REVIEW ARTICLE

Royal Australasian College of Surgeons

Fluorescence imaging in reducing anastomotic leak after left-sided colorectal resections: a systematic review and updated meta-analysis

Mufaddal Kazi *†‡ Atul Ajith *‡ Abhiram Bhoyar§ and Raghav Yelamanchi *‡

*Department of Surgical Oncology, Tata Memorial Hospital, Mumbai, India
†Department of Surgical Oncology, Advanced Centre for the Treatment, Research, and Education in Cancer, Navi Mumbai, India
‡Department of Surgical Oncology, Homi Bhabha National Institute, Mumbai, India and
§Department of Surgical Oncology, Ranchi Cancer Hospital and Research Centre, Ranchi, India

Key words
anastomotic leak, colorectal surgery, fluorescence, indocyanine green, meta-analysis.

Correspondence
Mufaddal Kazi, Division of Gastrointestinal Surgical Oncology, Department of Surgical Oncology, Tata Memorial Hospital and Advanced Centre for Treatment, Research, and Education in Cancer, Homi Bhabha National Institute, Mumbai 400012, India.
Email: mufaddalkazi@live.com

M. Kazi MS, MCh; **A. Ajith** MS; **A. Bhoyar** MS; **R. Yelamanchi** MS.

Accepted for publication 1 August 2024.

doi: 10.1111/ans.19201

Abstract

Background: The objective of this systematic review and meta-analysis was to pool randomized trials of patients undergoing left-sided colorectal anastomosis, comparing the use of fluorescence perfusion imaging versus visual inspection in reducing anastomotic leaks.
Methods: Databases searched included PubMed, Cochrane Library, Scopus, CINHAL (EBSCO), and Google Scholar based on the concepts: randomized, colorectal, anastomotic leak, and fluorescence imaging. The risk of bias was assessed using RoB2 and the certainty of the evidence with the GRADE Pro tool. The analysis used the log odds ratio for dichotomous data with 95% confidence intervals. Back-transformation of the log odds to odds ratio was performed for the summary of findings. All syntheses used the Random-effects model.
Results: Six randomized trials were included with 1949 patients and 204 events (leaks). Three trials included exclusively rectal cancer patients, while the other three involved benign and malignant pathologies of the sigmoid and rectum. The use of ostomy and preoperative radiation was variable. None of the studies had a high risk of bias. The pooled odds ratio for anastomotic leak reduction with Indocyanine Green (ICG) fluorescence was 0.586 (95% CI: 0.434–0.792). An absolute reduction of 4.7% in leak rates was observed, with no statistical heterogeneity ($I^2 = 0$; $p = 0.529$). Due to clinical heterogeneity, the quality of evidence was rated moderate.
Conclusions: The use of ICG is associated with reduced leak rates following left-sided colorectal anastomosis with moderate confidence. ICG may be considered a standard of care given the clinically significant benefit in decreasing anastomotic leaks.

Introduction

Anastomotic leaks are the bête noire of colorectal surgery, and leaks are a dreaded complication that surgeons attempt to pre-empt and prevent. Amongst the factors that can be modified, the vascularity of the bowel ends to be anastomosed remains a crucial variable. Traditionally, visual inspection of bowel colour, pulsations, and bright bleeding at cut edges was relied upon to confirm vascularity. However, with the near-universal adoption of minimally invasive surgery, intracorporeal anastomosis, and natural orifice specimen extraction, many conventional methods to assess bowel perfusion cannot be reliably performed. The use of fluorescence imaging may overcome the subjectiveness of visual inspection and is not very resource-intensive.

Multiple randomized trials have investigated the utility of indocyanine green (ICG) fluorescence angiography (FA) for colorectal anastomotic leaks with variable results.[1–4] Several meta-analyses have also been reported to overcome the variability in the results for left-sided anastomosis using ICG FA.[5–8] The most recent meta-analysis synthesized the results from four randomized controlled trials (RCT) and demonstrated a risk difference of 4.5% (p-0.031) for anastomotic leaks with the use of FA.[5]

The present systematic review and meta-analysis (SRMA) aimed to update the previous meta-analysis and also search unpublished literature resources to reduce publication bias. The objective of the present SRMA is to include randomized trials of patients

undergoing left-sided colorectal anastomosis comparing the use of ICG FA against visual inspection alone to reduce AL.

Methods

The study protocol was preregistered in PROSPERO (CRD42024530466) and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) were used for reporting the study.

Eligibility criteria

The Population, Intervention, Control, Outcomes, and Studies (PICOS) framework was used to define the inclusion criteria for studies in the SRMA. Patients undergoing left-sided colorectal resection with primary anastomosis with or without a proximal diversion formed the population. The resection could be for benign or malignant pathologies and the anastomosis should be between colon and colon or colon and rectum. Any surgical approach, minimally invasive or open, for the resection and anastomosis was allowed. The intervention was the use of ICG FA for perfusion assessment of the bowel ends after resection. The control arm for the studies was the visual assessment of bowel vascularity. The primary outcomes of studies should be AL and we included only RCTs for the present SRMA.

