Systematic review, meta-analysis and trial sequential analysis of randomized controlled trials on the impact of indocyanine green fluorescence angiography for anastomotic leakage in colorectal surgery

Francesco Brucchi, Luigi Boni, Sara Lauricella, Richard Sassun, Gianlorenzo Dionigi, Giovanni Taffurelli, Isacco Montroni, Elisa Cassinotti, Ludovica Baldari

PII: S0039-6060(26)00331-4

DOI: https://doi.org/10.1016/j.surg.2026.110406

Reference: YMSY 110406

To appear in: *Surgery*

Received Date: 10 March 2026

Revised Date: 10 June 2026

Accepted Date: 16 June 2026

Please cite this article as: Brucchi F, Boni L, Lauricella S, Sassun R, Dionigi G, Taffurelli G, Montroni I, Cassinotti E, Baldari L, Systematic review, meta-analysis and trial sequential analysis of randomized controlled trials on the impact of indocyanine green fluorescence angiography for anastomotic leakage in colorectal surgery, *Surgery* (2026), doi: https://doi.org/10.1016/j.surg.2026.110406.

Indocyanine Green Fluorescence Angiography Significantly Reduces Anastomotic Leakage in Colorectal Surgery

Systematic review, meta-analysis & trial sequential analysis of 7 RCTs

Study Design and Sample

7 RCTs
randomized trials · 2020–2025

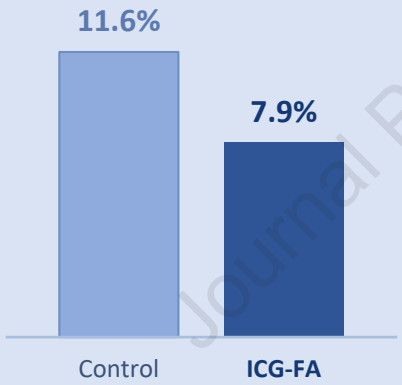
4,636 patients
2,318 ICG vs 2,318 control

Colorectal resections with primary anastomosis · PRISMA · PROSPERO-registered

Low risk of bias (RoB2) · GRADE high · $I^2 = 0\%$

Major Result

Anastomotic leak rate



−31%
relative risk reduction

RR 0.69
95% CI 0.58–0.82
p < 0.001

NNT = 27 · treat 27 to prevent one leak

TSA: evidence conclusive — required information size reached

Conclusions and Clinical Implications

- **ICG fluorescence angiography significantly reduces anastomotic leakage in colorectal surgery.**
- TSA confirms the evidence is conclusive — no further trials needed for the overall outcome.
- Routine use is justified, particularly in low / left-sided colorectal resections.

SURGERY

Brucchi F, Boni L, Lauricella S, et al.

Two-Sentence Article Summary

This systematic review and meta-analysis of six randomized controlled trials involving 3,500 patients evaluated whether indocyanine green (ICG) fluorescence angiography reduces anastomotic leakage in colorectal surgery. The pooled analysis showed that ICG significantly lowers leak rates compared with standard assessment, and trial sequential analysis suggests that the current evidence is sufficient to support its routine use for intraoperative perfusion assessment.

Title Page

Article type: Meta-analysis

Full title of the manuscript: Systematic review, meta-analysis and trial sequential analysis of randomized controlled trials on the impact of indocyanine green fluorescence angiography for anastomotic leakage in colorectal surgery

Authors: Francesco Brucchi [1], Luigi Boni [1,2], Sara Lauricella [4], Richard Sassun [6], Gianlorenzo Dionigi [2,5], Giovanni Taffurelli [4], Isacco Montroni [4], Elisa Cassinotti [1,3], Ludovica Baldari[1]

Affiliations:

1) Department of General and Minimally Invasive Surgery, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. Via Francesco Sforza 35, 20122, Milan, Italy.

2) Department of Pathophysiology and Transplantation University of Milan, 20122 Milan, Italy

3) Department of Scienze Cliniche e delle Comunità, University of Milan, Italy. Via Festa del Perdono 7, 20122, Milan, Italy.

