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Publication Date
2017-07-25

Peer reviewed

The Role of Fluorescent Angiography in Anastomotic Leaks

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ABSTRACT

Anastomotic leaks following colorectal anastomosis has substantial implications including increased morbidity, longer hospitalization, and reduced overall survival. The etiology of leaks includes patient factors, technical factors, and anastomotic perfusion. An intact anastomotic blood supply is especially crucial in the physiology of anastomotic healing. To date, no established intraoperative methods have been developed that reliably and reproducibly identify and prevent leak occurrence. Recently, fluorescent angiography (FA) with indocyanine green (ICG) has emerged as an innovative modality for intraoperative perfusion assessment. ICG-FA can be performed before or after intestinal resection or, alternatively, after creation of the anastomosis. Angiographic assessment with near-infrared camera filters allows determination of perfusion adequacy, guiding additional intestinal resection and anastomotic revision. Early clinical experiences with ICG-FA demonstrated safety and feasibility. Large, multi-center prospective trials, such as the Perfusion Assessment in Laparoscopic Left-Sided/Anterior Resection Study (PILLAR II), demonstrated ease of use with remarkably low anastomotic leak rates after ICG-FA-guided intraoperative revision. Current randomized control trials featuring utilization in ICG-FA in low anterior resection are currently underway and will further clarify the role of ICG-FA in leak identification and prevention. Apart from colorectal surgery, FA has also been successfully employed in other surgical disciplines such as plastic surgery, vascular surgery, foregut surgery, urology, and gynecology.

Introduction

Anastomotic leak (AL) is a devastating complication after colorectal surgery with substantial implications toward morbidity, hospital cost, and survival. In the international, multicenter colorectal cancer laparoscopic or open resection (COLOR II) trial, incidence of anastomotic leak following colorectal anastomosis is cited at approximately 10–13% in open and laparoscopic proctectomy; variability in reported leak rates in current literature are primarily due to a prior lack of uniformity in definition.[1,2] The International Study Group of Rectal Cancer has subsequently defined AL as an intestinal defect in either a suture or staple line leading to communication between the intraluminal and extra-luminal compartments. Three primary grades are defined for AL: Grade A: leaks without change in patient management, Grade B: leaks requiring intervention with reoperation, and Grade C: leaks requiring laparotomy.[3]

Multiple studies have illustrated the deleterious consequence of AL. Cases of leak defined as Grade B and C have been associated with increased overall number of days spent in the intensive care unit.[3] AL has been independently associated with multiple postoperative complications including acute renal/respiratory failure, urinary tract infection, deep venous thrombosis, and myocardial infarction.[4] Cases of AL after colorectal resection have demonstrated higher rates of postoperative surgical site infection, 1.3 times higher rates of 30-day readmission, an average increase in length of index hospitalization by 7.3 days, and an average increase in hospital cost by approximately $24,129 per case of AL.[5] In cases of mid-to-low rectal cancer that underwent sphincter-preserving operations, development of AL has been associated with unfavorable cancer-relapse survival and overall survival.[6] As evidenced by the significant burden AL poses on healthcare, it is crucial that we establish diagnostic methods that allow early identification and management of leaks and, ideally, methods to predict and prevent leaks.

Figure 1. PINPOINT® Endoscopic Fluorescence Imaging System.

Etiology of Anastomotic Leaks

The etiology of AL is multifactorial including patient factors, technical factors, and perfusion of the anastomosis. Major patient factors associated with leaks include male sex, level of the anastomosis, tobacco use, preoperative radiation, and the presence of adverse intraoperative events.[4,7,8] These patient characteristics are markers of a highrisk anastomosis. Additional technical factors that contribute include anastomotic tension, poor tissue apposition, local spillage, and low pelvic anastomosis. Finally, adequate tissue perfusion is requisite for prevention of anastomotic leaks. Unfortunately, surgeons generally demonstrate poor subjective accuracy when attempting to predict leaks; Karliczek at al. demonstrated inferior sensitivity (62%) and specificity (52%) when surgeons attempted to predict leaks through global clinical risk assessment alone, with substantially low overall predictive value (11%).[9] Moreover, intraoperative endoscopic evaluation of rectal anastomoses has yet to demonstrate a substantial change in leak rate.[10] This warrants the development of alternative and supplemental diagnostic tools to assist in the prediction of leaks.

