34 ICG Image-Guided Surgery with the Assessment for Anastomotic Safety

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34.1 Introduction/Background

The practice of gastrointestinal anastomosis in humans has existed since the early 1700s, when Ramdohr, surgeon to the Duke of Brunswick, successfully utilized an invagination technique to treat a complete transection of the intestine in a soldier and in the resection of an incarcerated hernia [1, 2]. Anastomosis was highly controversial at the time, however, with many surgeons holding to the belief that injuries to the bowel were best treated by ostomy or by allowing the body to heal without intervention [1]. It was not until 1826 when Antoine Lembert described the importance of serosal apposition that bowel anastomosis became more widespread [3]. In the 200 years since, gastrointestinal anastomosis has become routine in the treatment of conditions ranging from trauma to cancer. While far safer and more successful today than in prior centuries, anastomotic leak remains one of the most feared complications of any anastomotic procedure. Many factors contribute to this complication, from patient-related factors such as nutritional status or diabetes to procedural details such as blood loss or location of the anastomosis. One contributor that has been studied recently is the vascular supply to the anastomosis. As technology has evolved, our ability to see and measure blood flow intraoperatively has improved, particularly with near-infrared imaging and fluorophores such as indocyanine green dye. In this chapter, we will explore the history of gastrointestinal anastomosis, consequences of anastomotic leak, and techniques for ensuring anastomotic integrity including fluorescence angiography with indocyanine green.

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34.1.1 History of GI Anastomosis

Ramdohr's technique from 1730 included inserting one end of the severed bowel into the other and securing with a single suture that was then brought out of the abdomen to secure the bowel to the abdominal wall and allow for future removal of the suture [1]. Modifications of this technique over the next century continued to be minimally effective owing largely to the practice of approximating the mucosa to the serosa [1]. After Lembert's description of serosal apposition, the next major development affecting the success of bowel anastomosis was Sir Joseph Lister's introduction of aseptic silk suture and the application of the concept of aseptic surgery to

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intestinal wounds in the 1860s [1]. Other major innovations and breakthroughs over the next 150 years include improved understanding of wound healing, the development of surgical stapling devices, the advent of endoscopy and laparoscopic surgery, and the debut of the surgical robot [4]. The foundational tenets have remained since those early times, though, of minimizing tension, aseptic technique, and approximation of appropriate layers of tissue.

In the modern era, emphasis has shifted from surgical innovation to the practice of evidence-based medicine and the analysis and application of large amounts of data. Anastomotic leak is perhaps the most feared complication following gastrointestinal surgery and has thus been studied extensively. One of the difficulties in studying anastomotic leak, however, is heterogeneity in the definition of anastomotic leak. In 2001, Bruce et al. published a systematic review examining definitions of anastomotic leak in the literature and found 13 different definitions of upper gastrointestinal leak and 29 different definitions of lower gastrointestinal leak, and that a 1991 proposal for a standard definition by the UK Surgical Infection Study Group ("the leak of luminal contents from a surgical join between two hollow viscera. The luminal contents may emerge either through the wound or at the drain site, or they may collect near the anastomosis, causing fever, abscess, septicaemia, metabolic disturbance and/or multiple-organ failure. The escape of luminal contents from the site of the anastomosis into an adjacent localized area, detected by imaging, in the absence of clinical symptoms and signs should be recorded as a subclinical leak") was not adopted in any other studies [5, 6]. In 2010, the International Study Group of Rectal Cancer proposed an alternative definition, "a defect of the intestinal wall at the anastomotic site (including suture and staple lines of neorectal reservoirs) leading to a communication between the intra- and extraluminal compartments," which was the foundation for the International Multispecialty Anastomotic Leak Global Improvement Exchange definition [7, 8]. Unfortunately, this definition has also rarely been used in the published literature. This prompted Daniel et al. to attempt to find a consensus definition using the Delphi method, but only 7/15 (47%) of scenarios achieved consensus [9]. While this underlines one of the ongoing difficulties in understanding gastrointestinal anastomosis and anastomotic leak, it does not invalidate much of what has been shown.

There have been many studies that have identified and investigated various factors that are associated with and may be predictive of anastomotic leak. This has obvious clinical implications, as determining which factors are associated with anastomotic leak may allow for improved preoperative risk assessment and counseling, potential correction of modifiable risk factors, or alterations in the surgical plan (such as making use of a protective stoma in a higher-risk anastomosis). There are a number of ways of classifying these risk factors, including patient-related versus procedure-related and modifiable versus nonmodifiable. Patient-related factors include prior radiotherapy, higher American Society of Anesthesiologists (ASA) score (>2), renal disease, obesity, diabetes, steroid treatment, preoperative leukocytosis, anemia, malnutrition, male sex, smoking, excess alcohol use, chemotherapy, prior abdominal surgery, anticoagulant use, and nonsteroidal anti-inflammatory (NSAID) use [8, 10–34]. Of these, NSAID use, anticoagulant use, excess alcohol intake, smoking, malnutrition, anemia, steroid treatment, and obesity could be considered modifiable. Procedure-related factors are need for blood transfusion/significant blood loss, duration of the operation, type of procedure/anastomosis (especially low rectal anastomosis), conduit used (for esophageal procedures), emergency operation, contamination of the operative field, intraoperative complications, and surgeon experience [8, 10, 12, 14–16, 19, 22, 23, 25, 26, 31, 33–38]. In this group, intraoperative complications, contamination, conduit used, duration of the operation, and blood loss/transfusion may be considered modifiable. Because of heterogeneity in definitions of anastomotic leak, there is debate about the significance of some of these risk factors. Those that are most agreed upon include male sex and low anastomosis for pelvic surgery, ASA class >2, smoking, immunosuppression, malnutrition, type of procedure, duration of sur-

