



Intraluminal Anastomotic Assessment Using Indocyanine Green Near-Infrared Imaging for Left-Sided Colonic and Rectal Resections: a Systematic Review

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Abstract

Background Indocyanine green fluorescence angiography (ICG-FA) has been used in colorectal surgery to assess anastomotic perfusion and reduce the risks of anastomotic leaks. The main objective of this paper is to review the data on the transanal application of ICG-FA for the intraluminal assessment of colorectal anastomosis.

Methods A literature search was conducted for articles published between 2011 and 2021 using PubMed and Cochrane databases, related to the application of ICG for the intraluminal assessment of colorectal anastomosis. Original scientific manuscripts, review articles, meta-analyses, and case reports were considered eligible.

Results A total of 305 studies have been identified. After abstract screening for duplicates, 285 articles remained. Of those, 271 were not related to the topic of interest, 4 were written in a language other than English, and 4 had incomplete data. Six articles remained for the final analysis. The intraluminal assessment of colorectal anastomosis with ICG-FA is feasible, safe, and may reduce the incidence of leaks.

Conclusion The intraluminal assessment of anastomotic perfusion via ICG-FA may be a promising novel application of ICG technology. More data is needed to support this application further to reduce leak rates after colorectal surgery, and future randomized clinical trials are awaited.

Keywords Intraluminal ICG · taTME · Total mesorectal excision · Indocyanine green · Anastomotic leak · Rectal resection · Colorectal surgery · Fluorescence

Introduction

Anastomotic leak (AL) is one of the most devastating complications in colorectal surgery, with a reported incidence ranging from 5 to 24%, despite progressive advances in surgical technique.^{1–5} Besides the impairment of functional outcomes and the detrimental effects on the quality of life of an AL occurring after colorectal surgery, an AL following cancer resection can have even more devastating consequences, as it can delay the start of adjuvant therapy

with a subsequent increased risk of local recurrence and reduced survival.^{6–8} Several risk factors for its occurrence have been identified, including patient comorbidities and technical aspects. Among them are the surgical procedure type, operative time, anastomotic configuration, number of linear stapler firings, height, tension, and poor perfusion of the anastomosis,^{9–14} and the exposure to neoadjuvant chemoradiotherapy.¹⁵ Different techniques to test the integrity and perfusion of colorectal anastomosis have been developed over time, although their adoption among surgeons differs among institutions. One of the most promising tools to reduce AL after colorectal surgery is indocyanine green fluorescence angiography (ICG-FA) for the intraoperative evaluation of bowel perfusion. ICG is administered intravenously, and real-time vascular perfusion is evaluated from the serosal coloring detected with visible high-definition endoscopic fluorescence or near-infrared (NIR) spectroscopic laparoscopic cameras. Some authors, however, have questioned the use of ICG-FA due to inherent limits of the

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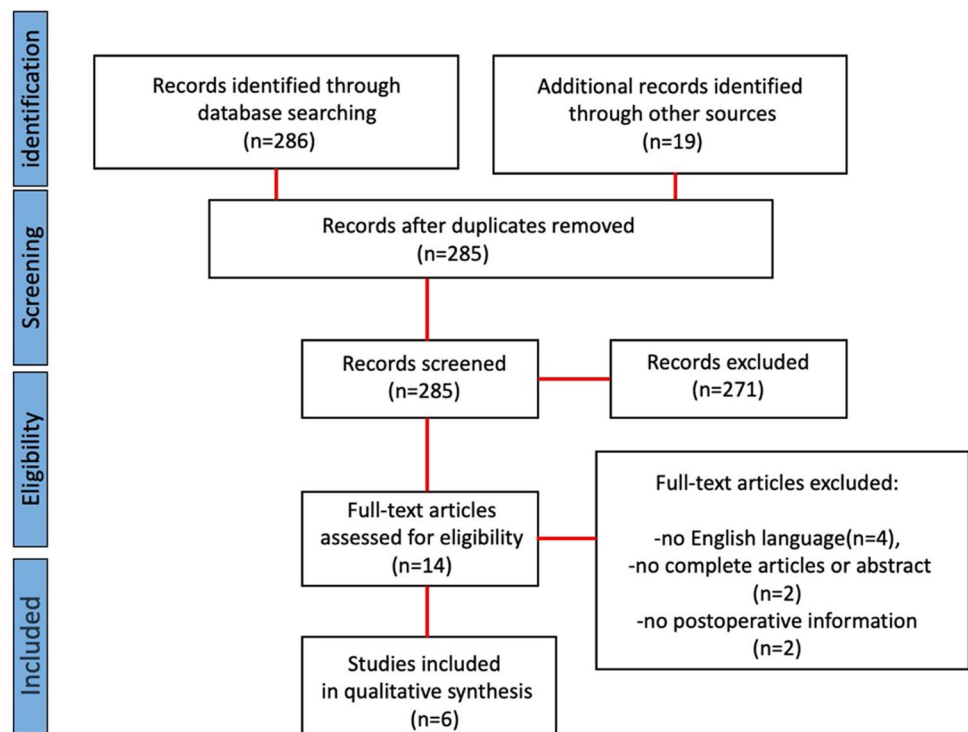
technique. For example, the observation from outside the lumen cannot assess the whole circumference of the anastomotic site, perfusion evaluation before the anastomosis is constructed cannot predict the final changes in perfusion after the anastomosis is completed, and the distal side of the anastomosis is often hard to evaluate. The intraluminal assessment of ICG uptake can overcome all these limitations. The main objective of this paper is to review the data on the transanal application of ICG-FA for the intraluminal assessment of colorectal anastomosis.