It has been widely understood that an intact blood supply is crucial in the physiology of anastomotic healing. Local tissue oxygenation secondary to vascular perfusion has been found to be crucial in establishing anastomotic viability.[11,12] Moreover, contemporary colorectal literature has advocated high pedicle ligation in achieving optimal oncological yield.[13] This high ligation of the inferior mesenteric artery and/or vein may be necessary for reach of the proximal colonic segment in colorectal anastomosis, but may result in reduced left colonic perfusion, requiring greater dependency on collateral circulation from the marginal artery of Drummond. In fact, high ligation of the inferior mesenteric artery prior to resection and anastomosis has been demonstrated to be an independent predictor of AL.[14] Given the aging population currently undergoing colorectal surgery, comorbid vascular disease must also be considered when estimating sufficiency of intestinal blood supply.

Validation of perfusion has been attempted through multiple techniques. Scanning laser Doppler can identify erythrocyte frequency change and can subsequently determine perfusion. Vignali et al. utilized Doppler flowmetry to measure proximal and distal stump oxygen content after resection in patients undergoing stapled straight anastomoses to the rectum. Substantial reduction in proximal and distal intestinal tissue oxygenation was illustrated in anastomoses that developed leaks. In this study, anastomotic revision was performed if the Doppler revealed tissue oxygenation to be less than 50%. Despite employing this parameter, the cohort still demonstrated a largely unchanged clinical leak rate (14.5%).[15] Thus, despite establishing a meaningful correlation between tissue oxygenation and leaks, Doppler flowmetry was unable to substantiate a significant clinical benefit. Visible light spectroscopy examines scattering and absorption of oxy/deoxyhemoglobin. In small pilot studies, visible light spectroscopy has verified reduction in tissue oxygenation and association with AL.[16,17] Ultimately, however, none of these techniques have been readily adopted largely due to reproducibility, ease of use, and feasibility in both open and laparoscopic techniques.[10,18]

Introduction to Fluorescent Angiography

Fluorescent angiography (FA) has recently emerged as an innovative new modality that provides feasible intraoperative assessment of colorectal perfusion, thereby guiding appropriate resection and anastomosis. This technology utilizes an exogenous fluorophore, indocyanine green (ICG). ICG is a sterile, water soluble, tricarbocyanine molecule that rapidly binds to plasma proteins after administration, permitting real-time evaluation of organ perfusion.[19] ICG remains intravascular with minimal interstitial leakage, making it an excellent choice for perfusion angiography; the liver clears it in approximately three to five minutes. ICG demonstrates an excellent safety and tolerability profile, with extremely rare incidence of side effects such as hypotension, tachycardia, dyspnea, anaphylactic shock, and urticaria.[20,21] After absorbing near-infrared (NIR) light between 800–810 nm, ICG emits light at 830 nm that can be captured by utilizing a near-infrared camera filter. This wavelength additionally permits deep tissue penetration with visualization of deeper structures. Preliminary animal model experimentation demonstrated that FA accurately represented hypoperfusion in perfused pig colons after segmental arterial resection.[22] Multiple NIR systems are currently utilized for FA; these include PINPOINT® (Novadaq Technologies Inc., Mississauga, Canada) (Fig. 1), Firefly™ (Intuitive Surgical Inc., Sunnyvale, California), SPY Elite® Kit (LifeCell Corporation, Bridgewater, New Jersey), IC-View© (Pulsion Medical Systems AG, Munich, Germany), and D-Light (Storz, Tuttlingen, Germany). The da Vinci® Si Surgical System (Intuitive Surgical Inc., Sunnyvale, California) features a robotic console that utilizes the FireFly™ system.[10,21]