Table 34.1 Risk factors for anastomotic leak

Risk factor type	*Potentially modifiable*	*Nonmodifiable*
Patient-related factors	*NSAID use* *Anticoagulant use* *Excess alcohol intake* *Smoking* *Malnutrition* *Anemia* *Steroid treatment* *Obesity*	*Prior radiation* *ASA class* *Renal disease* *Diabetes* *Leukocytosis* *Male sex* *Chemotherapy* *Prior abdominal surgery*
Procedure-related factors	*Intraoperative complications* *Contamination* *Conduit* *Duration of surgery* *Blood loss* *Perioperative transfusion*	*Type of procedure/anastomosis* *Emergency operation* *Surgeon experience*

gery, conduit used, emergency surgery, and blood loss/transfusion (Table 34.1).

34.1.2 Consequences of Anastomotic Failure/Leak

These many studies investigating possible risk factors for leak are driven by the potentially severe consequences of this complication. Of most importance, mortality is increased in patients experiencing anastomotic leak, with some studies showing rates above 20% [10, 23, 26, 39–41]. Additionally, in colorectal cancer cases, anastomotic leak is associated with increased local and distant recurrence as well as cancer-specific and all-cause long-term mortality [40–43]. Anastomotic leak is also associated with increased hospital length of stay (Frasson et al. found a median 23 days versus 7 days) and increased expense, with costs estimated at $95,550 versus $26,420 (USD) for standard inpatient costs [10, 23, 44]. Finally, patients who experience an anastomotic leak have lower quality of life and satisfaction with their quality of care and surgeon [45].

Morbidity related to anastomotic leak (and leak rates) varies depending on the operation performed and the type of anastomosis that is made. For esophagectomy, leak rates vary from 1.6% to 53%, and the leak rate is significantly higher for cervical compared to thoracic anastomosis (a meta-analysis by Biere et al. showed an odds ratio [OR] of 3.43) [46, 47]. It is still considered a viable option, however, given the higher morbidity associated with an intrathoracic leak, which may lead to severe infectious complications such as mediastinitis, empyema, or pneumonia. Colorectal leak rates similarly depend on location and type of anastomosis, with low pelvic (distal colorectal, coloanal, or ileoanal) rates between 1% and 20%, colo-colonic rates between 0% and 4%, and ileocolic rates between 0.02% and 7% [40, 48]. Outside of low pelvic anastomoses, several studies have shown highest leak rates for colo-colonic anastomosis, such as may be performed for a transverse colectomy, or segmental left colectomy [40, 49]. The risk associated with ileocolic anastomosis compared to other anastomoses is less well-established, with some recent studies showing higher leak rates than high colorectal anastomoses and others showing no difference or even lower leak rates [16, 31, 40, 49]. The sequelae depend largely on the severity of the leak, with more severe leaks often requiring takedown of the anastomosis and permanent stoma [39].

34.1.3 Techniques for Ensuring Anastomotic Integrity and Avoiding Leak

Considering the numerous potential adverse effects of anastomotic leak and the number of nonmodifiable risk factors that are associated with leak, much thought has been devoted to possible

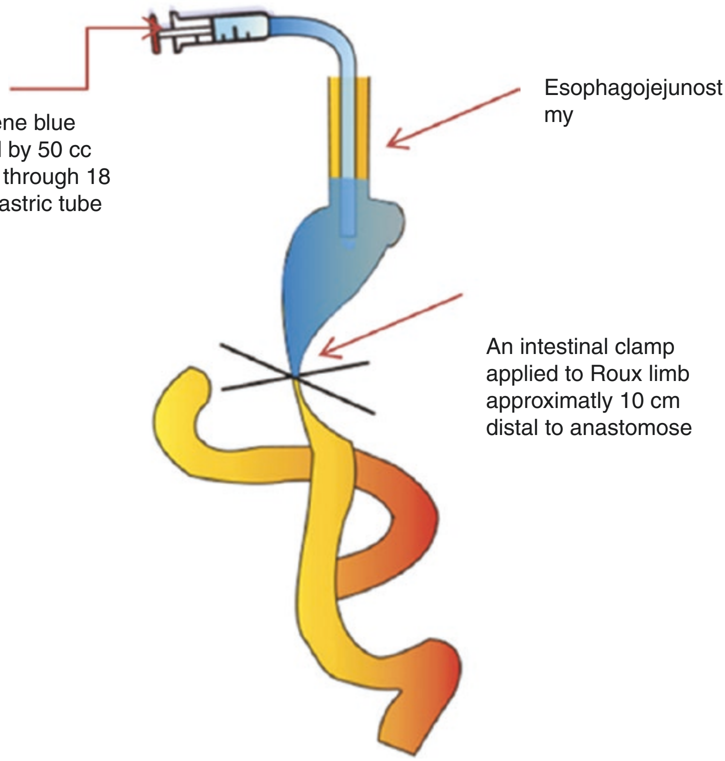

Fig. 34.1 Schematic representation of technical method of methylene blue test [56]