Methods

This review focuses on two key questions: how effective is the intervention in reducing postoperative complications after colorectal surgery, and what are its effects on patient outcomes? The PRISMA 2020 (preferred reporting items for systematic reviews and meta-analyses) guidelines have been followed.¹⁶ The PRISMA diagram is shown in Fig. 1. A literature search was conducted using PubMed and Cochrane databases for eligible articles from 2011 to 2021. A combination of keywords was searched: “indocyanine green fluorescence angiography,” “intraluminal indocyanine green,” “colorectal surgery,” “endoscopic colorectal anastomoses assessment,” “colonic perfusion assessment,” and

“anastomotic leak.” Inclusion criteria were original scientific manuscripts, review articles, meta-analyses, case reports, English language, and articles regarding the intraluminal assessment of colorectal anastomosis with ICG-FA. No limitation was applied to study type, sample size, and patient age. Exclusion criteria were articles with incomplete data, incorrect or repeated citations, and unrelated to the review topic. Studies were also excluded whether, after construction of the anastomosis and injection of ICG bolus, the endoscopic assessment of the proximal and distal mucosal perfusion was not performed. Additionally, studies that did not report the number of patients, without a clear definition of intraluminal viability or incomplete postoperative follow-up were not deemed eligible for the analysis. SL and DP double screened titles and abstracts and checked full texts against eligibility criteria. Disagreements were resolved by discussion or, if unresolved, through arbitration with a third reviewer (PS). For each study, the following data were extracted: number of patients, study design, median age, benign or malignant indication, level of anastomosis from the anal verge (cm), postoperative complications, and anastomotic leakage. The Joanna Briggs Institute (JBI) Critical Appraisal checklist tools were used to assess the methodological quality of the studies. The risk of bias in the included studies was assessed using the Risk Of Bias In Non-Randomized Studies—of Interventions (ROBINS-I) tool.¹⁷

Fig. 1 Flow diagram of the study



Results

A total of 305 articles have been identified, and 285 remained after removing duplicates (Fig. 1). After the abstract screening, 271 studies were excluded because they were not related to the topic of interest, and the other 8 articles were for the following reasons: non-English language ($n=4$), incomplete article or abstract ($n=2$), and incomplete or lacking postoperative information ($n=2$). Six articles remained for the final analysis (Table 1).

The JBI checklists evaluation is reported in Tables 2 and 3. Overall quality criteria were fulfilled.

The use of intraluminal perfusion assessment of colorectal anastomoses was first described by Sherwinter DA et al.¹⁸ using the PINPOINT® Endoscopic Fluorescence Imaging System (Novadaq, ON, Canada) on a cohort of 7 patients undergoing low anterior resection (LAR) for both benign and malignant disease. The study was later prolonged with the inclusion of 13 more patients.¹⁹ All patients received mechanical bowel preparation and perioperative antibiotics. All operations were performed

laparoscopically using a standardized double-stapled technique. After completion of the anastomosis, a single bolus of 2.5 mg of ICG was administered intravenously, providing fluorescent imaging of mucosal and anastomotic blood flow. Out of the 20 patients in this study, 4 exhibited flow abnormalities on transanal ICG evaluation. In 2 cases, hypofluorescence coincided with visual signs of hypoperfusion in white light. Thus, the surgical team decided to perform a diverting loop ileostomy. In the other 2 cases, blood flow abnormalities were apparent on ICG, and there were no changes to the operative strategy. Both patients developed a peri-anastomotic collection and were successfully treated conservatively with antibiotics. The remaining 16 patients were discharged home without complications with a mean hospital stay of $4.75 (\pm 1.0)$ days.