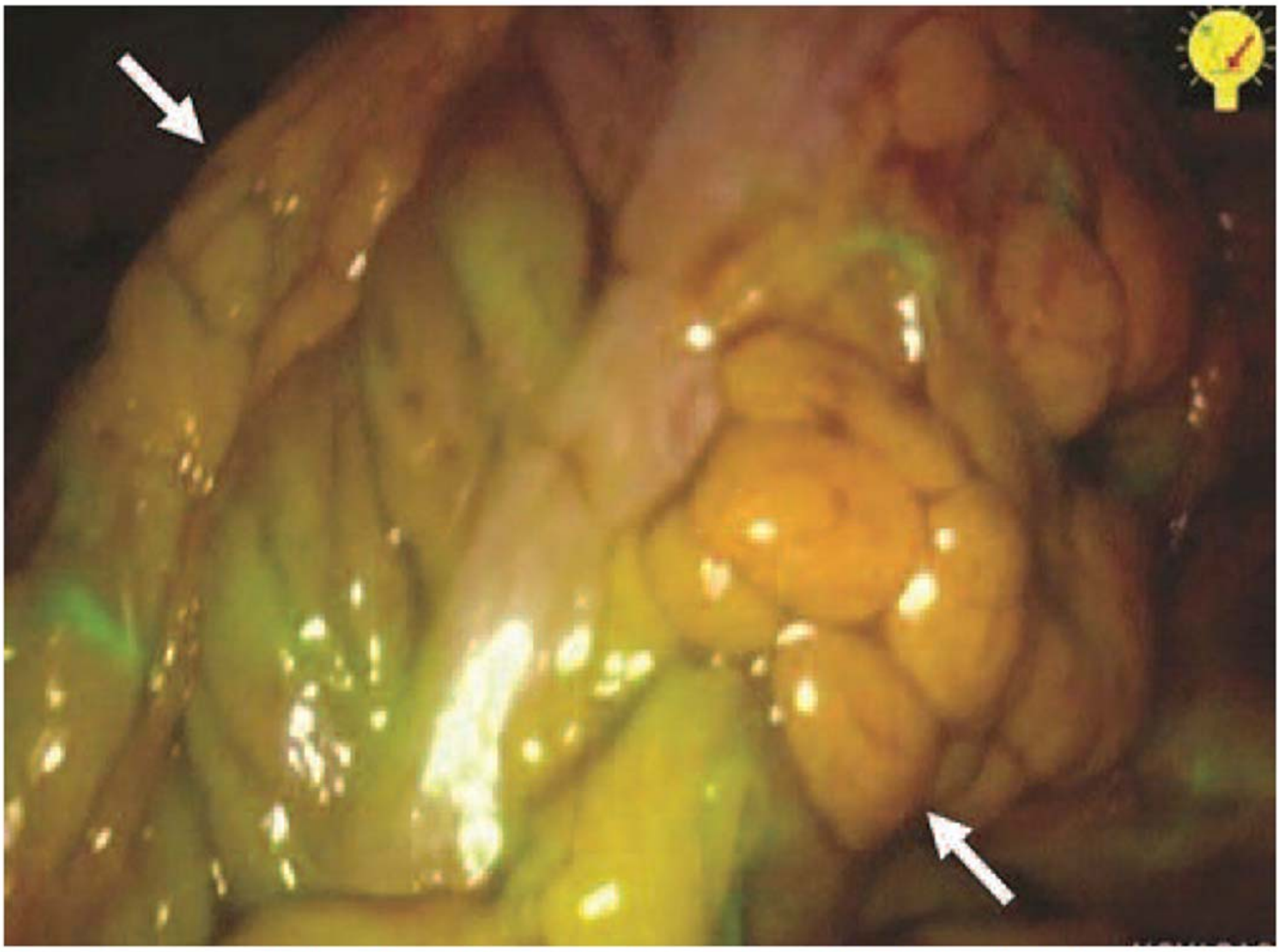

Figure 2. Laparoscopic view of a mobilized colon after vascular pedicle ligation, but prior to resection. Near infrared indocyanine green fluorescent angiography allows demarcation (white arrows) of the vascular supply, assisting in identification of a transection point.

Operative Utilizations

ICG FA is typically utilized after complete colorectal mobilization, division of the blood supply, and distal intestinal transection. Studies that have examined FA in left colectomy first complete splenic flexure mobilization, medial to lateral dissection of the descending colon, ligation of the vascular pedicle (inferior mesenteric artery and/or vein), and distal division of the colon.[19] In similar fashion, utilization of FA in cases of low anterior resection first mandates total mesorectal dissection to the pelvic floor with division of the rectum below the pathology with complete mesenteric division of the descending and sigmoid colon.[21] The surgeon has the option of assessing perfusion of the intestine either before or after resection. Visualization of the proposed intestinal transection point is performed with NIR imaging on either an open or laparoscopic basis (Fig. 2). Based on the adequacy of perfusion on FA, the surgeon can elect to proceed with the proposed transection point for subsequent anastomosis or extend the proposed resection proximally and/or distally based on adequacy of flow. Alternatively, resection of intestinal segment can be initially performed with subsequent angiographic examination of

