.
- Rates of both acute and chronic proctitis have been decreasing with improved radiation therapy techniques that allow the targeted delivery of higher doses of radiation.
- The paucity of well-controlled, blinded, randomized studies makes it impossible to fully assess the comparative efficacy of the different endoscopic and medical therapies for chronic radiation proctitis. Despite this limitation, endoscopic therapies, particularly argon plasma coagulation (APC), seem to be the most effective in managing well-defined bleeding from radiation proctitis.
- Although focal ablative tools such as lasers, contact probes, and APC may be helpful when bleeding occurs from a limited number of identifiable ectatic vessels, a larger field of arteriovenous malformations or oozing may be more difficult to control.
- Methods allowing a broader field of treatment, such as formalin instillation or the newer methods of radiofrequency ablation (RFA) and cryotherapy, may theoretically be advantageous in this setting. In particular, the unexpected finding of neosquamous epithelialization with RFA may have further advantages in preventing recurrent symptoms and needs to be further evaluated in larger randomized trials.

INTRODUCTION

Radiation therapy is commonly used as part of the multidisciplinary treatment strategies of pelvic malignancies of gynecologic, urologic, and anorectal origin with well-established benefits. Radiation proctitis following pelvic radiation therapy can range from a dose-limiting side effect in its acute stage to major morbidity affecting health-related quality of life in its chronic stage. Many series have suggested an

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incidence of 5% or less after pelvic radiation, but a review of published controlled trials of adjuvant therapies suggests that 30% might be more realistic (Fig. 1).[1] There are also data to suggest that the proportion of patients who seek help for subsequent symptoms represent only a fraction of affected patients.[2]

Patients with prostate, cervical, and anal cancers are the most commonly affected, although the epidemiology of radiation proctitis is difficult to characterize because of the range of cancers for which pelvic radiation therapy is used, and the diversity of dosing regimens and modes of therapy. Predisposing factors that may be associated with increased risk of late complications of radiation include preexisting comorbid conditions, tumor stage, total radiation dosage, the volume treated, dose distribution, and concurrent therapies.[3] Most radiation oncologists now rely on advanced techniques, such as the use of three-dimensional treatment planning software, to target maximal dose to the intended organ while minimizing exposure to the rectum. Despite this, in a randomized control trial on dose escalation using three-dimensional treatment planning and conformal radiotherapy among patients with prostate cancer, a third of patients had more than 25% of their rectal volume exposed to radiation therapy. This exposure resulted in a doubling of the 5-year risk for development of late radiation proctitis (37% vs 13% among patients with <25% of rectal volume exposed).[4]

No standard guidelines exist for diagnosis and management of radiation proctitis. This article reviews the definitions, staging, and clinical features of radiation proctitis, and then summarizes the different modalities currently available for the treatment of acute and chronic radiation proctitis.

DEFINITIONS

Acute radiation proctitis refers to radiation-induced injury during the time of radiation therapy and for a short period (up to 6 months) after completion, usually defined as 6 months. Nearly all patients develop at least transient symptoms consistent with this acute process.

Chronic radiation proctitis can continue from the acute phase or begin after a variable latent period (typically at least 90 days). Most patients develop symptoms at a median of 8 to 12 months after completion of radiotherapy.[5]

HISTOLOGIC AND CLINICAL FEATURES OF ACUTE VERSUS CHRONIC RADIATION PROCTITIS

In the acute phase of radiation proctitis, extensive mucosal inflammation, eosinophilic infiltration of the submucosa, crypt atrophy, and crypt abscesses are observed on