techniques for intraoperative assessment of the anastomosis and avoidance of breakdown. It is natural for surgeons to rely on their experience and intuition in assessing an anastomosis. One of the longest-standing practices for evaluating an anastomosis and/or evaluating the bowel prior to dividing or creating an anastomosis is visual inspection and palpation. This includes ensuring adequate perfusion by dividing the bowel where it does not appear dusky, by palpating for a pulse in the mesentery, and by watching for sufficient bleeding from the cut edge. It also includes searching the anastomosis for any visible or palpable defects, assessing the tension on the anastomosis, and ensuring the integrity of the doughnuts left from circular staple fires. Unfortunately, surgeons' impression of the risk of anastomotic leak has been shown to be unreliable [50].

Another method that has been studied is the air leak test (ALT). In this technique for colorectal surgery, the newly created anastomosis is submerged under irrigation fluid, the proximal bowel is occluded, and the distal bowel is insufflated by endoscope. For a foregut procedure, the bowel distal to the anastomosis would be occluded and proximal bowel insufflated. Lack of an airtight anastomosis is proven by escape of insufflation into the irrigant appearing as bubbles. This allows for immediate revision or repair by oversewing the area of leak and additional protection in colorectal surgery by proximal diversion if that was not previously planned. In some studies, positive ALT in colorectal anastomosis (indicating air leak was present) has been associated with higher rates of clinical leak despite repair than an initially negative test [51, 52]. Allaix et al. found no clinical leaks in patients who had repair of an anastomosis following a positive ALT, though, and multivariate analysis showed ALT was independently associated with reduced rates of clinical leak [53]. Repair of air leak in esophagojejunostomy has also been shown to be effective at preventing future clinical leaks, though some patients with negative leak tests will go on to develop anastomotic leak [54].

Testing the anastomosis by distention of the lumen with dilute methylene blue dye rather than air has also been utilized (Figs. 34.1 and 34.2). Studies of both colonic and esophagojejunal

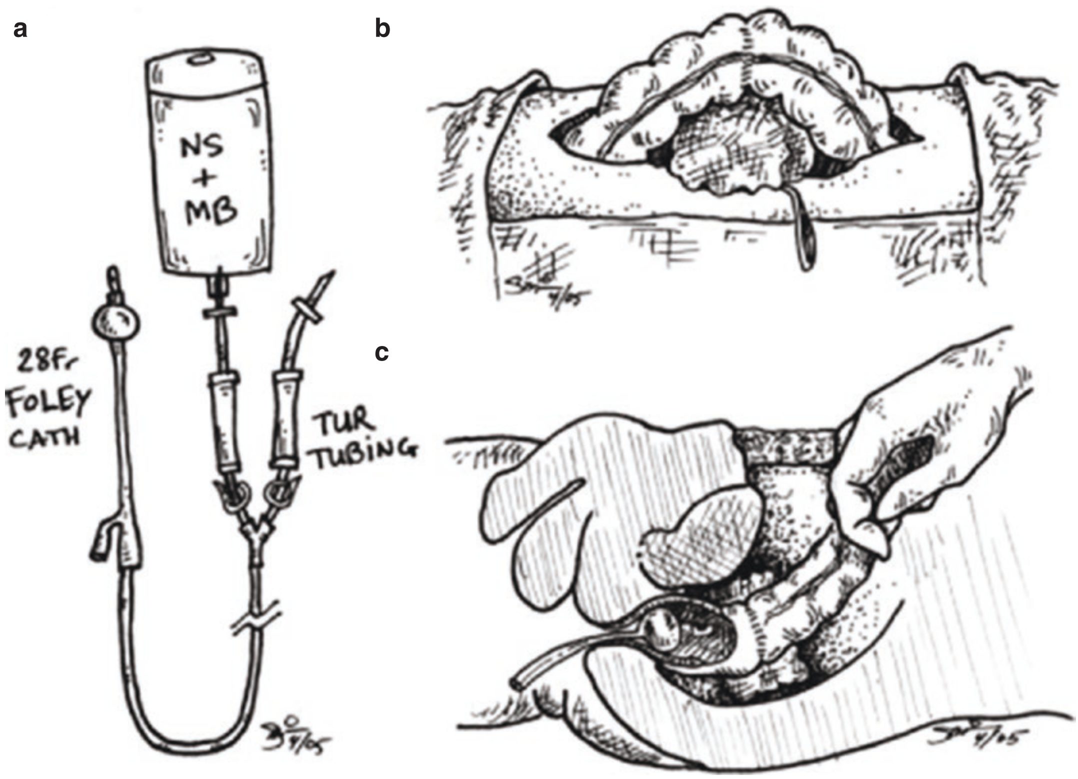

Fig. 34.2 MBE apparatus and method. (**a**). Apparatus for methylene blue enema. (**b**). Anastomosis with gauze pads beneath: (**c**). Cross-sectional view (pelvis) [55]

anastomoses have shown no clinical leaks following repair of anastomoses with a positive methylene blue dye test, though patients with negative tests may still develop leak [55, 56].