Jafari et al.²⁰ provided the results of a multicenter prospective, open-label clinical trial of 139 patients undergoing LAR for rectal cancer (25%) or left colectomy for diverticulitis (44%) and colon cancer (21%). The mean level of anastomosis was 10 ± 4 cm from the anal verge. Splenic flexure mobilization was performed in 81% and high ligation

Table 1 Studies reporting the use of intraluminal NIR-ICG

Author, year	Sherwinter et al. ¹⁸	Sherwinter et al. ¹⁹	Jafari MD et al. ²⁰	Amagai H. et al. ²¹	Mizrahi I et al. ²²	Otero-Piñeiro AM et al. ²³
No of patients	7	20	139	69	54	284
Study design	Prospective, single center	Prospective, single center	Prospective, multi-center	Prospective, single center	Retrospective, multicenter	Comparative retrospective, single center
Median age, years	70 (51–85)	67 (42–98)	58 (44–72)	na**	63 (51–75)	68
Malignant indication	4	13	64	69	0	284
Benign indication	3	7	75	0	54	0
Complications	0	2	23	na**	19	108
Anastomotic leaks	0	2	2	9	2	25
Level of anastomosis, cm, from the anal verge < 8 cm	0	4	36	na**	0	284
Total no. of patients						
Level of anastomosis, cm, from the anal verge 8–9 cm	2	1	16	na**	54	0
Total no. of patients						
Level of anastomosis, cm, from the anal verge > 10 cm	5	15	87	na**	19	0
Total no. of patients						

*AL anastomotic leak

**NA not available

Table 2 JBI's critical appraisal checklist for case series studies Q1–10

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Sherwinter et al. ¹⁸	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA
Sherwinter et al. ¹⁹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA
Jafari MD et al. ²⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Amagai H. et al. ²¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

NA not applicable, UC unclear

(Q1: Were there clear criteria for inclusion in the case series? Q2: Was the condition measured in a standard, reliable way for all participants included in the case series? Q3: Were valid methods used for identification of the condition for all participants included in the case series? Q4: Did the case series have consecutive inclusion of participants? Q5: Did the case series have complete inclusion of participants? Q6: Was there clear reporting of the demographics of the participants in the study? Q7: Was there clear reporting of clinical information of the participants? Q8: Was the outcomes or follow-up results of cases clearly reported? Q9: Was there clear reporting of the presenting site(s)/clinic(s) demographic information? Q10: Was the statistical analysis appropriate?)

Table 3 JBI's critical appraisal checklist for case–control studies. Q1–10

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Mizrahi I et al. ²²	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Otero-Piñeiro AM et al. ²³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

NA not applicable, UC unclear

(Q1: Were the groups comparable other than the presence of disease in cases or the absence of disease in controls? Q2: Were cases and controls matched appropriately? Q3: Were the same criteria used for identification of cases and controls? Q4: Was exposure measured in a standard, valid and reliable way? Q5: Was exposure measured in the same way for cases and controls? Q6: Were confounding factors identified? Q7: Were strategies to deal with confounding factors stated? Q8: Were outcomes assessed in a standard, valid and reliable way for cases and controls? Q9: Was the exposure period of interest long enough to be meaningful? Q10: Was appropriate statistical analysis used?)

of the inferior mesenteric artery in 61.9% of patients. The use of ICG-FA (single bolus of 3.75 to 7.5 mg ICG intravenously) changed surgical plans in 11 patients (8%) without the occurrence of leaks. The changes included the revision of the point of proximal colon transection in 9 cases (6.5%), the takedown and revision of the anastomosis after transanal perfusion assessment in 1 patient, and confirmation of the viability of anastomosis in 1 case with concerns of malperfusion under white light. In the latter case, the transanal ICG-FA altered the intraoperative plan for diversion to no diversion. The overall complication rate reported in the study was 17%. Anastomotic leaks occurred in 2 patients (1.4%) that were successfully treated conservatively. This study presents a moderate risk of bias after the ROBIN-I assessment.

The study from Amagai H. et al.²¹ was conducted prospectively on 71 patients undergoing left-sided colectomy or rectal surgery. All patients received standard bowel preparation and antibiotic prophylaxis the day before the operation. ICG was administered intraoperatively at a dosage of 0.2 mg/kg. Side-to-side anastomoses were performed in 16 cases, side-to-end in 40 cases, and end-to-end in 13 cases. One case of side-to-end anastomosis and three cases of end-to-end anastomosis were hand-sewn. Anastomotic leaks occurred in nine patients (13%); two

required reoperation, and the remaining were treated with antibiotics and drainage. The group of Amagai was one of the first to attempt to correlate the quantification of ICG fluorescence with the risk of dehiscence. Fluorescence was measured using the ImageJ software (National Institutes of Health, Maryland, USA), and a time-intensity fluorescence curve was created. The authors then localized the areas of the anastomosis with the highest and lowest fluorescence intensity and the contrast pattern of the mucosa. Significant differences in the time from ICG injection to maximum fluorescence ($p = 0.015$) and in time from the initial coloring to maximum fluorescence ($p = 0.04$) were evident in cases where a leak occurred. However, the described ICG quantification method was deemed impractical by the same authors for real-time intraoperative use. Therefore, they visually analyzed the contrast pattern of the colonic mucosa. The areas showing the lowest fluorescence location in the proximal and distal intestine that lacked visible vessels after ICG injection had a significantly higher incidence of leaks than those in which vessels were depicted ($p = 0.031$ and $p = 0.030$, respectively). Some of the areas in which vessels were not characterized by ICG fluorescence observation from the luminal side corresponded to the leakage points. This

study presents a moderate risk of bias after the ROBIN-I assessment.