Information sources and search strategy

The databases searched were PubMed, Cochrane Library, Scopus, CINHAL (EBSCO), and Google Scholar on 13 March 2024. The search was carried out using keywords, medical subject headings (MeSH) and its equivalents, Boolean operators, wild cards, and explode functions by one author (MK). No time filters were applied, however, we included studies available or translated into English. The detailed line-by-line search strategy is presented in supplement S1 for each database along with the number of results obtained. The search strategy was based on the following four concepts: randomized, colorectal, anastomotic leak, and fluorescence imaging. Backward citation chasing was performed on the items selected for full-text review and of previous meta-analyses on the same topic. Unpublished manuscripts, preprints, and conference or abstract presentation searches were done through Google Scholar. Backward citation search of references selected for full-text review and review articles on the same topic were also included.

Study selection and data extraction

Two authors (AA and RY) independently performed the initial screening of titles and abstracts after deduplication of results using the web software Rayyan.[9] All conflicts were resolved by the third author (MK). After the title and abstract screening, eligible studies underwent full-text screening by two authors (MK and RY). The same PICOS criteria mentioned above were used for screening.

The final data extraction was performed in duplicate (AA and RY) while conflicts and discrepancies were resolved in consultation with a third author (MK). The following data were collected: Name, first author, duration, and year of publication of study; population (benign, malignant) and location of pathology (left colon, rectum); demographic characteristics (age, gender, and body mass index); treatment factors (preoperative radiation, surgical approach, location of anastomosis, operative time, diverting ostomy); ICG FA features (platform, dose, interval between injection and assessment, margin revision); and outcome variables (AL, overall complications, reoperation rate).

AL was defined using the International Study Group of Rectal Cancers (ISGRC) and categorized as A, B, and C depending on the severity and the need for interventions.[10] AL grade A are largely asymptomatic leaks and result in no change in clinical management. AL grade B are those requiring interventions but not relaparotomy, while grade C leaks are those requiring reoperations. Operative complications were classified as per the Clavien-Dindo scale and major complications were defined as those ≥IIIA.[11]

Dichotomous outcomes were extracted as frequencies and proportions while continuous outcomes were recorded as means and standard deviations (SD). When individual studies reported medians with interquartile range, they were converted to means and SD using the R package 'estmeansd 0.2.1'.[12]

Risk of bias

The risk of bias (RoB) assessment was performed using the revised Cochrane Risk of Bias tool (RoB 2) for randomized trials.[13] RoB was independently evaluated by two authors (AA and AB) and disagreements were resolved by a third author (MK). Similarly, the quality and confidence of the evidence were evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach for each outcome measure.[14] The assessment of certainty of evidence will be presented using the Summary of Findings (SoF) table.

Data analysis

The Metafor (R package) was used for meta-analysis treatment effect calculation.[15] The analysis was carried out using the log odds ratio as the outcome measure for dichotomous data with 95% confidence intervals (CI). Back-transformation of the log odds to odds ratio (OR) was carried out for the summary of findings.[16] Continuous data were presented with mean differences as the summary estimate. Non-comparative pooled proportions were presented as raw proportions with 95% CI. A random-effects model was fitted to the data. The amount of heterogeneity (i.e., tau^2), was estimated using the DerSimonian-Laird estimator.[17] In addition to the estimate of tau,[2] the Q-test for heterogeneity and the I^2 statistic are reported.[18] When I^2 was >75%, studies were deemed to have high statistical heterogeneity, between 25% and 75% as medium, and <25% as low heterogeneity. All results were presented with 95% confidence intervals and with a P-value threshold of 0.05. Funnel plots and Egger's regression were not used for assessing publication bias since the SRMA did not have 10 or more studies for synthesis. Sensitivity analysis was performed by excluding studies contributing to clinical heterogeneity.

Results

Study selection

A total of 973 references were found in the initial literature search and backward citation of selected references (Fig. 1). After deduplication, 506 references were screened for eligibility based on title and abstracts. Eight articles underwent full-text screening, and two were excluded as they were study protocols alone.[19,20] A total of six RCTs were included for review and synthesis with 1949 patients and 204 events (anastomotic leaks).

Study characteristics

All studies were published in the last 5 years and included patients between 2015 and 2022. The included studies had representation from North America, Russia, Europe, East Asia and the Middle East.[1–4,21,22] While three studies included only cancer patients with rectal anastomosis,[2,3,21] three other studies included both benign and malignant processes in the sigmoid or the rectum with an anastomosis ≤15 cm from the anal verge.[1,4,22] The proportion of preoperative radiation use was variable and the majority had patients who underwent minimally invasive surgery alone except in two studies where open operations were also included.[1,2] The primary outcome for all studies was AL of any grade as per the ISGRC classification at 30 days (Table 1).