4) Colorectal Surgery Unit, Fondazione IRCCS Istituto Nazionale Dei Tumori, Via Venezian 1, 20133, Milan, Italy

5) Division of Surgery, Istituto Auxologico Italiano IRCCS (Istituto Di Ricovero E Cura a Carattere Scientifico), Via Giuseppe Mercalli, 30, 20122, Milan, Italy

6) General Surgery Unit, Division of General Surgery, Pio XI Hospital, Desio, MB, Italy.

Corresponding author: Dr. Francesco Brucchi, Address: Via Francesco Sforza 35, 20122, Milan, Italy; telephone number: +39 0255035610; fax number: +39 0255033468 mail: francesco.brucchi@unimi.it

Prospero registry

Registration number: CRD42024622843

Abstract (335 words)

Background: Fluorescence angiography (FA) is increasingly used to reduce AL in colorectal surgery, yet conclusive evidence on its protective effect remains limited. This systematic review with meta-analysis and trial sequential analysis (TSA) of randomized controlled trials (RCTs) aimed to assess the effectiveness of FA using indocyanine green (ICG) in reducing anastomotic leakage (AL) and determine whether current evidence is sufficient to draw definitive conclusions.

Methods: A systematic review was conducted following PRISMA guidelines, with a comprehensive search of PubMed, Embase, Scopus, and Cochrane databases up to March 1, 2026. All RCTs evaluating intraoperative ICG use for AL prevention in colorectal surgery were included. The natural logarithm of the risk ratio [log(RR)] was calculated using random-effects models. The risk of bias was assessed with RoB2, and evidence quality was evaluated using the GRADE framework.

Results: Seven RCTs involving 4636 patients (2318 ICG, 2318 controls) were included. The AL rate was 7.9% in the ICG group versus 11.6% in the control group (RR 0.69; 95% CI 0.58–0.82; $p < 0.001$), with negligible heterogeneity ($I^2 = 0\%$). TSA demonstrated that the cumulative Z-curve crossed the monitoring boundary for benefit, indicating that the required information size had been reached. Subgroup analysis showed a significant reduction in AL in low colorectal or coloanal anastomoses (RR 0.63; 95% CI 0.51–0.76; $p = 0.002$). FA significantly reduced both grade A leaks (RR 0.54; 95% CI 0.32–0.92; $p = 0.006$) and grade B+C leaks (RR 0.67; 95% CI 0.48–0.93; $p = 0.006$). Postoperative complications were modestly reduced in the ICG group (RR 0.90; 95% CI 0.82–0.99; $p = 0.035$), while no significant differences were observed in operative time, length of hospital stay, or reoperation rate.

Conclusion: FA significantly reduces AL rate in colorectal surgery. TSA confirms that the required information size has been reached for the overall analysis, supporting the robustness of this finding. However, the subgroup analysis of low anastomoses has not yet reached the required information size, and further targeted trials are warranted to confirm the benefit in specific subgroups.

Funding: No funding was received.

Keywords: fluorescence angiography, anastomotic leakage, indocyanine green, ischemia, colorectal cancer, colorectal surgery, systematic review, meta-analysis.

Introduction

Despite pivotal steps forward of the surgical technique, anastomotic leakage (AL) is still one of the most devastating complications of colorectal surgery, with reported incidences ranging from 6 to 20% [1, 2]. This complication represents a major clinical challenge, being associated with poor postoperative outcomes such as perianastomotic abscess, peritonitis, septic shock, and increased mortality [3]. Moreover, AL negatively impacts oncological outcomes, increasing the risk of local recurrence and reducing long-term survival [4, 5]: for these reasons, any effort to prevent AL is crucial for patients.

Several risk factors for AL have been identified, including male sex, advanced age, comorbidities, immunosuppression, poor nutritional status, preoperative radiochemotherapy, tumor size, anastomosis close to the anal canal, low perfusion, and technical features [6, 7]. As proper oxygenation and vascular supply of the anastomotic site is mandatory to allow tissue healing, many techniques and technologies have been introduced in surgical practice to confirm them. More recently, indocyanine green (ICG) fluorescence angiography (FA) has been proposed and widely adopted in clinical practice to assess tissue perfusion in real time, particularly during colorectal surgery [7, 8]. Indeed, this technology enables surgeons to confirm the proper vascularization or to identify poorly perfused areas and to adjust the surgical plan, by changing the bowel transection line.