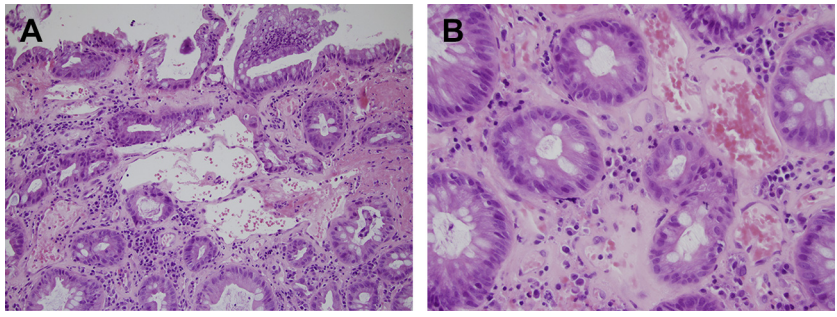

Fig. 1. Radiation proctitis. (*A*) Magnification ×20. (*B*) Magnification ×40. (*Courtesy of* Ilke Nalbantoglu, MD, Department of Pathology, Washington University, St Louis, MO.)

histology. This damage causes symptoms such as diarrhea, mucus discharge, cramping, bloating, tenesmus, anal pain or incontinence, and minor rectal bleeding. Of these symptoms, the most common is diarrhea, which affects from 50% to 75% of patients.[6]

Chronic damage is characterized by obliterative enteritis with ulceration and fibrous induration of the gut.[7] The cardinal sign of chronic radiation proctitis that distinguishes it from acute radiation proctitis is the presence of small-vessel vasculopathy.[8] Clinical manifestations of chronic radiation damage are characterized by rectal urgency, incontinence, pain, bleeding, mucous discharge, and strictures. Rectal fistula or perforation can, rarely, occur.

CLASSIFICATION

Most studies grade late rectal adverse events using the Radiation Therapy Oncology Group scoring criteria, shown in **Table 1**.[9] The objective of a more specific rectal toxicity profile is to help physicians and patients make more informed management decisions after radiation therapy.

DIAGNOSIS

In most patients, the diagnosis can be confirmed by colonoscopy or sigmoidoscopy. Mucosal features consistent with radiation injury include pallor with friability, and telangiectasias.[10] Although mucosal biopsies are not diagnostic, they can help to exclude other causes of proctitis such as infection or inflammatory bowel disease. Rectal biopsy to evaluate rectal bleeding because of radiation proctitis seems to be an important factor in the development of rectal fistulas.[11] For this reason, rectal biopsies should be performed judiciously depending on the clinical indication as well as the dose and fractionation of previous pelvic radiation therapy. If required, they should be directed at the posterior and lateral walls to avoid the irradiated areas in patients with prior prostate therapy.[12]

PREVENTION

The main approach to the prevention of radiation proctitis is the use of newer conformal radiation therapy techniques. These advances include intensity-modulated radiation

Table 1
Modified Radiation Therapy Oncology Group rectal toxicity scale

Grade 1	Mild and self-limiting	Minimal, infrequent bleeding or clear mucus discharge, rectal discomfort not requiring analgesics, loose stools not requiring medications
Grade 2	Managed conservatively, lifestyle (performance status) not affected	Intermittent rectal bleeding not requiring regular use of pads, erythema of rectal lining on proctoscopy, diarrhea requiring medications
Grade 3	Severe, alters patient lifestyle	Rectal bleeding requiring regular use of pads and minor surgical intervention, rectal pain requiring narcotics, rectal ulceration
Grade 4	Life threatening and disabling	Bowel obstruction, fistula formation, bleeding requiring hospitalization, surgical intervention required

therapy and intensity-guided radiation therapy, and minimize the dose of radiation to the rectum while maximizing dose to the tumor.

Amifostine is a prodrug that is metabolized to a thiol metabolite that is thought to scavenge reactive oxygen species. When administered intravenously, it has shown some promise in small trials with short follow-up in preventing symptoms of acute proctitis as well as decreasing the severity of chronic proctitis symptoms.[13–15] Sucralfate has also been evaluated for prophylaxis against acute radiation injury. However, placebo-controlled phase III trials have detected no benefit from either topical or oral sucralfate.[16,17]

TREATMENT

Potential therapy for chronic radiation proctitis includes 3 broad categories (**Table 2**)[18]:

(1) Medical: enemas, oral agents, topical applications, and oxygen therapy.

(2) Endoscopic: argon plasma coagulation (APC), laser, cryotherapy, and electrocoagulation.