Risk of bias

There were no serious concerns in any of the studies, however, some concerns in the domains of measurement of outcomes and

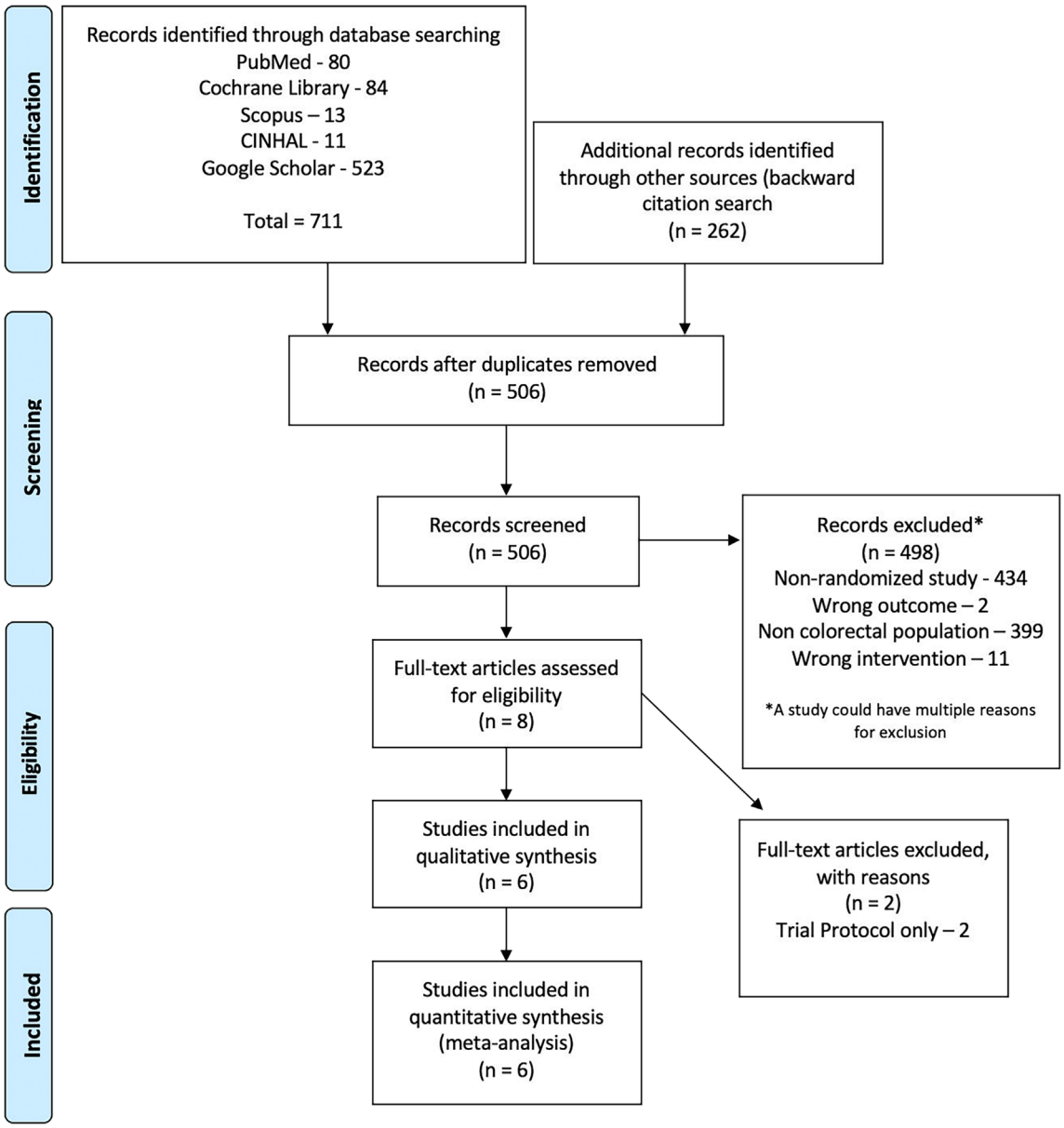

Fig. 1. PRISMA flow chart.

Table 1 Study characteristics

Study name (Region)	First author/ year	Period of study	Inclusion	N (ICG/Control0	%Rectum (ICG/Control)	% Prior Radiation (ICG/Control)	%MIS (ICG/Control)	%Ostomy (ICG/Control)	ICG platform	Primary outcome	Funding
Italian	De Nardi 2019	2016–2017	Benign or malignant; anastomosis ≤15 cm	118/122	47.5/43.5	23.7 /17.2	100/100	N/A	Karl Storz	AL @ 30d; Any grade	None
FLAG (Russia)	Alekseev 2020	2017–2019	Benign or malignant; anastomosis ≤15 cm	187/190	59.4/55.3	10.7/10	46.5/40.5	71.1/70.5	Karl Storz	AL @ 30d; Any grade	Government
PILLAR III (USA)	Jafari 2021	2015–2017	Malignant; rectum only	178/169	100/100	63.5/65.7	84.4/86.2	73.7/80.4	Stryker	AL @ 30d; Any grade	Stryker
EssentiAL (Japan)	Watanabe 2023	2018–2021	Malignant; rectum only	422/417	100/100	5.2/7.4	100/100	50.5/54.9	Stryker	AL @ 30d; Any grade	Stryker
Polish	Gach 2023	2020–2021	Malignant; rectum only	41/35	100/100	70.7/85.7	100/100	0/0	Karl Storz	AL @ 30d; Any grade	Institutional
Egyptian	Eltaweel 2024	2022	Benign or malignant	50/50	48/43.2	28/23.5	100/100	N/A	N/A	AL @ 30d; Any grade	None