the proximal and distal intestinal segments. Different ICG administration regimens have been utilized to illustrate vascular perfusion. Boni et al. documented effective FA with weight based bolus doses of ICG at 0.2 mg/Kg.[19,21] After FA, standard air leak testing of the anastomosis can be performed within the preferences of the operating surgeon. After creation of the anastomosis, repeat ICG bolus administration may be performed with repeat perfusion assessment (Fig. 3). Intraluminal FA examination has also been performed by means of proctoscopy; this permits additional confirmation of viability by thorough examination of the peri-anastomotic mucosa (Fig. 4).[8]

EARLY CLINICAL TRIALS WITH FLUORESCENT ANGIOGRAPHY

Adoption of FA has gradually increased over the past decade as demonstrated through multiple single and multi-institutional trials. Moreover, utilization of this technique has been illustrated in both colectomy and proctectomy. Kudzus et al. detailed an early retrospective study that examined laser FA in patients undergoing colorectal resection for malignancy. Over a five-year period (1998–2003), patients operated with FA were matched against a control population on the basis of age, tumor stage, resection type, anastomosis technique, stoma utilization, and intraoperative transfusion requirements. Kudzus and colleagues included cases of right, left, and segmental colon resection. Of the 201 patients in the ICG-FA cohort, 13.9% required revised resection into better-perfused tissue. Patients treated with FA demonstrated a 4% overall reduction in surgical revision for AL during the postoperative course ($p < 0.05$).[23] This reduction in reoperation for AL was further demonstrated in critical subgroups, including patients over the age of 70 and cases of hand-sewn anastomosis. Length of stay was substantially reduced as well in the FA cohort. In similar fashion, Boni et al. retrospectively examined implementation of FA in 107 patients undergoing colorectal resection, demonstrated 100% feasibility, yielding a 3.7% anastomotic revision rate with no episodes of anastomotic leaks.[19]

It has been well documented that anastomosis below the peritoneal reflection has a substantial increase in anastomotic leak rate; a multicenter study by Kockerling et al. revealed a 2.9% leak rate in colo-colonic anasto-moses compared to 12.7% in colorectal anastomoses.[24] Jafari and colleagues illustrated the applicability of FA to proctectomy as well. In this retrospective case control analysis, patients undergoing hybrid laparoscopic/robotic proctectomy for rectal cancer underwent intraoperative ICG-FA with the Firefly™. Nineteen percent of the ICGFA group underwent revision of the colonic transection point to a more proximal (well-perfused) location. Compared to the control group that yielded a leak rate of 18%, the FA cohort experienced a substantially lower rate of AL at 6%. Notably, the median level of anastomosis was lower in the FA cohort at 3.5 cm compared to the control group (5.5 cm), further demonstrating the benefit of FA in this higher-risk ultra-low rectal cancer subset.[21]

Kin and colleagues demonstrated equivocal AL outcomes with FA. In this retrospective study case matched by anastomotic level, sex, age, and use of a diverting ileostomy, 5% of patients who received intraoperative FA underwent additional colon resection prior to anastomosis. The FA cohort experienced a leak rate of 7.5% compared to the control group (6.4%), =0.67). Kin et al. conceded multiple notable limitations including the inability to control for confounding in a retrospective study as well as the small sample that was inadequate to detect a 1–2% difference in leak rates at 80% power.[25] This body of literature has made it apparent that larger prospective trials will be necessary to definitively demonstrate the impact of FA. Kin et al. conceded multiple notable limitations including the inability to control for confounding in a retrospective study as well as the small sample that was inadequate to detect a 1–2% difference in leak rates at 80% power.[25] This body of literature has made it apparent that larger prospective trials will be necessary to definitively demonstrate the impact of FA.