Table 2
Potential therapy for chronic radiation proctitis

	Type of Therapy	Proposed Mechanism	Role
Medical therapies	Butyrate	Nutrient for healing colonocytes	Used primarily in acute radiation proctitis
	5-Aminosalicylic acid derivatives	Antiinflammatory	As first-line therapy in chronic radiation proctitis with mixed results
	Sucralfate	Prevents microvascular injury	
	Metronidazole	Antiinflammatory	
	Short-chain fatty acid	Nutrient for healing colonocytes	
	Vitamin A	Antiinflammatory	
	Topical formalin	Chemical cauterization	
	Hyperbaric oxygen	Promotes healing	Not widely available but shows some efficacy
Endoscopic therapies	Dilatation		For radiation-related strictures
	Heater and bipolar cautery	Thermoelectric cauterization	More effective than medical therapies, especially in controlling rectal bleeding, but not widely available; APC is preferred to laser coagulation or cryotherapy
	Nd:YAG, KTP laser	Noncontact electrocoagulation	
	Cryotherapy	Thermal cauterization	
	Argon plasma coagulation	Noncontact electrocoagulation	
	Radiofrequency ablation	Noncontact electrocoagulation	
Surgical therapies	Diverting ostomy	Diversion of fecal stream	High risk of postoperative morbidity; reserved for severe rectal strictures and rectal fistulas
	Reconstruction with flaps	Vascularized tissue mobilized	
	Proctectomy	Removal of damaged tissue	

Abbreviations: APC, argon plasma coagulation; KTP, potassium titanyl phosphate; laser Nd:YAG, neodymium/yttrium aluminum garnet argon.

(3) Surgical: there have been no large controlled trials evaluating the different treatments for radiation proctitis, and management strategies are derived primarily from institutional experience, case reports, and small clinical trials.

MEDICAL THERAPIES

Butyrate

Butyrate is used primarily in acute radiation proctitis, for which it has shown some benefit in hastening recovery,[19,20] and other treatments have not been shown to be efficacious. Butyrate is the main short-chain fatty acid (SCFA) used by colonocytes for nutrition and this is attributed to its protective effect during recovery from radiation trauma.

Amino Salicylic Acid Derivatives

Antiinflammatory agents in this group, such as sulfasalazine and mesalazine, have been reported to have a role in the management of radiation proctitis.[21] The antiinflammatory actions of 5-aminosalicylic acid (5-ASA) occur through a variety of mechanisms, most notably via a reduction of prostaglandin production.[22,23] At first, it was thought that 5-ASA was an effective medical agent for the treatment of chronic radiation proctitis.[22] However, several small trials of 5-ASA for radiation proctitis have produced mixed results. Some produced symptomatic improvement or no clinical changes, whereas others produced worsening of clinical symptoms.[21,24–26] Other antiinflammatory agents that are used in combination with sulfasalazine or 5-ASA include oral or rectal steroids such as prednisone, betamethasone, or hydrocortisone. Steroids have multiple mechanisms of action that produce antiinflammatory effects, which range from stabilization of lysosomes in neutrophils to prevent degranulation to upregulation of antiinflammatory genes via binding to glucocorticoid receptors.[27] The efficacy of corticosteroids alone has been poorly studied and anecdotal clinical experience with this approach has been disappointing.

Sucralfate

Several reports have suggested that topical sucralfate may improve symptoms of radiation proctitis or proctosigmoiditis.[22,28–31] Sucralfate is a highly sulfated polyanionic disaccharide. Its postulated mechanisms of action include a reduction in the extent of microvascular injury and protection of epithelial surfaces from radiation damage.[32,33]

In a prospective, double-blind trial, 37 patients with proctosigmoiditis were randomly assigned to a 4-week course of oral sulfasalazine (3.0 g/d) plus prednisolone enemas (20 mg twice daily) or sucralfate enemas (2.0 g twice daily).[22] Clinical improvement was noted in both groups at the end of the study. However, the response was better for sucralfate enemas alone, which were also better tolerated.