ICG, indocyanine green; MIS, minimally invasive surgery.

reporting of results were noted in all but two studies[3,4] (Fig. 2). The majority of the concerns did not qualify for a high risk of bias (Supplement S2). Two studies (De Nardi *et al*. and Watanabe *et al*.) had no concerns in any of the domains,[3,4] while three studies were either stopped prematurely due to poor accrual (Jafari *et al*. and Alekseev *et al*.) or had unplanned, mid-study analysis (Gach *et al*).[1,2,21]

Results of individual studies

All studies demonstrated a reduction in AL at point estimates (4% to 18% reduction) with the use of ICG FA except for Jafari *et al*. (0.6% reduction).[2] A similar magnitude of risk reduction was observed in clinically significant anastomotic leaks as well (Table 2). Overall complications were reported by five studies, and the studies by De Nardi *et al*., Gach *et al*., and Eltaweel *et al*. showed a significant reduction in overall as well as major complications (≥grade IIIA).[4,21,22] Change in colonic transection line in the ICG arm was reported by four studies and varied from 2.4% to 19.3%.[1,3,4,21,22] No major differences in operatives were recognized.

One study reported separate leak rates in the two arms for patients with left or sigmoid resections and those with rectal resections,[1] while the other two studies which included sigmoid and rectal cancers, did not report individual leak rates. A significant difference was found only for low anastomosis (14.4% *vs*. 25.7%; ICG *vs*. Control). Similarly, only one study provided a separate OR for AL in patients with diverting stoma (OR - 0.819 95% CI: 0.468–1.433) and those without stoma (OR: 0.349; 95% CI: 0.141–0.860); and that for AL in patients after preoperative radiation (OR: 2.333; 95% CI: 0.354–15.36) or after upfront operation (OR: 0.564; 95% CI: 0.347–0.917).[3] Synthesis was not performed for these subgroups since only one study provided their respective outcome measures.

Results of syntheses

All six studies were included in the primary analysis for AL (Fig. 3). There was no statistical heterogeneity in the results ($I^2 = 0$; p – 0.529) and the pooled OR for AL reduction with the use of ICG FA was 0.586 (95% CI: 0.434–0.792). An absolute reduction of 4.7% in leak rates was observed from the baseline of 12.8% in the control group, and this translated into 49 fewer leaks per 1000 patients with left-sided anastomosis. For clinically significant AL (Grade B/C), the pooled OR with ICG use was 0.625 (95% CI: 0.437–0.894) without heterogeneity ($I^2 = 4\%$; p – 0.391) resulting in an absolute 2.9% reduction.

Overall operative complications were reported by five studies (Supplement S3). There was low heterogeneity ($I^2 = 18.34\%$; P – 0.311) and the pooled OR was 0.74 (95% CI: 0.545–1.005) with an absolute 4.1% reduction. Similarly, major complications (≥Grade IIIA) decreased by 1.4% with an OR of 0.802 (95% CI: 0.537–1.199). Operative time was not different between the intervention and control arm (mean difference of 2.51 min) with moderate heterogeneity in results ($I^2 = 60.16\%$; P – 0.045). The pooled proportion of patients in the ICG arm that required margin revision for poor perfusion was 9% (95% CI: 1%–17%) with high heterogeneity ($I^2 = 92\%$; $P < 0.01$).[1,3,4,21]

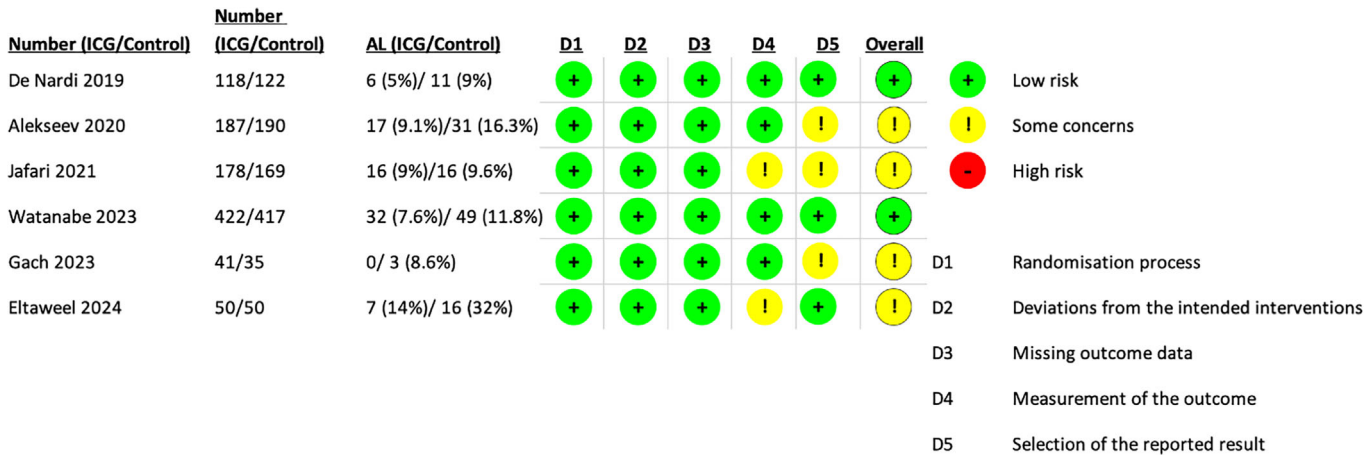

Fig. 2. Risk of bias assessment.