Prospective Clinical Studies in Fluorescent Angiography

The Perfusion Assessment in Laparoscopic Left-Sided/Anterior Resection (PILLAR II) study is the largest multicenter prospective trial to date examining the benefits of ICG-FA. Spanning over 11 centers in the United States, PILLAR II employed ICG-FA at two critical operative points: first, the point of proximal bowel transection immediately preceding anastomosis and second, endoscopic examination of the intestinal mucosa after completion of the rectal anastomosis. PILLAR II authors reported a 99% success rate with FA with excellent feasibility and operator use despite the absence of any training cases.[18] Mean level of anastomosis was approximately 10 $\pm$ 4 cm with high ligation of the inferior mesenteric artery performed in 61.9% of cases. ICG-FA led to change in operative approach approximately 8% (11/139 cases) of the time, most commonly involving the proximal colonic transection point. The entire cohort demonstrated a 1.4% anastomotic leak rate, with no occurrence of AL among the 11 revised cases.[8] Had these 11 cases not undergone revision and subsequently developed leaks, the cohort AL rate would have increased to 9.3%; this illustrates a speculated 7.9% absolute risk reduction through FA. In a smaller single-institution prospective trial by Kawada et al. featuring 68 patients, ICG-FA instigated change in the proximal transection margin by 5 mm in 26.5% of the cohort. In 4.4% of the study group, greater than 50 mm of proximal intestinal revision was indicated by ICG. Kawada and colleagues again demonstrated a low rate of AL at 4.5%, substantially impacted by revision in nearly 30% of cases.[18,26] In another prospective multicenter series, Hellan et al. equivalently described a 40% change in proximal transection location with FA, yielding a leak rate of 5%.[27]

In January 2015, enrollment was initiated in the first randomized, controlled parallel multi-center study examining ICG-FA, entitled: “Perfusion Outcomes with PINPOINT® Near Infrared Fluorescence Imaging in Low Anterior Resection (PILLAR IIII)”. Targeted toward high risk, low anterior resection for rectal and rectosigmoid cancer, PILLAR III has an estimated enrollment of 500–1000 patients in an adaptive design study with a planned study completion date of July 2017. The primary outcome will be a measurement of anastomotic leak rate in experimental and control cohorts; secondary outcomes will include evaluating intraoperative utility and feasibility with ICG-FA and estimating rates of postoperative abscess requiring surgical management.[28] In similar fashion, James et al. have discussed a planned multicenter randomized control trial undertaken over a five-year period in the United Kingdom and other major European centers that is similarly intended to study differences in AL rates with FA. To sufficiently power the study to demonstrate a 33% reduction in AL with FA, James and colleagues have planned to enroll 732 patients in each study arm.

Additional topics revolving around ICG-FA use in colorectal surgery may require further research and clarification. Foremost, an optimal dose and timing for ICG prior to NIR angiography has yet to be clarified; our current body of literature has revealed multiple differing bolus regimens with no clearly established regimen that takes into account quicker washout in the vascular system.[19] Moreover, it is uncertain if slow uptake of ICG or altered washout rates are predictive of leaks in colorectal anastomoses, necessitating further research on this topic. Secondly, evaluation of ICGFA imaging relies on the interpretation of the surgeon that implicitly can bear a subjective component. Currently, no strictly objective quantification of signal intensity is present; however, preliminary

work on colonic segments from porcine models may build the foundation for analytic methods that can quantify peak signal intensity from ICG-enhanced NIR imaging.[29] Finally, further enhancement in FA devices, such as utilization in flexible endoscopes, may potentially offer additional diagnostic value as well as operator dexterity.

Outside of colorectal surgery, FA continues to be readily utilized in other surgical fields including foregut, gynecologic, and urological operations. Shimada et al. reviewed 40 cases of esophagectomy that underwent ICG-FA prior to reconstruction. The cohort itself featured both thoracic and cervical esophageal cancer, featuring gastric conduit, colonic interposition, and free jejunal graft. Based on appearance and strength of fluorescence after ICG bolus, additional venous or arterial anastomosis could be added at the surgeon’s preference. FA facilitated venous anastomotic revision in 12.5% of the study group. When adequate angiographic visualization of small vessel vasculature in the conduit was achieved, no cases of leaks were observed; conversely, a 16% (3/18) leak rate was demonstrated when adequate vasculature was not visualized.[30] Moreover, reduction in the ICG-fluorescence stream in a gastric conduit (compared to the greater curvature vasculature) has been significantly linked with increased incidence of intraoperative blood loss and anastomotic leaks ($p < 0.01$).[31] To date, no randomized control trials examining the role of ICG-FA in esophagectomy are published. Outside of AL prevention, substantial development in novel NIR-fluorescence modalities has already commenced. Iatrogenic ureteral injuries can be substantial intraoperative complications that occur with an incidence of 0.7–10% in conjunction with colorectal and gynecologic operations.[32] Recently, methylene blue fluorescence imaging has been described as an alternative to prophylactic ureteral stent placement. Yeung et al. documented 10 successful cases of intravenous methylene blue administration with subsequent ureter identification;

continued fluorescent signal was demonstrated for up to 75 minutes after injection.[33] Alternatively, Martinelli et al. reported on a novel use of ICG-NIR fluorescence in hysteroscopic sentinel lymph node mapping and harvesting. Their series yielded comparable detection rates to conventional radioactive tracer series.[34]