Another report from the same investigators included 26 patients with moderate to severe radiation proctosigmoiditis who were treated with sucralfate enemas (20 mL of a 10% suspension twice daily) until bleeding stopped or failure of therapy was acknowledged.[28] A good response (decreased number of episodes of bleeding) was observed in 77% of patients by 4 weeks, and 92% by 16 weeks. These results await confirmation in larger controlled trials.

Metronidazole

Metronidazole is a nitroimidazole whose complete mechanism of action is unclear but is thought to be via the reduction of the nitro group in an anaerobic environment.[34] The efficacy of metronidazole was evaluated in study that included 60 patients with rectal bleeding and diarrhea who were randomly assigned to treatment with mesalamine

plus betamethasone enemas with or without oral metronidazole.[35] The incidence of rectal bleeding and mucosal ulcers was lower in the metronidazole groups at 1, 3, and 12 months. Diarrhea and edema were also reduced in this group.

SCFA Enemas

SCFAs are the preferred nutrients for colonocytes and also exert a trophic effect on the colonic mucosa by stimulating a physiologic pattern of proliferation and promoting cellular differentiation. Their use may be impaired in chronic radiation proctitis. Radiation-associated mucosal atrophy may interfere with mitochondrial fatty acid oxidation, and supplementation of SCFA in the form of enemas could overcome this deficiency and improve the energy supply to colonocytes. Moreover, the dilatory effect of SCFA on arteriolar walls may also contribute by improving mucosal ischemia. Fatty acid enemas have been effective for treatment of diversion colitis, and some case reports suggest a possible benefit in radiation proctitis.[36] However, no significant improvement in symptoms was found in a placebo-controlled study.[37]

Vitamin A

Oxidative stress is thought to be a major mechanism in the development of chronic radiation proctitis, and agents with antioxidant properties such as vitamins A and C have been used in an attempt to limit tissue damage related to oxidation. In a study by Kennedy and colleagues,[38] which only included 10 patients, the use of vitamins E and C significantly decreased the rate of diarrhea and urgency. Another study was a pilot, placebo-controlled trial involving 18 patients with radiation proctitis.[39] Response (defined as a reduction in 2 or more symptoms by at least 2 points on a validated scale) was observed significantly more often in the group randomized to retinol palmitate (vitamin A). In addition, 5 placebo nonresponders subsequently responded to active treatment during crossover.

Formalin

Rubinstein and colleagues[40] reported the first published successful use of 4% formalin in a patient who had required colostomy and 39 U of blood transfusion. Application directly to the mucosa produces local chemical cauterization, reducing bleeds by sealing the neovascularized telangiectatic spots and ulcers. The success of bleeding control is related to the accurate localization and application of formalin to all the affected points. Several variations in technique have been described. Most commonly, the treatment consists of proctoscopy with direct application with a cotton tip applicator or gauze of 4% or buffered 10% formalin in contact with the hemorrhagic rectal mucosa or of instillation into the rectum of 20 to 100 mL of 3.6% to 4% solution. Direct contact of the formalin with the anoderm should be avoided because it can be irritating to the skin. Endoscopic flushing out of residual formaldehyde with saline is usually recommended. The success in controlling bleeding ranges from 80% to 100% but there is real, albeit small, risk of pelvic sepsis, rectal wall necrosis, or development of rectovaginal fistulae.[41] The risk of late strictures or incontinence is also real and is increased in patients with anal cancer treated with radiation.[42] Given these complications, the use of formalin should be restricted to patients with hemorrhagic proctitis.

Hyperbaric Oxygen

The theoretic benefit of hyperbaric oxygen therapy may be via inhibition of bacterial growth, preservation of marginally perfused tissue, and inhibition of toxin production. Hyperbaric oxygen therapy has an angiogenic effect and has been shown to cause an

8-fold or 9-fold increase in the vascular density of soft tissues compared with air-breathing controls.[43] Several studies have suggested a marginal benefit, although this has never been well defined.[44–47] Assessment of response has tended to be a vague description of the resolution of symptoms instead of a tangible system that can be used for statistical analysis.