Table 2 Study outcomes

Study	Leak (ICG/Control)	AL: B + C (ICG/Control)	Operative time – Mean (SD) ICG/Control (min)	Change in transection line (%)	Complications (ICG/Control)	CDC ≥3a (ICG/Control)
De Nardi 2019	6 (5%)/11 (9%)	6 (5.8%)/10 (8.2%)	205.1 (67.6)/197.9 (62.5)	9.3	19 (16.1%)/32 (26.2%)	11 (9.3%)/14 (11.5%)
Alekseev 2020	17 (9.1%)/31 (16.3%)	10 (5.34%)/10 (5.26%)	186.5 (60.9)/182 (52.8)	19.3	23 (12.3%)/25 (13.2%)	8 (4.3%)/7 (3.7%)
Jafari 2021	16 (9%)/16 (9.6%)	12 (6.9%)/14 (8.6%)	NA	NA	NA	NA
Watanabe 2023	32 (7.6%)/49 (11.8%)	20 (4.7%)/34 (8.2%)	318.7 (116.3)/346.5 (152.8)	2.4	82 (19.4%)/89 (21.3%)	23 (5.4%)/27 (6.5%)
Gach 2023	0/3 (8.6%)	0/3 (8.6%)	132.4 (39.6)/128.6 (37.7)	7.3	6 (14.6%)/7 (20%)	1 (2.4%)/3 (8.6%)
Eltaweel 2024	7 (14%)/16 (32%)	6 (12%)/13 (25.5%)	NA	NA	7 (14%)/16 (32%)	4 (8%)/7 (14%)

AL, anastomotic leak; CDC, Clavien-Dindo classification; ICG, indocyanine green; NA, not available.

Sensitivity analysis

Sensitivity analysis for the primary outcome (AL) was performed by excluding studies that had heterogeneous patient populations (benign and malignant, left colon and rectum). Synthesis with three studies that included rectal cancers alone with low anterior resection was performed.[2,3,21] With low heterogeneity ($I^2 = 14.71\%$; P – 0.310), the OR favoured the use of ICG (OR – 0.683; 95% CI: 0.428–1.089). Another sensitivity analysis was performed by excluding the two studies that also had open operations[1,2] (Supplement S4). The OR for AL was 0.538 (95% CI: 0.365–0.794) without any heterogeneity ($I^2 = 0\%$).

Certainty of evidence

Due to serious clinical heterogeneity between studies, the meta-analysis for every outcome was rated down by one level, despite minimal statistical heterogeneity. For all the secondary outcomes, indirectness led to another step down in the certainty of evidence (Table 3). For the primary outcome (AL), there was moderate confidence in the estimated effect size, while for the secondary outcomes, there was limited certainty (Supplement S5).

Discussion

The present meta-analysis included six randomized trials of 1949 patients with left-sided colorectal anastomosis and compared the use of ICG FA against visual inspection of bowel ends with the primary aim of reducing ALs. There was a 4.7% absolute reduction in leaks, translating into 49 fewer leaks for every 1000 anastomosis. There was moderate certainty in the evidence synthesized and the estimates generated.

The use of ICG FA is an attractive and convenient method of assessing perfusion of organs besides its other myriad uses. In colorectal surgery, and especially in minimally invasive surgeries, conventional methods to assess perfusion (bleeding of edges, pulsations, bowel colour) fall short and do not provide a sense of objectivity. Using fluorescence perfusion imaging overcomes these challenges, and besides providing enhanced infrared visualization of vascularity, it also can now quantitatively assess the perfusion.[23]

Few meta-analyses of studies using ICG in colorectal surgery have shown that in non-randomized and randomized trials, leak rates are lower with the use of ICG FA.[5–8] The last meta-analysis of RCTs had four studies and 1510 patients and demonstrated a 4.9% absolute reduction in ALs.[5] However, since there have been