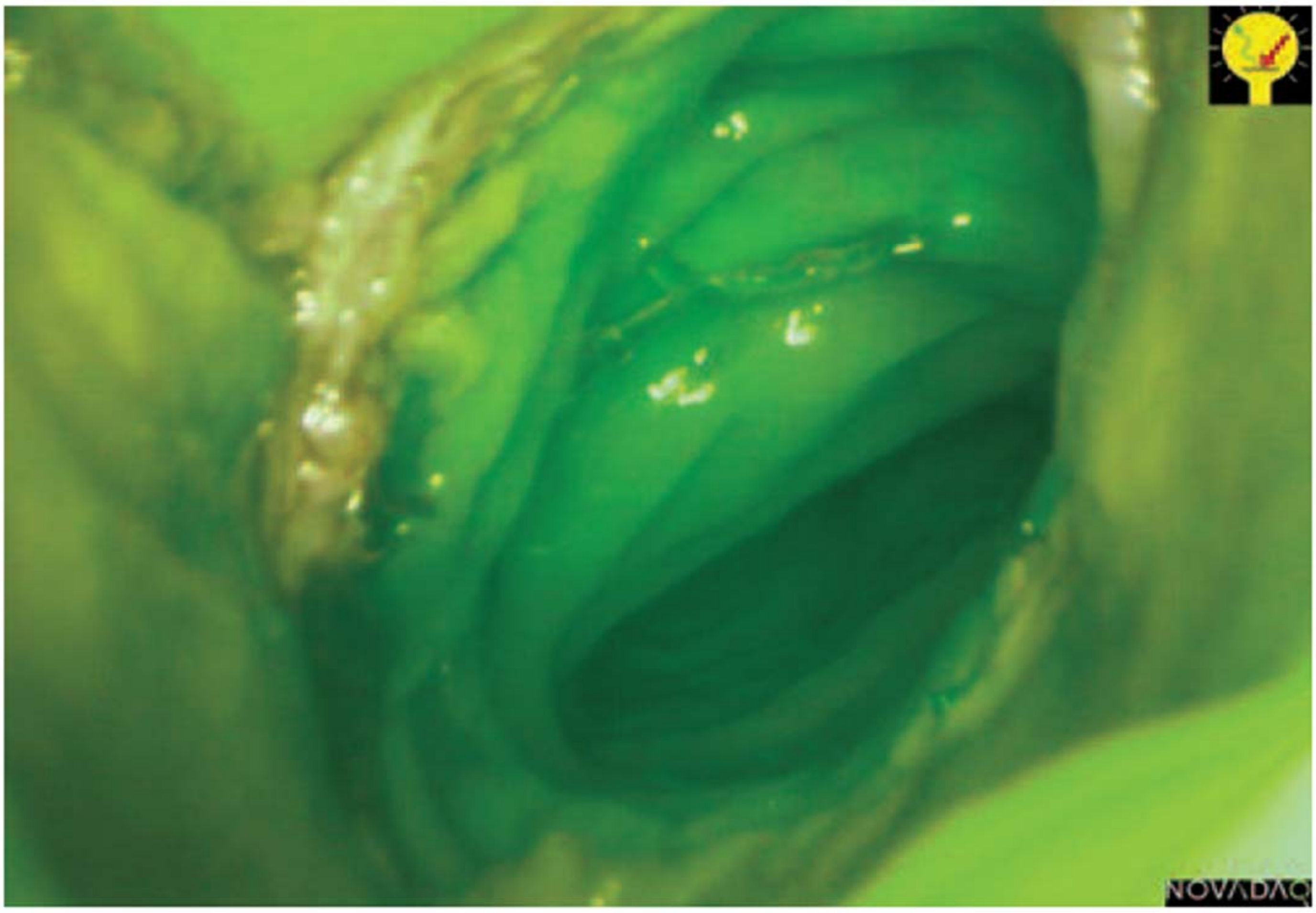

Figure 4. Intraluminal examination of a well-perfused anastomosis through proctoscopy with indocyanine green fluorescent angiography.