Mizrahi I et al.²² evaluated the impact of ICG-FA on any change in proximal resection margin and/or anastomotic leak following transanal total mesorectal excision (taTME) for rectal cancer in a retrospective dual center cohort study. All patients had preoperative mechanical and antibiotic bowel preparation. In the application of bowel perfusion, ICG was used in the range of 0.1–0.3 mg/kg. All patients followed an enhanced recovery after surgery protocol. Fifty-four patients (31 males, 23 females; mean age 63 ± 12 years) were included; 30 (55%) received neoadjuvant chemoradiation therapy. The average anastomotic height was 3.6 cm from the anal verge, 8 (14.5%) patients required intersphincteric dissection, and 46 (85%) had loop ileostomy.

The study did not restrict the type of anastomotic technique; that was left to the surgeon's judgment. In 44.5% of the cases, the anastomosis was hand-sewn and stapled in the remaining 55.5%.

A straight anastomosis was created in 26 patients (48%), a side-to-end in 20 (37%), and a colonic J pouch in 8 (15%). The use of endoluminal ICG-FA led to a change in the proximal resection margin in 10 patients (18.5%), one of whom had an anastomotic leak, although ICG-FA showed adequate blood supply to the anastomosis. This patient had a straight anastomosis, requiring reintervention with the creation of a loop ileostomy. A second patient undergoing an intersphincteric dissection with the construction of a hand-sewn colonic J pouch-anal anastomosis 2 cm from the anal verge and a diverting loop ileostomy without a change in the proximal resection margin after ICG-FA also had an anastomotic leak. In this case, the patient did not require reintervention and was treated conservatively. The overall leak rate of the study was 3.7%. The splenic flexure was not mobilized, and the specimen was extracted transanally in both patients who suffered a leak. This study presents a moderate risk of bias after the ROBIN-I assessment.

The largest study on the assessment of ICG-FA for the evaluation of the mucosa by transanal visualization was conducted by Otero-Piñero AM et al.²³ on 284 rectal cancer patients undergoing taTME. The patients were divided into two groups: no ICG-FA assessment (204 patients) and ICG-FA assessment (80 patients). The study's primary aim was to compare anastomotic leak rates among groups. The use of ICG-FA altered the surgical plan in 23 patients (28.7%), changing the proximal colonic transection in 22 cases. In the remaining case, the transanal assessment showed insufficient anastomotic perfusion that led to splenic flexure mobilization with an improvement of tissue perfusion. Anastomotic leaks occurred in 23 cases (11.3%) in the non-ICGA group vs. two (2.5%) cases in the ICGA group ($p=0.020$). Univariate analysis identified three variables to be associated with the risk of developing anastomotic leak: transabdominal

specimen extraction (OR 2.551; 95% CI 1.031–6.317, $p=0.043$), diverting stoma (OR 0.265; 95% CI 0.114–0.612, $p=0.002$), and ICG-FA (OR 0.204; 95% CI 0.047–0.888, $p=0.034$). This study presents a moderate risk of bias after the ROBIN-I assessment.

Discussion

AL remains the most feared complication after colorectal resections. Prevention and management of AL are challenging, with treatment strategies ranging from conservative management to radiological, endoscopic, or surgical interventions.

Because of the multitude of factors that contribute to its occurrence, a reliable predictor of anastomotic leakage is not available. Some studies support the concept that altered microperfusion is the predominant factor resulting in AL in cases where a negative air leak test and complete proximal and distant doughnuts were achieved at the surgery.^{14,24} In a prospective study by Vignali et al., a linear correlation was found between reduced blood flow measured intraoperatively by a laser-Doppler probe at the proximal or rectal stump and the occurrence of AL.²⁴ They found that a blood flow reduction in microperfusion of 16% occurred in patients who ended up developing a leak vs. 6.1% observed in patients without AL.

Several factors can impact perfusion, including anatomic variations in the blood supply to the anastomotic conduit, low perfusion pressure probably associated with atherosclerotic or microvascular disease, injury to the vasa recta from excessive dissection, twisting of the mesentery, and undue tension on the anastomosis. Hence, strategies to assess colonic vascular perfusion intraoperatively are of significant interest and may help identify occult bowel ischemia and help decrease the rate of AL.