ENDOSCOPIC THERAPIES

Endoscopic Dilation

Balloon dilation can be effective in patients with obstructive symptoms from radiation-related strictures who do not respond to stool softeners, provided that the strictured segment is short.[48] The risk of perforation is increased in patients with long or angulated strictures. Such patients may require surgery if obstruction is clinically significant.

Endoscopic Lasers and Cryoablation

The potassium titanyl phosphate (KTP) and neodymium/yttrium aluminum garnet argon (Nd:YAG) lasers have been used to coagulate bleeding ectatic vessels throughout the gastrointestinal tract.[49–53] However, these devices are not widely available.

Nd:YAG laser has a low affinity for hemoglobin and H_2O but is well absorbed by tissue protein, thus making it ideal for deeper vessel coagulation. The potential benefit of this approach was shown in a report in which the Nd:YAG laser was used in 9 patients, of whom 6 required periodic blood transfusion; bleeding was reduced to only occasional spotting in 6 patients, with only 1 continuing to require periodic blood transfusions during follow-up of 24 months.[50] Transmural necrosis, fibrosis, stricture formation, and rectovaginal fistula are some of the complications reported with use of Nd:YAG.

The KTP laser uses the beam from the Nd:YAG laser that is passed through a KTP crystal, reducing the wavelength by half (532 nm).[30] At this wavelength, the energy is absorbed by hemoglobin and the depth of penetration is shallower (1–2 mm) than hat of Nd:YAG, hence the risk of transmucosal damage resulting in necrosis or stricture is less.

In small pilot studies of 7 to 10 patients with radiation proctitis, response to cryoablation spray ablation with a decrease in rectal telangiectasia density and improvement in radiation proctitis symptom severity has been seen.[54,55] One patient suffered cecal perforation caused by gas overdistention. Controlled trials are needed to establish the safety and efficacy of cryoablation for radiation proctitis.

Endoscopic Bipolar and Heater Probe

The advantage of bipolar electrocoagulation and the heater probe compared with laser therapy is that they cause less tissue injury, and permit tangential application of cautery, and that the equipment needed is widely available and inexpensive. The disadvantage is char formation on the tip of the probe, leading to decreased treatment efficiency and requiring repeated cleaning.

These techniques were evaluated in a study involving 21 patients with chronic recurrent hematochezia and anemia caused by radiation-induced injury who were followed for 12 months.[56] Patients were treated with either bipolar coagulation probe or heater probe therapy as needed. Severe bleeding diminished significantly after these treatments compared with the previous 12 months of medical therapy (75% vs 33% and 67% vs 11%, respectively). The decreased rate of bleeding was accompanied by an improvement in the hematocrit in both groups; there were no major complications.

Endoscopic APC

Laser therapy for hemorrhagic chronic radiation proctitis has largely been supplanted by APC, which is less expensive, easier, safer, and more widely available. APC uses high-frequency energy transmitted to tissue by ionized gas. Unlike traditional bipolar devices, the current jumps from the probe to the target lesion, with the arc being broken once the tissue is desiccated. The theoretic advantage is a uniform, more predictable, and limited depth of coagulation (0.5–3 mm),[34] which minimizes the risks of perforation, stenosis, and fistulization. APC has been used to treat a wide spectrum of bleeding lesions in the gastrointestinal tract and has been shown to be effective in controlling bleeding caused by radiation proctitis, although it may require multiple sessions (usually at 4-week intervals).[57–59] Some patients may experience postprocedure rectal pain and cramps, but major complications are rare. Special care is required to avoid spraying too close to the dentate line. In addition, APC may control bleeding even after other treatment methods have failed.[60,61]

Endoscopic Radiofrequency Ablation

Zhou and colleagues[62] reported successful use of endoscopic radiofrequency ablation (RFA) in treating 3 patients with lower gastrointestinal bleeding from chronic radiation proctitis, including 2 who failed other therapies. In all cases, the procedure was well tolerated and hemostasis was effectively achieved after 1 or 2 sessions. Reepithelialization by neosquamous mucosa was observed over areas of prior hemorrhage with no stricturing or ulceration during follow-up of up to 19 months.