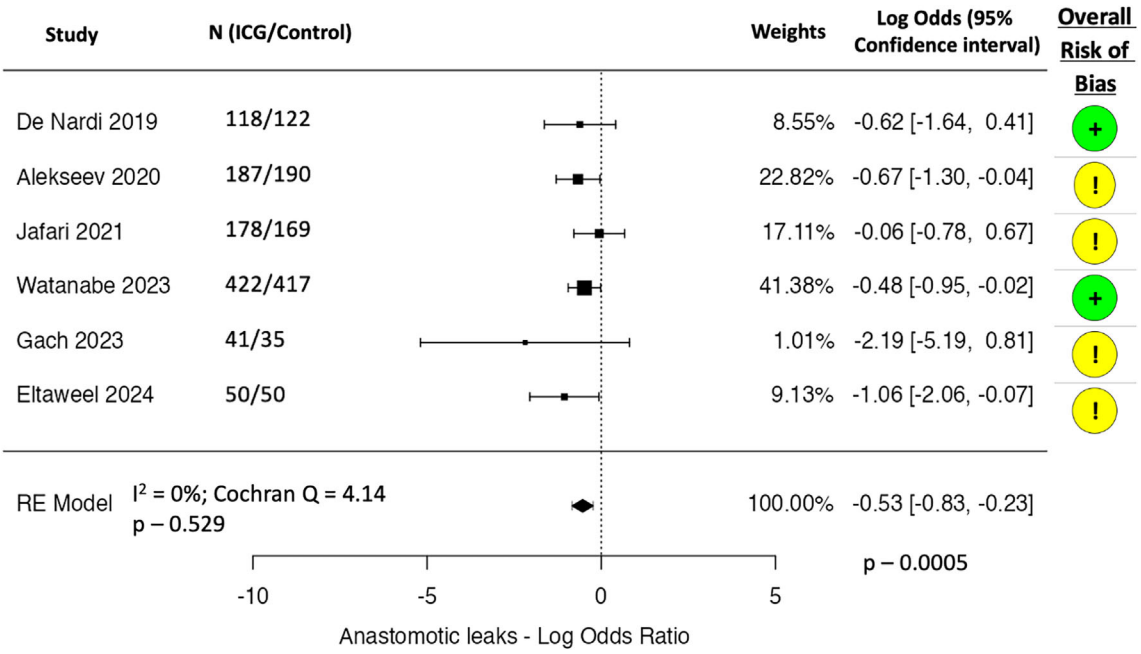

Fig. 3. Forest plot for anastomotic leaks.

two more RCTs published since then, we decided to carry out an SRMA to include them and search for other similar publications and presentations of results.

All the included studies showed results in the same direction, of similar magnitude, and with overlapping confidence intervals, except for the study by Jafari *et al.*[2]; this led to minimal statistical heterogeneity within the studies, benefitting the certainty of estimates. Despite the absence of statistical heterogeneity, differences in patient population, pathology, preoperative radiation use, surgical approach, level of anastomosis, and the use of diversion ostomy, made the studies clinically heterogeneous. To overcome some of these, we carried out two sensitivity analyses based on the subgroup information provided in the texts and supplements of the respective trials.

The first sensitivity analysis excluded studies that enrolled patients with benign pathologies or sigmoid resections and the other analysis excluded studies that had open resections. Both of them found that ICG reduced AL to the same extent. For rectal cancers alone, a previous meta-analysis did commendable work in combining two RCTs with low anterior resections with two other trials that provided subgroup data.[5] We did not want to duplicate the work already done since they found a similar reduction in leak rates. Although desirable to perform separate analyses for patients with or without a stoma and patients with prior radiation, only one study provided individual estimates of these subgroups.[3]

None of the included studies had a high RoB, however, some concerns arose due to the lack of blinding of the assessor.[2] Although anastomotic leaks appear to be objectively defined by the ISGRC classification, Grade A leaks can potentially be misclassified especially when documentation by contrast study in the presence of a diverting stoma is not mandated as in the study by Eltaweel *et al.*[22] Another area of concern was the sample size recalculation,[1] trial stopping mid-way due to poor accrual,[2] and unplanned analysis during the study[21]; all of which can lead to false positive results. Overall, none of the studies had a RoB that warranted a sensitivity analysis.

We decided to downgrade the level of evidence generated due to clinical heterogeneity despite including only randomized trials without high RoB or statistical heterogeneity. Nonetheless, there were studies representing almost every region of the world and all patients had an anastomosis ≤15 cm from anal verge; these make the results generalizable to the entire population of patients undergoing restorative sigmoid or rectal resections.

Amongst other endpoints studied, grade B/C leaks, operative complications, and high-grade (≥IIIA) complications showed improvement as well with the use of ICG with variable degrees of heterogeneity. The rate of margin revision in the ICG arm was 9%, ranging from 2.4% to 19.3%. A direct correlation between margin revision and AL was not found. Intuitively, the AL reduction should be higher where the proportion of margin revision was more. However, this was not always the case and there is an element of subjectivity concerning the acceptable intensity of fluorescence. Objective quantitative perfusion assessment can remove subjectivity and should be incorporated in future studies.[23]

The PILLAR III study is the only one that did not show a benefit with ICG.[2] Reasons for the same are not very clear, but ALs are multifactorial and the study did not report on the margin revision rates. However, the confidence intervals of the estimate overlap with those of the other included studies, and thus, the point estimates could simply be due to random sampling. Although AL is an important endpoint, with experience, the additive benefit of ICG

Table 3 Summary of findings

Use of fluorescence perfusion imaging compared to visual inspection of bowel ends for left-sided colorectal anastomotic leak prevention