The use of ICG-FA has been reported in colorectal surgery for both benign and malignant diseases applied to different surgical approaches (laparoscopic, robotic, and transanal).^{19,25,26} The use of such technology has increased considerably in recent years as a complementary tool for surgeons to assess intestinal serosal microcirculation in real time. Therefore, ICG-FA has become a precious and objective method for surgeons to obtain well-perfused anastomosis.

Revision rates of colonic resection margins following ICG-FA and colorectal leak rates are variably reported in current literature.^{20,27,28} According to the meta-analysis conducted by Blanco-Collino et al. that included 4 retrospective non-randomized studies and one prospective cohort study, the intraoperative use of ICG fluorescence following elective rectal surgery resulted in a lower AL rate compared to standard of care (1.1% vs. 6.1%, respectively).²⁹ The recent

meta-analysis²⁹ reported pooled outcomes for 1302 patients from 5 non-randomized studies that compared the intraoperative use of ICG-FA in 555 patients with the standard of care in 747 patients. A change in the proximal colonic resection margins occurred in 7.4% of patients in the ICG group. However, no significant differences in AL rates were observed between groups ($p=0.10$). The meta-analysis was limited by the retrospective nature of most of the studies included in the pooled analysis (4/5) and by randomized studies, which presented a moderate risk of bias when the quality of studies was assessed.

In a multicenter prospective phase II trial involving 504 patients undergoing elective colorectal surgery for benign or malignant indications, the use of ICG-NIR resulted in a change of proximal colonic resection margins in 29 patients (5.8%) with no subsequent AL.³⁰ The results observed in the ICG group were compared to data collected from 1173 patients undergoing colorectal surgery in the same study centers before or during the study period without the use of ICG-NIR. The overall leak rate for colorectal resections where ICG-NIR was not used was 5.8% compared with 2.6% (12 of 453) in the cohort where NIR-ICG imaging was used ($p=0.009$). The retrospective case-matched study by Kin et al. reported questionable results when ICG-FA was performed to assess vascular bowel perfusion for minimizing the risk of AL.³¹ Six hundred nine patients underwent colorectal resections for benign and malignant indications during a 7-year study period; intraoperative ICG-FA was used in 224 patients with outcomes compared with 384 patients in whom ICG-FA was not used. Although no significant difference in AL rate was observed between groups (7.5% vs. 6.4%, $p=0.67$), the use of ICG-FA altered the proximal resection point in 8 patients. However, only the perfusion of the proximal bowel was assessed; the perfusion to the rectal stump was not confirmed.

More recently, in a multicenter randomized trial involving 240 patients undergoing laparoscopic colorectal resections, 118 were enrolled in the ICG-FA group, while 122 were in the control group without ICG. A change in the planned proximal colonic resection margins was observed in 13% of patients in the ICG-FA group. However, the AL rate was found not statistically different between the groups (5% vs. 9%, $p>0.05$): this divergent result casts doubts about the role of ICG-FA in preventing postoperative anastomotic dehiscence.³²

Overall, the data published so far supports the use of ICG perfusion in colorectal surgery to test anastomotic vascular perfusion at two critical points: just before bowel resection and after completion of the anastomosis. Benefits of ICG-FA include confirmation of adequate or inadequate perfusion, especially in high-risk anastomoses and in scenarios where the adequacy of bowel perfusion is questionable.

Regardless of the surgical approach, tumors in the middle and lower third of the rectum pose a significant challenge to the surgeon, especially in patients with a deep and narrow pelvis, males, obese, following neoadjuvant chemoradiation,

and those with a bulky tumor. The distal transection in the deep and narrow pelvis using the currently available laparoscopic or robotic staplers can be difficult and may require multiple linear stapler firings, which may be associated with increased rates of AL.

The introduction of total mesorectal excision (TME) as the gold standard for the surgical management of rectal cancer has increased the rate of sphincter-preserving surgery with low anastomoses, resulting in an overall increase in AL rates.³³ Surgery for rectal cancer has progressed greatly, and the development of minimally invasive approaches to TME has garnered considerable interest in the last few decades. Since its introduction, transanal total mesorectal excision (taTME) has been adopted by colorectal surgeons worldwide. It is advantageous in patients with a narrow pelvis that would otherwise make a transabdominal approach difficult.³⁴ Transanal total mesorectal excision (taTME) utilizes a “bottom-up” approach to perform rectal and mesorectal dissection. It is mainly used for distal rectal tumors to ensure a complete TME specimen and negative margins in low-lying tumors that might otherwise require an abdominoperineal resection. Considering the higher reported incidence of AL on the international registry during taTME performed with low and ultralow coloanal anastomoses (7.8% vs. 5.4% among the initial 720 registry cases), there has been a growing interest in incorporating strategies, such as intraoperative perfusion assessment of high-risk anastomoses during taTME to mitigate the risk of AL.³⁵