Conclusion

Given the substantial healthcare burden of intraoperative complications, FA represents an innovative, versatile technology with widespread application in multiple surgical domains. Colorectal leak itself is a complex diagnosis that is not readily identifiable by the surgeon; to date, no surgical method or intraoperative technology has proven to reliably and effectively identify AL. ICG-FA offers an *in-situ* intraoperative method that permits early identification of vascular conditions that lead to leaks, thereby offering early curative action. As evidenced by multiple large trials featuring colorectal resection, ICG-FA is a feasible, readily applicable utility by multiple institutions, guiding intraoperative revision in 3.7–13.9% of cases.[8,18,19,23,25] In the largest prospective series to date, PILLAR II, Jafari and colleagues demonstrated that ICG-FA guided resections yielded a leak rate of 1.4%, substantially lower than contemporary literature standards. Current randomized control trials such as PILLAR III will further clarify the benefits ICG-FA conveys toward leak identification and prevention
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Author Disclosures

Dr. Stamos is a principal investigator, speaker, and consultant for Novadaq Technologies Inc.

Dr. Jafari is a consultant for Medrobotics Corporation and receives an educational grant from Medtronic, Inc.

References

1. Shogan BD, Carlisle EM, Alverdy JC, et al. Do we really know why colorectal anastomoses leak? J Gastrointest Surg 2013;17(9): 1698–707.

2. van der Pas MH, Haglind E, Cuesta MA, et al. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. The Lancet Oncology 2013;14(3):210–8.

3. Rahbari NN, Weitz J, Hohenberger W, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery 2010; 147(3):339–51.

4. Kang CY, Halabi WJ, Chaudhry OO, et al. Risk factors for anastomotic leakage after anterior resection for rectal cancer. JAMA surgery 2013;148(1):65–71.

5. Hammond J, Lim S, Wan Y, et al. The burden of gastrointestinal anastomotic leaks: an evaluation of clinical and economic outcomes. J Gastrointest Surg 2014;18(6): 1176–85.

6. Jager T, Nawara C, Neureiter D, et al. Impact of anastomotic leakage on long-term survival in mid-to-low rectal cancer. Der Chirurg; Zeitschrift Fur Alle Gebiete Der Operativen Medizen 2015;86(11):1072–82.

7. 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.

8. Jafari MD, Wexner SD, Martz JE, et al. Perfusion assessment in laparoscopic leftsided/anterior resection (PILLAR II): a multiinstitutional study. J Am Coll Surg 2015; 220(1):82–92.e1.

9. Karliczek A, Harlaar NJ, Zeebregts CJ, et al. Surgeons lack predictive accuracy for anastomotic leakage in gastrointestinal surgery. Int J Colorectal Dis 2009;24(5):569–76.

10. James DR, Ris F, Yeung TM, et al. Fluorescence angiography in laparoscopic low rectal and anorectal anastomoses with pinpoint perfusion imaging—a critical appraisal with specific focus on leak risk reduction. Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland 2015;17 Suppl 3:16–21.

11. Kingham TP, Pachter HL. Colonic anastomotic leak: risk factors, diagnosis, and treatment. J Am Coll Surg 2009;208(2):269–78.

12. Frasson M, Granero-Castro P, Ramos Rodriguez JL, et al. Risk factors for anastomotic leak and postoperative morbidity and mortality after elective right colectomy for cancer: results from a prospective, multicentric study of 1102 patients. Int J Colorectal Dis 2016;31(1):105–14.

13. Al-Asari SF, Lim D, Min BS, et al. The relation between inferior mesenteric vein ligation and collateral vessels to splenic flexure: anatomical landmarks, technical precautions and clinical significance. Yonsei Medical Journal 2013;54(6):1484–90.

14. Trencheva K, Morrissey KP, Wells M, et al. Identifying important predictors for anastomotic leak after colon and rectal resection: prospective study on 616 patients. Ann Surg 2013;257(1):108–13.

15. Vignali A, Gianotti L, Braga M, et al. Altered microperfusion at the rectal stump is predictive for rectal anastomotic leak. Dis Colon Rectum 2000;43(1):76–82.