Finally, intraoperative endoscopy is another common procedure for anastomotic evaluation. It has the potential to identify leak, bleeding, a narrow or nonpatent anastomosis, or poor perfusion. Its efficacy in preventing postoperative anastomotic leak or bleeding is unclear, however [57–59].

One frustration for surgeons is the persistence of postoperative anastomotic leak even when intraoperative testing is negative. It has been hypothesized that this may be due to inadequate perfusion to the anastomosis to allow healing, with subsequent breakdown [60, 61]. This highlights the importance of ensuring a good blood supply while creating the anastomosis. While there are several possible ways to do this, one that has had encouraging early results is fluorescence angiography with indocyanine green dye (ICG).

34.2 Indocyanine Green in Perfusion Assessment

ICG is a sterile, water-soluble, essentially nontoxic medical dye that may be injected intravenously. It was first studied in humans in the 1950s and 1960s, where it was used to determine cardiac output and blood flow to the liver [62]. In ensuing decades, it was studied extensively in ophthalmic imaging, where its safety was confirmed [63, 64]. At the turn of the century, its use remained largely limited to ophthalmologic applications and determination of hepatic function. As digital imaging resolution improved, it saw expanded use. It was approved for neurosurgical applications in the early 2000s and was then adopted in breast, general, and plastic surgery for evaluation of skin-flap viability; in vascular surgery in assessing peripheral vasculature for limb ischemia; in endocrine and head and neck surgery to detect and evaluate perfusion to parathyroid glands; in bariatric and foregut surgery and surgical oncology in assessing upper gastrointestinal anastomoses or predicting viability; in colorectal surgery in evaluating lower gastrointestinal anastomoses; in gynecologic surgery in imaging vaginal cuff perfusion; in various surgical subspecialties in lymphatic imaging; in general and hepatobiliary surgery in visualizing biliary system anatomy; and in cardiac surgery for intraoperative coronary artery bypass graft assessment [61, 65–80].

34.2.1 Background and Properties of ICG

ICG is a tricarbocyanine compound that may be reconstituted in aqueous solution for intravascular injection. It is relatively unstable in solution (it will degrade within approximately 10 hours) and sensitive to light, so it must be kept in crystal form with minimal exposure to light until it is ready for use. It circulates bound to plasma proteins (primarily albumin) with minimal leakage into the interstitium. It is cleared by the liver and excreted into bile with a half-life of approximately 3–4 minutes [81, 82]. This allows for multiple injections during a single procedure, with a second injection feasible within 15 minutes [81]. Standard doses are typically less than 2 mg/kg, and several studies have shown that a dose of 2.5 mg may be effective [75, 83, 84]. This is far less than the estimated LD_{50} of 50–80 mg/kg [81]. The primary exception to its excellent safety profile is in patients with an allergy to iodine. It is thought that there may be cross-reactivity with the iodide component of ICG that could lead to hypotension or even anaphylactic shock [85].

ICG absorbs near-infrared (NIR) light with a peak absorption at approximately 800 nm and emits a fluorescent signal at 832 nm that may be detected by various imaging modalities but is outside the spectrum of visible light. This is actually advantageous in its surgical application, as the near-infrared light that must be used to provoke fluorescence probes several millimeters deeper into tissues than white light [81]. There are currently a number of commercially available systems that may be utilized for NIR fluorescent imaging with ICG. These include Firefly® Fluorescent Imaging for the Da Vinci surgical robot (Intuitive Surgical, Inc., Sunnyvale, CA) and PINPOINT® endoscopic fluorescence imaging, Spy Elite®, and SPY Portable Handheld Imager (SPY-PHI)® for open surgery (Stryker, Kalamazoo, MI), among others.

34.2.2 Current Uses of Indocyanine Green in Perfusion Assessment

Many surgical fields have taken advantage of these properties of ICG for a variety of applications. A number of these are related specifically to the evaluation of blood flow or organ perfusion.

In neurosurgery, vascular surgery, and cardiac surgery, ICG angiography can be used to visualize vessels and identify potential anomalies, such as primary non-patency, aberrant anatomy, occlusions, or arteriovenous malformations [66]. In some cases, though, ICG angiography may not be as effective as other options. Because of the limited tissue penetration of near-infrared light and fluorescent signal, some important abnormalities might result in inadequate visualization of the vessels/blood flow. This could include severe atherosclerotic disease or an aneurysm sac filled with clot. Additionally, it may be used to assess perfusion in cases of peripheral arterial disease (PAD), critical limb ischemia (CLI), amputation, or trauma [65, 86–89]. This can predict the adequacy of treatment for PAD or CLI, determine the appropriate level for amputation and likelihood of healing, and guide treatment decisions in trauma.