Endoscopic intraluminal assessment of mucosal perfusion in high-risk anastomoses provides a 360-degree view of the bowel, which is otherwise not easily achievable. Transanal ICG-FA provides additional confirmation of anastomotic integrity by assessing vascular perfusion of the entire circumference of stapled or hand-sewn anastomosis. To date, just a few studies have reported the use of ICG-FA for endoscopic assessment of vascular perfusion of the anastomosis.^{18,23} Sherwinter DA et al. were the first to describe the rectal mucosal flow transanally on a small cohort of patients undergoing LAR.^{18,19} A qualitative evaluation of the intraluminal intensity of ICG uptake was performed. The subjective nature of these data clearly limits any conclusion regarding the positive predictive value of an abnormal ICG angiogram.

Jafari et al. provided the results of the largest published prospective case series.²⁰ The study reported an AL rate of 1.4% ($n=139$), with no leakages in 11 patients (7.9%) who had a change in the surgical plan after ICG-FA. The take-down and revision of the anastomosis after transanal perfusion assessment occurred in 1 patient while serosal signal was present. The work of Amagai H et al.²¹ was one of the first to conduct a quantitative analysis of colon perfusion using ICG-FA. The work of Mizhray I et al. was the first to report outcomes of FA exclusively during taTME.²² No discrepancy of FA in the

extra or intraluminal assessment of the adequacy of vascular perfusion during taTME was demonstrated; hence, no surgical revision of the anastomoses was required. The decision to perform a protective stoma, the splenic flexure mobilization, and the anastomotic configuration were left to the surgeon's judgment. These variations added an important selection bias, especially when focusing on AL, and the small sample size limited the strength of their conclusions. In the study reported by Otero-Piñero AM et al., the transanal assessment showed insufficient anastomotic perfusion in one patient while serosal signal was present.²³ This led to splenic flexure mobilization, and tissue perfusion improved without further measures. A key limitation was the retrospective nature and the small size of the study.

The use of intraluminal NIR-ICG has several advantages. First, the mucosa is more susceptible than the serosa to alterations in perfusion, and adequate serosal perfusion may not imply adequate mucosal perfusion. During laparoscopic LAR and when combined with taTME, it might be challenging to assess perfusion of the rectal stump from a transabdominal approach, especially during very low dissection. On the other hand, endoscopic intraluminal assessment of the anastomosis provides a 360-degree evaluation of the bowel above and below the anastomosis, including low and ultralow coloanal anastomoses that would otherwise be inaccessible in the extraluminal assessment using a transabdominal approach. Intraluminal perfusion assessment of low colorectal anastomoses using this ICG-FA platform is quick and can easily be performed by a single operator at any time during the case. Since the camera is connected to the fluorescence imaging system, the entire surgical team can visualize the transanal images on the monitor. In addition, intraoperative proctoscopy allows for assessing the integrity of the anastomotic line and provides an air leak test at the same time. Both perfusion and structural defects of the anastomosis can be identified and corrected with this single diagnostic modality.

Even though ICG-FA has shown to be promising in the extra or intraluminal assessment of the adequacy of vascular perfusion of high-risk colorectal anastomoses, there are still some limitations in surgical practice that need to be overcome.

Following intravenous injection of ICG, assessment of the adequacy of colonic perfusion is subject to variable interpretation. Despite some recent exceptions, most NIR imaging systems cannot quantify tissue perfusion; thus, the determination of adequate perfusion is determined by subjective measures with no clear cut-off to guide the surgeon on the adequacy or inadequacy of anastomotic perfusion. The work by Amagai et al. highlights the need to better quantify anastomotic perfusion with ICG-FA.²¹ Further studies focusing on quantitative rather than qualitative fluorescence assessment at the anastomosis level are awaited.

Additionally, due to the costs associated with the devices, many facilities still do not have the technology to perform endoluminal perfusion assessment, and although several devices from many different companies are commercially available, to date, no study comparing platforms and systems has been conducted. Further studies incorporating other NIR imaging systems will be necessary to demonstrate the impact of endoscopic anastomotic perfusion assessment in preventing AL.

Higher-quality studies are needed to evaluate better the dual role of extra and intraluminal ICG-FA perfusion assessment in preventing AL rates, ideally large prospective randomized controlled trials (RCTs). The low level of evidence supporting the routine use of ICG-FA in colorectal surgery stems from poorly designed observational, retrospective case-control studies and prospective non-randomized trials. As a result, there is a lack of consensus on the optimal technique for ICG-FA (dose, timeline for perfusion assessment) and the clinical benefits of routine use in colorectal surgery.