Several benefits of RFA have been found compared with other endoscopic treatments for radiation proctitis. The tightly spaced bipolar array of the RFA catheter limits the radiofrequency energy penetration, restricting the RFA treatment to the superficial mucosa, thereby avoiding deep tissue injury in ischemic mucosa and the resulting ulceration and stricturing. RFA also allows broader areas of tissue to be treated simultaneously compared with the point-by-point approach required with heater or bipolar probes. The energy delivered to the surface is consistent and reproducible, thus reducing operator dependence and overtreatment, which may lead to perforations or ulcerations. In addition, the unexpected finding of squamous reepithelialization seen after RFA results in the lack of stricturing and ulceration that is often seen after other thermal ablative procedures.[63]

SURGICAL THERAPIES

Surgery should be reserved for patients who have intractable symptoms such as strictures, pain, or bleeding, because it may be technically demanding because of adhesions and other radiation damage in the pelvis. Fewer than 10% of patients eventually require surgery,[64] which is usually for intractable bleeding, perforation, strictures, and fistulas.

Fecal Diversion

Diverting the fecal stream with a colostomy or ileostomy decreases symptoms of pain, tenesmus, drainage, and infection, and can also improve symptoms related to incontinence and stricture. It has a limited effect on bleeding, although at least one study has shown improvement in bleeding as well.[65] In some patients, a complete diversion improves symptoms and their quality of life to the point that they do not require any further intervention[6,64,66,67] even though the underlying problem is not directly addressed. In one review of 48 patients who had been referred for severe refractory radiotherapy complications that had failed initial treatment, surgery

was generally required for patients who presented with a fistula, and permanent diversion was more likely in patients with severe radiation enteritis and distal colonic strictures.[68]

Repair/reconstruction

Local excision and reconstruction such as an advancement flap, although technically feasible, are limited by the presence of poorly vascularized tissues and low healing rates.[69] An exception is the treatment of rectourethral or rectovaginal fistula with a pedunculated gracilis or a Martius flap to facilitate healing by introducing well-vascularized healthy tissue, and preliminary or synchronous diversion of stool and of the urinary stream with an ostomy and a catheter, respectively, is required. Although these procedures may be a technical success, they often result in unacceptable long-term morbidity, including complicated scarring, stricture, and incontinence.

Proctectomy/pelvic Exenteration

Complete rectal resection may be the only option in some patients, such as in cases of complicated fistulous disease, especially when accompanied by significant pain and incontinence, or in cases of severe and intractable bleeding, because diversion rarely controls the bleeding completely. Although this is a definitive treatment, it is accompanied by significant morbidity, including exceedingly high rates of anastomotic leaks in cases of reconstruction and high rates of perineal wound complications when reconstruction is not attempted.[6,67] When surgical treatment is needed, most studies have poor outcomes with high complication rates (15%–80%), and mortalities of 3% to 9%.[64,66,67]

SUMMARY

Radiation proctitis is a common complication of radiation therapy but most instances of proctitis are self-limited and respond to medical management. Rates of both acute and chronic proctitis have been decreasing with improved radiation therapy techniques that allow the targeted delivery of higher doses of radiation.

Because of the paucity of well-controlled, blinded, randomized studies, it is not possible to fully assess the comparative efficacy of the different endoscopic and medical therapies for chronic radiation proctitis. Despite this limitation, endoscopic therapies, particularly APC, seem to be the most effective in managing well-defined bleeding from radiation proctitis and may have some impact on other symptoms as well.[70] Although focal ablative tools such as lasers, contact probes, and APC may be helpful when bleeding occurs from limited number of identifiable ectatic vessels, a larger field of arteriovenous malformations or oozing may be more difficult to control. Methods allowing broader fields of treatment, such as formalin instillation, or the newer methods of RFA and cryotherapy may therefore theoretically be advantageous in this setting. In particular, the unexpected finding of neosquamous epithelialization with RFA may have further advantages in preventing recurrent symptoms[63] and needs to be further evaluated in larger randomized trials.

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