This ability of ICG angiography to assess perfusion has found particular value in gastrointestinal surgery. Because adequate blood supply is essential to healing an initially watertight anastomosis and preventing breakdown and leak, various techniques have been employed by surgeons to attempt to ensure that there is sufficient blood flow to the area. These have included subjective and potentially unreliable indicators such as bowel wall color, bleeding at the cut edge of the

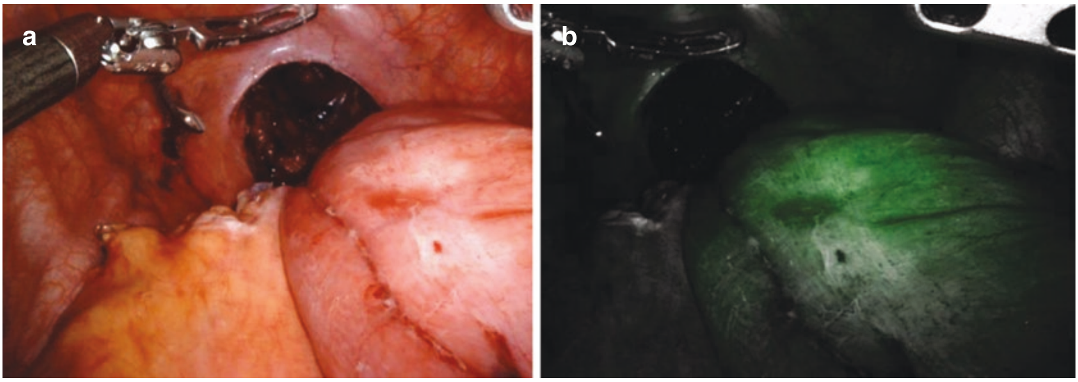

Fig. 34.3 Visualization of a J-pouch prior to anal anastomosis under white light (**a**) and near-infrared light with after injection of ICG (**b**)

bowel, the presence of detectable Doppler signals in the mesentery, and palpable pulses at vessels such as the marginal artery for distal colon/rectal resection or in the right gastroepiploic artery for esophagectomy [60, 90]. Some drawbacks are that these techniques may poorly reflect the microperfusion at the level of the anastomosis, might not reflect the perfusion from both the distal and proximal sides of the anastomosis, or might not be available with minimally invasive surgical technique. ICG angiography is quick, safe, and intuitive and may better represent the true perfusion to the anastomosis (Fig. 34.3).

34.2.2.1 Colorectal Surgery

ICG angiography has been studied in colorectal surgery since at least 2010, when Kudszus et al. published their retrospective study demonstrating an association between the use of ICG angiography and reduced leak rates and hospital length of stay [91]. Since that time, dozens of studies have been performed (Table 34.2), many of limited quality and often with conflicting results [60, 61, 70, 72, 91–121]. There are several studies of note, however, including recent randomized controlled trials.

PILLAR II

The Perfusion Assessment in Laparoscopic Left-sided/Anterior Resection (PILLAR II) study by Jafari et al. is one of the landmark studies on ICG angiography in colorectal surgery [70]. It was the first moderate-sized prospective, multicenter study on the topic, with 139 patients included. They included patients 18 or older undergoing laparoscopic or robot-assisted left colectomy or anterior resection with planned anastomosis 5–15 cm from the anal verge. They used the PINPOINT endoscopic fluorescence imaging system to assess perfusion just prior to bowel transection and transanally after the anastomosis was performed.

Their results showed successful fluorescence imaging in 98.6% of patients leading to an alteration in surgical plan/care in 7.9% of patients. This was primarily a change in planned transection line (6.5%) of patients, though transanal assessment necessitated takedown and revision of the anastomosis in one patient. There was also one patient in whom transanal fluorescence imaging confirmed adequate perfusion to the anastomosis after concerns arose under traditional methods of assessment. Notably, none of the patients who experienced a change in surgical plan developed anastomotic leak. Overall, two patients developed leak (1.4%) and both resolved with conservative treatment. This is far lower than previously reported leak rates.

There are some limitations to the study. There was a lack of standardization across institutions in operative technique and perioperative care. The “standard of care” or “traditional” assessment of the anastomosis was also not standardized. There was also no control group with whom to compare outcomes, so the low leak rate may be more reflective of surgeon experience and skill at

Table 34.2 Studied uses of ICG angiography in colorectal and foregut surgery with literature support

Field of surgery	Potential uses for ICG angiography	Supporting studies
Colon and rectal surgery	Changing resection margin/ transection site	Observational feasibility [70, 72, 93, 96, 100, 105, 111], retrospective case series [94, 109, 121], retrospective cohort [61, 98, 104, 113, 119], retrospective matched-pairs [91, 116], prospective cohort [95, 110, 130], prospective multicenter cohort with mixed historical/concomitant controls [101], meta-analysis [122, 124, 126], randomized controlled trial [117, 118]
	Revising anastomosis	Observational feasibility [70, 106], retrospective cohort [119], prospective multicenter cohort with mixed historical/concomitant controls [101], meta-analysis [126]
	Determining need for protective ostomy	Observational feasibility [92, 93, 105, 108], meta-analysis [126]
	Predicting anastomotic leak	Observational feasibility [102, 106, 114, 115], retrospective case series [120]
	Reducing anastomotic leak rates	Randomized controlled trial [117], retrospective cohort [61, 98, 104, 119], retrospective matched-pairs [91, 116], prospective cohort [95], prospective multicenter cohort with mixed historical/concomitant controls [101], meta-analysis [122–126]
Foregut surgery	Changing resection margin	Observational feasibility [131–133], meta-analysis [127, 128]
	Revising anastomosis	Case series [134]
	Predicting anastomotic leak	Observational feasibility [90, 135], retrospective cohort [136], meta-analysis [129, 137]
	Preventing anastomotic leak	Retrospective cohort [138], meta-analysis [127–129]
	Predicting stricture	Case report [139], observational feasibility [135]

these primarily academic specialty practices. Finally, the intensity of the fluorescent signal was not measured quantitatively leaving the adequacy of perfusion on fluorescent imaging up to surgeon interpretation.