Patient or population: Left-sided colorectal anastomotic leak prevention

Setting: Within randomized controlled trials

Intervention: Use of Fluorescence perfusion imaging

Comparison: Visual inspection of bowel ends

Outcomes	Anticipated absolute effects[†] (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with visual inspection of bowel ends	Risk with use of fluorescence perfusion imaging				
Anastomotic leak	128 per 1000	79 per 1000 (60 to 104)	OR 0.586 (0.434 to 0.792)	1949 (6 RCTs)	⨁⨁⨁◯ Moderate[‡]	Use of Fluorescence perfusion imaging likely reduces anastomotic Leak.
Grade B/C anastomotic leaks	85 per 1000	55 per 1000 (39 to 77)	OR 0.625 (0.437 to 0.894)	1949 (6 RCTs)	⨁⨁◯◯ Low[‡,§]	Use of Fluorescence perfusion imaging may result in a reduction in grade B/C anastomotic leaks.
Complications	208 per 1000	162 per 1000 (125 to 208)	OR 0.740 (0.545 to 1.005)	1632 (5 RCTs)	⨁⨁◯◯ Low[‡,§,¶]	Use of Fluorescence perfusion imaging may result in a reduction in complications.
Major complications (≥Grade IIIA)	71 per 1000	58 per 1000 (40 to 84)	OR 0.802 (0.537 to 1.199)	1632 (5 RCTs)	⨁◯◯◯ Very low[‡,§,¶]	Use of Fluorescence perfusion imaging may reduce/have little to no effect on major complications (≥Grade IIIA) but the evidence is very uncertain.
Operative time	The mean operative time was 213.9 min	MD 2.51 min lower (16.9 lower to 11.8 higher)	-	1532 (4 RCTs)	⨁⨁◯◯ Low[§,¶,††]	Use of Fluorescence perfusion imaging may result in little to no difference in operative time.

CI, confidence interval; MD, mean difference; OR, odds ratio.

GRADE Working Group grades of evidence—*High certainty*: we are very confident that the true effect lies close to that of the estimate of the effect. *Moderate certainty*: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. *Low certainty*: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. *Very low certainty*: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[†]The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[‡]Clinical heterogeneity between study populations.

[§]Primary outcome was to measure leaks of any grade.

[¶]95% CI includes unity.

[††]Heterogeneity.

may be reduced. Yet, subclinical impaired perfusion that does not cause leaks often leads to strictures, which may be an essential outcome measure to study in the future. Although two trials reported stricture rates, their follow-up was insufficient.[4,22]

Limitations and future perspectives

One limitation in the conduct of this SRMA was the lack of individual patient data. Performing an individual patient data meta-analysis could have further decreased clinical heterogeneity by performing pooled subgroup analysis. Another shortcoming is the lack of inclusion of publications in languages other than English (or not translated into English) and that we did not systematically search for conference presentations in the conference proceedings publication that were not listed in the databases queried. Next, publication bias could not be assessed since the number of available high-quality studies was fewer than 10. Publication bias could potentially contribute to the observed positive influence of ICG.

At least five randomized trials comparing ICG use in preventing colorectal anastomotic leaks are currently ongoing which will update our current understanding of the effects that ICG has in reducing AL.[19,20,24–26] Future studies should use quantitative assessments of perfusion as well as stricture rates as an outcome measure.

Conclusion

The use of ICG reduces leak rates following left-sided colorectal anastomosis with a moderate degree of confidence. ICG may be

considered a standard of care given the clinically significant benefit in decreasing ALs.

Author contributions

Mufaddal Kazi: Conceptualization; formal analysis; investigation; methodology; project administration; resources; software; visualization; writing – original draft; writing – review and editing. **Atul Ajith:** Data curation; investigation; validation; writing – review and editing. **Abhiram Bhoyar:** Data curation; resources; validation; writing – review and editing. **Raghav Yelamanchi:** Conceptualization; data curation; resources; validation; writing – review and editing.

Conflicts of interest

None declared.

Registration

The study protocol was preregistered in PROSPERO (CRD42024530466).

Data availability statement

The data that support the findings of this study are available publicly.