IntAct is a prospective, unblinded, multicenter randomized controlled trial that will compare AL rates at 90 days postoperatively among 880 patients undergoing laparoscopic or robotic low anterior resection for rectal cancer with or without intraoperative FA.³⁶ Following ICG administration, intestinal vascular perfusion will be assessed in two critical steps: before bowel resection and after anastomosis construction, either intracorporeally or transanally. Clinical and radiological AL, changes in the planned resection margins, postoperative complications, quality of life, and a health economic evaluation will be examined as secondary outcomes.

Conclusion

Anastomotic perfusion assessment using ICG-FA during colorectal resections has shown promise in predicting and possibly preventing AL. Reliable identification of the demarcation line for ischemic tissue allows surgeons to revise the proximal transection margin to create a well-perfused anastomosis, thereby minimizing the risk of postoperative AL. More recently, transanal intraluminal assessment of anastomotic perfusion using ICG-NIR imaging is safe and feasible to evaluate anastomotic viability in real time. A dual extra and intraluminal approach for anastomotic perfusion assessment might particularly benefit high-risk anastomoses. Routine use of intraluminal ICG-NIR may become a standard tool in evaluating high-risk colorectal and coloanal anastomoses.

However, to date, large-scale prospective RCTs are lacking. Additionally, intraluminal perfusion assessment is only feasible for coloanal and colorectal anastomoses, but it is still not demonstrated for left-sided, transverse, or right-sided colonic anastomoses. New technologies incorporating fluorescence assessment in standard endoscopic equipment will be necessary.

Appendix

Table 4 PRISMA 2020 checklist

Title	Item#	Checklist item	Location where item is reported
Title	1	Intraluminal anastomotic assessment using indocyanine green near-infrared imaging for left-sided colonic and rectal resections: a systematic review	1
Abstract			2
Abstract	2	<p>Background: Indocyanine green fluorescence angiography (ICG-FA) has been used in colorectal surgery to assess anastomotic perfusion and reduce the risks of anastomotic leaks. The main objective of this paper is to review the data on the transanal application of ICG-FA for the intraluminal assessment of colorectal anastomosis.</p> <p>Materials and methods: A literature search was conducted for articles published between 2011 and 2021 using PubMed and Cochrane databases, related to the application of ICG for the intraluminal assessment of colorectal anastomosis. Original scientific manuscripts, review articles, meta-analyses, and case reports were considered eligible.</p> <p>Results: A total of 305 studies have been identified. After abstract screening for duplicates, 285 articles remained. Of those, 271 were not related to the topic of interest, 4 were written in a language other than English, and 4 had incomplete data. Six articles remained for the final analysis. The intraluminal assessment of colorectal anastomosis with ICG-FA is feasible, safe, and may reduce the incidence of leaks.</p> <p>Conclusions: The intraluminal assessment of anastomotic perfusion via ICG-FA may be a promising novel application of ICG technology. More data is needed to support this application further to reduce leak rates after colorectal surgery, and future randomized clinical trials are awaited.</p>	
Introduction			3
Rationale	3	Despite advances in surgical techniques, anastomotic leakage (AL) remains a devastating complication following colorectal surgery with significant morbidity. The prevention, improved diagnosis, and management of AL is the biggest challenge facing colorectal surgeons. Adequate blood perfusion is a key component of anastomotic integrity, and the risk of AL is minimized by intraoperative detection of bowel ischemia. As the mucosa is the most susceptible to ischemia, intraluminal assessment of perfusion may assist surgeons in determining the integrity of the anastomosis.	
Objectives	4	Our primary objective was to review the data on the transanal application of ICG-FA for the intraluminal assessment of colorectal anastomosis.	
Methods			3
Eligibility criteria	5	Inclusion criteria were original scientific manuscripts, review articles, meta-analyses, case reports, English language, and articles regarding the intraluminal assessment of colorectal anastomosis with ICG-FA. Exclusion criteria were articles with incomplete data, incorrect or repeated citations, and not related to the topic of the review. Studies were also excluded whether, after construction of the anastomosis and injection of ICG bolus, the endoscopic assessment of the proximal and distal mucosal perfusion was not performed. Additionally, studies that did not report the number of patients, without a clear definition of intraluminal viability or incomplete postoperative follow-up were not deemed eligible for the analysis.	
Information sources	6	The electronic research was carried out using PubMed and Cochrane databases and eligible articles were identified in the period 2011–2021.	
Search strategy	7	No limitation was applied to study type, sample size, and patient age. SL and DP double screened titles and abstracts and checked full texts against eligibility criteria. Disagreements were resolved by discussion or, if unresolved, through arbitration with a third reviewer (PS).	
Selection process	8	Included articles based on abstract review were analyzed in depth to assess whether the full text still met inclusion criteria. The reference list of identified review articles, meta-analysis, and included studies was hand-searched for additional references.	