Additional Prospective Studies

Since PILLAR II, several large prospective trials have been published, including two randomized controlled trials. Ris et al. prospectively studied 504 patients undergoing high anterior resection or reversal of Hartmann's or low anterior resection (LAR) with ICG angiography [101]. They found that 5.8% of patients required a change in site of transection after fluorescent imaging (additional resection between 0.5 and 20 cm) with leak rates of 2.4% overall, 2.6% for colorectal anastomosis, and 3% for LAR. These were significantly lower than for similar surgeries performed at the same facilities without fluorescent imaging perfusion assessment (5.8% overall, 6.9% for colorectal anastomosis, and 10.7% for LAR). They also found that five patients for whom a diverting ostomy was planned were able to forego diversion after fluorescent imaging assessment of the completed anastomosis and that this group had no leaks. Morales-Conde et al. prospectively collected data on 192 patients undergoing any colorectal surgery with anastomosis [110]. They separated their patients into groups based on the surgery performed, including right hemicolectomy, left hemicolectomy, anterior resection of the rectum (subdivided into LAR with partial mesorectal excision and ultra-LAR with total mesorectal excision), and segmental resection of the splenic flexure. They found that 18.2% of patients had a change in transection site based on ICG angiography, with rates over 25% in both the anterior resection and left hemicolectomy groups. Two patients had a transection line moved more distally based on fluorescence imaging, which might reduce tension on the anastomosis. Of the patients who had a change in transection line, 8.6% had an anastomotic leak. Overall leak rate was 2.6%. Alekseev et al. conducted a randomized controlled trial of patients undergoing sigmoid or rectal resection [117]. They analyzed 377 patients, 187 of whom were randomized to near-infrared fluorescent imaging perfusion assessment and 190 of whom were randomized to standard visual clinical assessment. Patients underwent elective resection of sigmoid or rectal neoplasms with colorectal anastomosis less than 15 cm from the anal verge and were followed for clinical leak up to 30 days postoperatively. If a clinical leak had not been detected, patients received a contrast enema or pelvic CT by 30 days postoperatively. They found that 19.2% of patients had insufficient blood supply to the planned transection site by ICG angiography, with up to 5 cm of additional bowel resected. Overall complication rates and grades were similar between groups. They did find a significantly lower rate of anastomotic leak in the ICG angiography group compared to the non-ICG group (9.1% vs 16.3%, p = 0.04). They found that this difference could be almost entirely attributed to asymptomatic low (4–8 cm from anal verge) radiological leaks (14.4% vs 25.7%, p = 0.04) and that were no significant differences in either high (8–15 cm from anal verge) anastomotic leaks or symptomatic low anastomotic leaks. De Nardi et al. also performed a randomized controlled trial of patients undergoing laparoscopic left-sided colon or anterior rectal resection with colorectal anastomosis between 2 and 15 cm from the anal verge with ligation of the IMA [118]. They included 240 patients in their analysis, 118 in the ICG angiography group and 122 in the control group. They powered their study to detect a difference in leak rates of 1.5% in the study group and 10% in the control group. They found a rate of changing the transection site of 11% in the ICG group, with additional resection ranging from 2 to 16 cm. They found no significant difference in leak rate between groups (5% in the ICG group and 9% in the control, p = 0.2). 16/17 anastomotic leaks were detected clinically, with just one asymptomatic leak found on routine imaging prior to closure of the protective ostomy. One patient in the control group died after developing anastomotic leak. Overall, these and other studies demonstrate that the use of ICG leads to a change in the transection site in a substantial minority of cases, with the potential to avoid malperfusion to the anastomosis, allow for a more distal transection site with less tension, or forego a protective ostomy and the requirement for an additional surgery. There is insufficient evidence at this time to state that it reduces the rate of anastomotic leak, however, despite the recent publication of the first two randomized controlled trials.