16. Hirano Y, Omura K, Tatsuzawa Y, et al. Tissue oxygen saturation during colorectal surgery measured by near-infrared spectroscopy: pilot study to predict anastomotic complications. World J Surg 2006;30(3): 457–61.

17. Karliczek A, Benaron DA, Baas PC, et al. Intraoperative assessment of microperfusion with visible light spectroscopy for prediction of anastomotic leakage in colorectal anastomoses. Colorectal Disease: the official journal of the Association of Coloproctology of Great Britain and Ireland 2010;12(10): 1018–25.

18. Mizrahi I, Wexner SD. Clinical role of fluorescence imaging in colorectal surgery a review. Expert Rev Med Devices 2016:1–8.

19. Boni L, David G, Mangano A, et al. Clinical applications of indocyanine green (ICG) enhanced fluorescence in laparoscopic surgery. Surgical Endoscopy 2015;29(7): 2046–55.

20. Alander JT, Kaartinen I, Laakso A, et al. A review of indocyanine green fluorescent imaging in surgery. Int J Biomed Imaging 2012; 940585.

21. Jafari MD, Lee KH, Halabi WJ, et al. The use of indocyanine green fluorescence to assess anastomotic perfusion during robotic assisted laparoscopic rectal surgery. Surgical Endoscopy 2013;27(8):3003–8.

22. Carus T, Dammer R. Laparoscop fluorescence angiography with indocyanine green to control the perfusion of gastrointestinal anastomoses intraoperatively. Surg Technol Int 2012;22:27–32.

23. Kudszus S, Roesel C, Schachtrupp A, et al. Intraoperative laser fluorescence angiography in colorectal surgery: a noninvasive analysis to reduce the rate of anastomotic leakage. Langenbecks Arch Surg 2010;395(8):1025–30.

24. Kockerling F, Rose J, Schneider C, et al. Laparoscopic colorectal anastomosis: risk of postoperative leakage. Results of a multicenter study. Laparoscopic Colorectal Surgery Study Group (LCSSG). Surgical Endoscopy 1999; 13(7):639–44.

25. Kin C, Vo H, Welton L, et al. Equivocal effect of intraoperative fluorescence angiography on colorectal anastomotic leaks. Dis Colon Rectum 2015;58(6):582–7.

26. Kawada K, Hasegawa S, Wada T, et al. Evaluation of intestinal perfusion by ICG fluorescence imaging in laparoscopic colorectal surgery with DST anastomosis. Surgical Endoscopy 2016; doi:10.1007/s00464-0165064-x. [Epub ahead of print]

27. Hellan M, Spinoglio G, Pigazzi A, et al. The influence of fluorescence imaging on the location of bowel transection during robotic left-sided colorectal surgery. Surgical Endoscopy 2014;28(5):1695–702.

28. Health USNIo. A Study Assessing Perfusion Outcomes with PINPOINT® Near Infrared Fluorescence Imaging in Low Anterior Resection (PILLAR III). 2016 (accessed 12/16/2016 2016).

29. Diana M, Agnus V, Halvax P, et al. Intraoperative fluorescence-based enhanced reality laparoscopic real-time imaging to assess bowel perfusion at the anastomotic site in an experimental model. Br J Surg 2015;102(2): e169–76.

30. Shimada Y, Okumura T, Nagata T, et al. Usefulness of blood supply visualization by indocyanine green fluorescence for reconstruction during esophagectomy. Esophagus: official journal of the Japan Esophageal Society 2011;8(4):259–66.

31. Koyanagi K, Ozawa S, Oguma J, et al. Blood flow speed of the gastric conduit assessed by indocyanine green fluorescence: New predictive evaluation of anastomotic leakage after esophagectomy. Medicine 2016;95(30):e4386.

32. Verbeek FP, van der Vorst JR, Schaafsma BE, et al. Intraoperative near infrared fluorescence guided identification of the ureters using low dose methylene blue: a first in human experience. J Urol 2013;190(2): 574–9.

33. Yeung TM, Volpi D, Tullis ID, et al. Identifying Ureters In Situ Under Fluorescence During

Laparoscopic and Open Colorectal Surgery. Ann Surg 2016;263(1):e1–2.

34. Martinelli F, Ditto A, Bogani G, et al. Laparoscopic Sentinel Node Mapping in Endometrial Cancer After Hysteroscopic Injection of Indocyanine Green. J Minim Invasive Gynecol 2017; 24(1):89–93.