Table 4 (continued)

Title	Item#	Checklist item	Location where item is reported
Data collection process	9	Two authors independently screened the articles identified by the database, performed data extraction, and assessed the methodological quality of the eligible articles. Any discrepancies were resolved through discussion. In case of discrepant judgments, a third author was involved	
Data items	10	For each study, the following data were extracted: number of patients, study design, median age, malignant or benign indication, level of anastomosis from the anal verge (cm), postoperative complications, and anastomotic leakage	
Study risk of bias assessment	11	The risk of bias in the included studies was assessed using the Risk Of Bias In Non-Randomized Studies—of Interventions (ROBINS-I) tool	
Effect measures	12	Methodological quality of the included articles was assessed independently by two authors with the use of JBI Critical Appraisal checklist	
Synthesis methods	13	Inclusion criteria were original scientific manuscripts, review articles, meta-analyses, case reports, English language, and articles regarding the intraluminal assessment of colorectal anastomosis with ICG-FA and identified in the period 2011–2021. Two independent reviewers screened based on the title and abstract. If there was no consensus, the full text was also screened independently by both reviewers. Any discrepancies were resolved through discussion. In case of discrepant judgments, a third author was involved. The reference list of identified review articles, meta-analysis, and included studies was hand-searched for additional references. For each study, the following data were extracted: number of patients, study design, median age, malignant or benign indication, level of anastomosis from the anal verge (cm), postoperative complications, and anastomotic leakage The Joanna Briggs Institute (JBI) Critical Appraisal checklist tools were used to assess the methodological quality of the studies. The potential role of publication bias was assessed using the Risk Of Bias In Non-Randomized Studies—of Interventions (ROBINS-I) tool	
Reporting bias assessment	14	The potential role of publication bias was assessed using the Risk Of Bias In Non-Randomized Studies—of Interventions (ROBINS-I) tool	
Certainty assessment	15	The data was summarized, and the quality of the evidence was assessed using the group of work Grading of Recommendations Assessment, Development and Evaluation (GRADE)	
Results			4
Study selection	16	16 A total of 305 articles have been identified, and 285 remained after removing duplicates. After the abstract screening, 271 studies were excluded, and six articles remained for the final analysis 16b Several studies were excluded for the following reasons: not related to the topic of interest, and the other 8 articles were for the following reasons: non-English language (n=4), incomplete article or abstract (n=2), incomplete or lacking postoperative information (n=2)	
Study characteristics	17	The characteristics of the included studies are presented in Table 1	
Risk of bias in studies	18	The studies presented a moderate risk of bias after the ROBIN-I assessment	
Results of individual studies	19	The characteristics of the individual studies are summarized in Table 1	
Results of syntheses	20	We found 6 studies which reported the use of ICG-FA for endoscopic assessment of vascular perfusion of the anastomosis. (Table 1). The intraluminal assessment of colorectal anastomosis with ICG-FA is feasible, safe, and may reduce the incidence of leaks. During laparoscopic LAR and when combined with taTME, it provides a 360-degree evaluation of the bowel above and below the anastomosis, including low and ultralow coloanal anastomoses that would otherwise be inaccessible in the extraluminal assessment using a transabdominal approach. Intraluminal perfusion assessment of low colorectal anastomoses using this ICG-FA platform is quick and can easily be performed by a single operator at any time during the case. In addition, intraoperative proctoscopy allows for assessing the integrity of the anastomotic line and provides an air leak test at the same time. Both perfusion and structural defects of the anastomosis can be identified and corrected with this single diagnostic modality	
Reporting biases	21	The studies presented a moderate risk of bias after the ROBIN-I assessment	
Certainty of evidence	22	The quality of the evidence according to GRADE is predominantly moderate	

Table 4 (continued)

Title	Item#	Checklist item	Location where item is reported
Discussion			5
Discussion	23	Intraluminal assessment of anastomotic perfusion using ICG-NIR imaging is a safe and feasible technique to evaluate anastomotic integrity in real time. It is particularly beneficial in very low anastomoses, those following radiation, and in the narrow pelvis Further studies focusing on quantitative rather qualitative fluorescence assessment at the level of the anastomosis are warranted	
Other information			
Registration and protocol	24	24a The study was not registered on PROSPERO	
Support	25	This study did not receive any funding	
Competing interests	26	All authors declare no conflict of interest	
Availability of data, code, and other materials	27	Data are not available in a public open-access archive	

Data Availability The authors confirm that the data supporting the findings of this study are available within the article and its appendix.

Declarations

Ethics Approval No ethical approval is required for this study.

Conflict of Interest The authors declare no competing interests.

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