Reviews and Meta-Analyses

In addition to original publications, the last several years have seen a number of systematic reviews and meta-analyses published regarding fluorescence angiography and colorectal surgery. The 2018 review by van den Bos et al. focused on ease of use, added case time, complications related to the technique, and costs [122]. Additional outcomes included changes to the operative plan, postoperative complications, and attempts to quantify the fluorescent signal. They included ten studies in their review and found a change in resection margin in 10.8% of cases. Anastomotic leak rate was 3.5% in the ICG angiography group and 7.4% in the traditional assessment group. Only two of the studies attempted to quantify the fluorescent signal. Shen et al. performed a review and meta-analysis the same year focusing on surgeries for colorectal cancer and including a control group [123]. They found four retrospective case-control studies for meta-analysis with a total of 1177 patients. They found a pooled odds ratio for anastomotic leak of 0.27 (p < 0.001) with the use of ICG angiography compared to traditional assessment. Blanco-Colino et al. similarly performed a 2018 meta-analysis and included all studies looking at anastomotic leak in colon or rectal resection with anastomosis [124]. They included five studies with 1302 total patients. They found a nonsignificant reduction in leak rate with ICG angiography (OR 0.51, p = 0.10). When limiting the analysis to cancer cases, they did find a significant reduction in leak rate (OR 0.34, p = 0.006). Rausa et al. performed a systematic review and meta-analysis in 2019 and included articles involving colorectal surgery with anastomosis and the use of one or more intraoperative anastomotic leak tests [125]. They included 11 studies and 3844 patients in their analysis. They found that the risk of leak was significantly lower in patients undergoing ICG angiography than in the control group (relative risk [RR] 0.44) and was also lower than the groups who had only ALT or intraoperative colonoscopy (IOC), though these did not reach statistical significance. Both the ALT and IOC groups had nonsignificant reductions in the risk of leak compared to control. Finally, Arezzo et al. conducted an individual participant analysis in 2020 from studies comparing ICG angiography to standard practice in assessment of anastomotic perfusion during rectal cancer operations and the influence on anastomotic leak [126]. They found 20 eligible studies including 15 published and 5 ongoing trials. 9 of the 20 authors responded (2 randomized trials and 7 non-randomized studies) and shared their data on a total of 1330 patients. There was a significantly greater rate of redoing the anastomosis in the ICG group compared to controls (2.0% vs 0.2%, $p = 0.011$), and 11.3% of patients required a change in the transection site after fluorescence angiography. There was a statistically significant reduction in odds of anastomotic leak with ICG perfusion assessment (OR 0.341, $p < 0.001$), with a leak rate of 4.2% in the ICG group and 11.3% in the controls. Subgroup analysis showed significantly reduced odds of leak with ICG angiography among male patients, patients older than 65 years, overweight patients (BMI ≥ 25 kg/m^2), and patients with anastomosis $\leq$6 cm from the anal verge. Overall, these studies support the thought that the use of ICG angiography is associated with lower leak rates. There remains insufficient data from randomized controlled trials to claim a causal relationship, but there are a number of studies underway that will help to definitively answer that question. Regardless, the literature to date has shown that ICG angiography may change transection site in up to 25% of cases, allowing some patients to have a more distal transection and less tension on the anastomosis, while others require up to 20 cm of additional bowel removed. It may also allow for more judicious use of diverting ostomies, potentially saving patients the recovery and costs associated with another surgery and the complications associated with an ileostomy.

34.2.2.2 Foregut Surgery

While the field of foregut surgery has seen fewer studies on the use of near-infrared imaging for perfusion assessment than has colorectal surgery, there have been a number of studies published since the late 2000s (Table 34.2). The majority of these have focused on perfusion assessment of the conduit following esophagectomy, though studies have been performed on gastrectomy for gastric cancer, preventing leak in bariatric surgery, and other topics (Fig. 34.4). Optimization of perfusion in esophagectomy is particularly important considering the potentially devastating consequences of leak with an intrathoracic anastomosis and that leak rates in cervical anastomosis are over 50% in some studies (though typically with less severe morbidity) [46].

The literature on ICG angiography in foregut surgery lacks good-quality prospective studies. Additionally, there have been few studies that have included a control group. Three recent meta-analyses do suggest that fluorescence angiography may be able to reduce leak rates in esophagectomy, though [127–129]. Van Daele et al. included 19 studies in their review and analyzed a total of 1192 patients, 758 who had perioperative ICG angiography performed and 434 for whom anastomotic site was determined based on clinical judgment [128]. They found that the surgical plan was

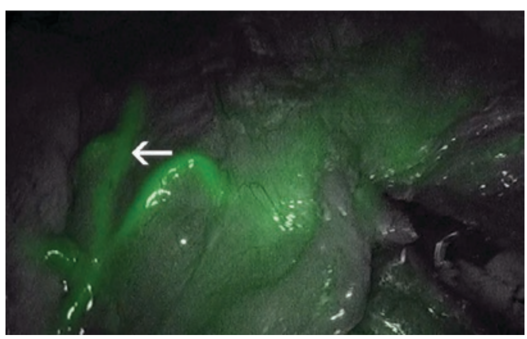

Fig. 34.4 Utilization of ICG fluorescence angiography to identify and preserve the gastroepiploic artery (arrow) while mobilizing the gastric conduit during esophagectomy