References

1. Alekseev M, Rybakov E, Shelygin Y, Chernyshov S, Zarodnyuk I. A study investigating the perfusion of colorectal anastomoses using fluorescence angiography: results of the FLAG randomized trial. *Colorectal Dis.* 2020; **22**: 1147–53.
2. Jafari MD, Pigazzi A, McLemore EC *et al*. Perfusion assessment in left-sided/low anterior resection (PILLAR III): a randomized, controlled, parallel, multicenter study assessing perfusion outcomes with PINPOINT near-infrared fluorescence imaging in low anterior resection. *Dis. Colon Rectum* 2021; **1**: 995–1002.
3. Watanabe J, Takemasa I, Kotake M *et al*. Blood perfusion assessment by indocyanine green fluorescence imaging for minimally invasive rectal cancer surgery (EssentiAL trial): a randomized clinical trial. *Ann. Surg.* 2023; **1**: e688–94.
4. De Nardi P, Elmore U, Maggi G *et al*. Intraoperative angiography with indocyanine green to assess anastomosis perfusion in patients undergoing laparoscopic colorectal resection: results of a multicenter randomized controlled trial. *Surg. Endosc.* 2020; **34**: 53–60.
5. Lucarini A, Guida AM, Orville M, Panis Y. Indocyanine green fluorescence angiography could reduce the risk of anastomotic leakage in rectal cancer surgery: a systematic review and meta-analysis of randomized controlled trials. *Colorectal Dis.* 2024; **26**: 408–16.
6. Lin J, Zheng B, Lin S, Chen Z, Chen S. The efficacy of intraoperative ICG fluorescence angiography on anastomotic leak after resection for colorectal cancer: a meta-analysis. *Int. J. Colorectal Dis.* 2021; **36**: 27–39.
7. Deng J, Hu W, Li Y *et al*. Meta analysis of indocyanine green fluorescence in patients undergoing laparoscopic colorectal cancer surgery. *Front. Oncol.* 2022; **12**: 1010122.
8. Arezzo A, Bonino MA, Ris F *et al*. Intraoperative use of fluorescence with indocyanine green reduces anastomotic leak rates in rectal cancer surgery: an individual participant data analysis. *Surg. Endosc.* 2020; **34**: 4281–90.
9. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst. Rev.* 2016; **5**: 210.
10. 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**: 339–51.
11. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann. Surg.* 2004; **240**: 205–13.
12. McGrath S, Zhao X, Steele R, Thombs BD, Benedetti A, DEPRESSion Screening Data (DEPRESSD) Collaboration. Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. *Stat. Methods Med. Res.* 2020; **29**: 2520–37.
13. Sterne JAC, Savović J, Page MJ *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **28**: l4898.
14. Schünemann H, Brożek J, Guyatt G, Oxman A (eds). *GRADE handbook for grading quality of evidence and strength of recommendations*. The GRADE Working Group, 2013 Updated October 2013. Available from: guidelinedevelopment.org/handbook.
15. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J. Stat. Softw.* 2010; **5**: 1–48.
16. Hu D, Wang C, O'Connor AM. A method of back-calculating the log odds ratio and standard error of the log odds ratio from the reported group-level risk of disease. *PLoS One* 2020; **15** [Cited 28 Apr 2024.] Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7053742/.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control. Clin. Trials* 1986; **7**: 177–88.
18. Cochran WG. The combination of estimates from different experiments. *Biometrics* 1954; **10**: 101–29.
19. Armstrong G, Croft J, Corrigan N *et al*. IntAct: intra-operative fluorescence angiography to prevent anastomotic leak in rectal cancer surgery: a randomized controlled trial. *Colorectal Dis.* 2018; **20**: O226–34.
20. Meijer RPJ, Faber RA, Bijlstra OD *et al*. AVOID; a phase III, randomised controlled trial using indocyanine green for the prevention of anastomotic leakage in colorectal surgery. *BMJ Open* 2022; **1**: e051144.
21. Gach T, Bogacki P, Orzeszko Z *et al*. Fluorescent ICG angiography in laparoscopic rectal resection – a randomized controlled trial. Preliminary report. *Wideochir Inne Tech Maloinwazyjne* 2023; **18**: 410–7.
22. Eltaweel MM, Mohamadain AH. The value of intraoperative indocyanine green angiography to assess anastomotic perfusion and leakage in patients undergoing laparoscopic colorectal resection: a randomized controlled clinical trial. *Al-Azhar Int. Med. J* 2024; **5** Available from: https://aimj.researchcommons.org/journal/vol5/iss1/10.
23. Van Den Hoven P, Osterkamp J, Nerup N *et al*. Quantitative perfusion assessment using indocyanine green during surgery — current applications and recommendations for future use. *Langenbecks Arch. Surg.* 2023; **408**: 67.
24. Acibadem University. The role of indocyanine green (ICG) fluorescence imaging on anastomotic leak and short-term outcomes in robotic colorectal surgery: a prospective randomized trial [Internet]. clinicaltrials.gov. Report No: NCT02598414; 2015 Available from: https://clinicaltrials.gov/study/NCT02598414

25. Helminen O. Indocyanine green fluorescence imaging in prevention of colorectal anastomotic leakage [Internet]. clinicaltrials.gov. Report No: NCT03602677; 2023 Available from: https://clinicaltrials.gov/study/NCT03602677
26. Centre Hospitalier Universitaire de Besancon. Intraoperative indocyanine green fluorescence angiography in colorectal surgery to prevent anastomotic leakage: a Single-blind Phase III Multicenter Randomized Controlled Trial (Intergroup FRENCH-GRECCAR Trial) [Internet]. clinicaltrials.gov. Report No: NCT05168839; 2024 Available from: https://clinicaltrials.gov/study/NCT05168839

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Data S1: Search strategy.
Data S2: Detailed risk of bias assessment.
Data S3: Forest plot for secondary outcomes.
Data S4: Forest plot for sensitivity analysis.
Data S5: GRADE assessment.