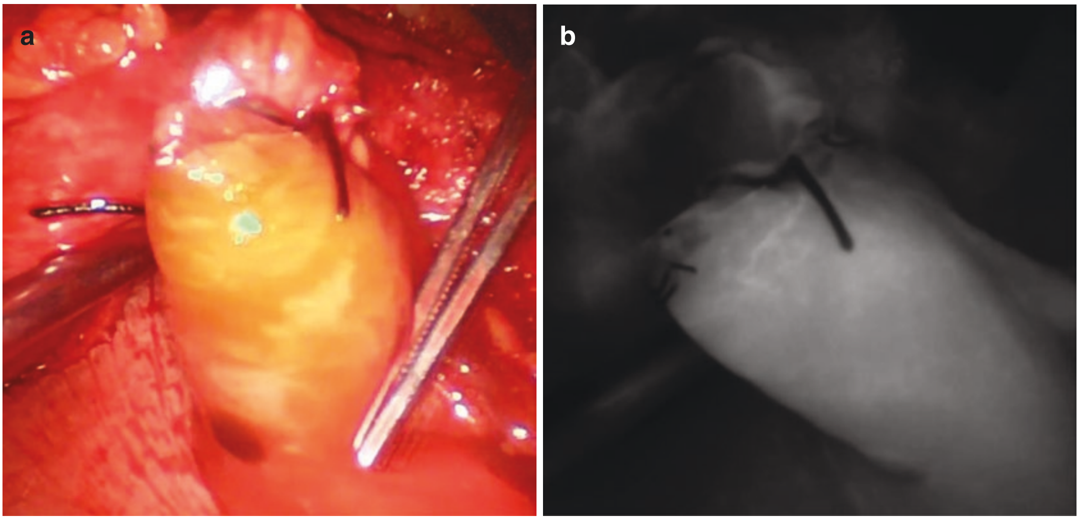

Fig. 34.5 Evaluation of the cervical esophagogastric anastomosis following esophagectomy. While the anastomosis appeared healthy under white light (**a**), ICG fluorescence angiography showed a lack of perfusion at the tip of the gastric conduit (**b**). This was resected and the anastomosis was redone with improved perfusion

altered in 12.4% of the ICG cases, with differing approaches based on study (e.g., additional resection and relocation of the anastomosis if conduit of sufficient length, using an end-to-end instead of end-to-side anastomosis, or creating additional vascular anastomoses) (Fig. 34.5). The leak rate among these patients was 6.5%, similar to the rate of 6.3% in 592 patients deemed to have good perfusion under fluorescence angiography. This was significantly less than the 20.5% leak rate in the non-ICG patients or the 47.8% leak rate in the group that had poor perfusion but no surgical alteration. Slooter et al. found 22 studies that met their criteria of studying ICG fluorescence angiography in esophagectomy [127]. They found a change in management rate of almost 25% among eight studies that included this outcome and a pooled incidence of anastomotic leak/graft necrosis among those patients of 14% compared to 11% overall in the ICG cohort. They also found an overall lower rate of anastomotic leak and graft necrosis in patients evaluated with ICG (OR 0.30). Ladak et al. found 17 studies that met their inclusion criteria [129]. Their meta-analysis included 1067 patients, 631 who received ICG angiography and 436 in the control group. Across all studies, they found a leak rate of 10.8%. In studies that included an intervention for poor perfusion by ICG angiography, the rate was 5.7% compared to 22.9% in the control group. Although each of these studies is limited by the significant heterogeneity and often poor quality of the studies that they included in their analysis, the results do suggest that ICG angiography has the potential to reduce leak rates in esophagectomy. There is just one randomized trial on ClinicalTrials.gov, and additional large prospective studies will be required to determine its optimal use.

34.3 Clinical Implications and Directions for Future Study

34.3.1 The Future of ICG in Perfusion Assessment and Anastomotic Safety

While the broad use of perfusion assessment with ICG at the time of anastomosis has yet to become standard of care, it is considered a best practice by many. There are several challenges to consider when applying this technology. First, access to this promising technology remains a challenge for many. As the data continues to support its routine use for gastroesophageal and intestinal surgery, it will become increasingly necessary to integrate this feature into all operative imaging systems. Additionally, quantifying perfusion and creating "perfusion metrics" has become an important area for investigation. Perfusion of an end organ can be impacted by several patient-related factors including blood pressure and heart rate, preexisting vascular disease, scarring, injury, and prior surgery. Perfusion metrics must then be correlated with patient outcomes to demonstrate clinical value. Early studies are beginning to show promise in this area of study [106, 114]. Finally, fluorescence angiography with ICG requires intravenous administration at the time of assessment and has a short half-life in the bloodstream before being washed out. For this reason, ICG is often given in repeated doses to visualize perfusion. Repeat subsequent doses can lead to a higher false positive signal of adequate perfusion as the background can build up. The appropriate dosing and time for expected visualization remains an enigma with most surgeons using a similar dose for all patients. The optimal "dose-to-signal" ratio should be validated for surgeons to fully realize the benefit of this information intraoperatively.

The future of perfusion angiography for anastomotic assessment is an exciting area for research and pharma/device development. The initial use of ICG for this purpose has shown great potential for reducing the most serious complication (anastomotic leak) for intestinal surgeons. Future directions for research include developing "perfusion metrics" which will guide surgical decision-making as it relates to patient health outcomes. Newer fluorophores and imaging technology combined with artificial intelligence and machine learning will all play an important role in the interpretation fluorescence angiography in the future, thus making perfusion testing at the time of anastomosis a necessary aspect of optimal surgical care.

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