Several studies have demonstrated the efficacy of ICG fluorescence angiography in reducing AL rates [8, 9]. To date, four meta-analyses of randomized controlled trials (RCTs) have investigated the protective effect of fluorescence angiography using ICG on anastomotic leakage. The study by Lucarini et al. (2024) [10] included four RCTs and focused exclusively on rectal surgery, whereas the meta-analyses by Meyer et al. (2022) [11] and Elmajdub et al. (2024) [12] included both colon and rectal resections. More recently, an additional meta-analysis of RCTs has been published, further supporting the potential protective role of fluorescence angiography in reducing anastomotic leakage after colorectal surgery [13]. However, the lack of definitive conclusions of these analyses was primarily due to the limited number of available RCTs, many of which had small sample sizes and contrasting results. A pivotal factor in conducting our study was the recent publication of the AVOID trial [14] , the IntAct trial [15] and the ICG-COLORAL trial [16] which included substantially larger numbers of patients.

The aim of this study is to provide an updated systematic review and meta-analysis of existing evidence to establish the role of fluorescence angiography in reducing anastomotic leaks in colorectal surgery.

Methods

Search strategy and selection criteria

The study was conducted following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [17]. The research protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42024622843 (http://www.crd.york.ac.uk/PROSPERO). A systematic search of the peer-reviewed literature published from January 1st, 2000, to March 1st, 2026, was conducted using the PubMed, Embase, Scopus, and Cochrane Library databases. Search strategies for each database were developed using various combinations of keywords (detailed in Supplementary Materials, Fig. 1s). For PubMed, the search query included the following terms: (("Indocyanine Green"[Mesh] OR

"ICG" OR "indocyanine green angiography" OR "indocyanine green fluorescence" OR "fluorescence imaging" OR "angiography") AND ("Perfusion"[Mesh] OR "perfusion" OR "fluorescence" OR "angiography" OR "tissue perfusion") AND ("Colorectal Surgery"[Mesh] OR "colorectal surgery" OR "rectal surgery" OR "colon surgery" OR "colorectal procedures" OR "colorectal anastomosis") AND ("Anastomotic Leak"[Mesh] OR "anastomotic leakage" OR "anastomosis failure" OR "leakage" OR "complication")). Additionally, the reference lists of all included articles were reviewed to identify any relevant studies that met the inclusion criteria. Two investigators (FB, LB) independently performed the literature search and data extraction using Rayyan systematic review software [18]. They assessed the eligibility of all preliminarily identified records independently, based first on the title and then on the abstract. After the preliminary selection, the full-text manuscripts of relevant studies were carefully reviewed to confirm eligibility and to extract useful information. Any disagreements regarding eligibility were solved by a third reviewer (SL). Studies were included based on the following criteria: 1) randomized controlled trials written in English; 2) patients undergoing colorectal surgery (population) using ICG fluorescence angiography (intervention), compared to conventional methods (control); 3) anastomotic leak reported as one of the outcomes (outcome). No geographic restrictions were applied. Non-randomized studies and papers reporting duplicative results from the same authors' group were excluded.

Data Extraction

Two authors examined the main features of each retrieved article and reported the following data: first author, year of publication, study type, country of origin, study design, study period, near-infrared fluorescence imaging system, ICG dosage, number of participants, patient demographics (age, gender, BMI, and ASA score), and surgical parameters (operative time, blood loss, and distance of the anastomosis from the anal verge). Given the heterogeneity in the definition of 'low anastomosis' across the literature [19, 20], we categorized all anastomoses resulting from Low Anterior Resection (LAR) as 'low.' This pragmatic approach ensures analytical consistency and is unlikely to alter the clinical interpretation of the findings. Nonetheless, we acknowledge that it may entail some degree of misclassification, as the definition of "low anastomosis" is not uniform across studies and not all anastomoses performed in the context of LAR are truly low. Clinical outcomes, including anastomotic leak (AL) rate and severity (graded according to the International Study Group of Rectal Cancer) [21], stoma rate, postoperative morbidity (minor and major, per Clavien–Dindo classification) [22], mortality, length of hospital stay, and reoperation rate, were also recorded. Data from all relevant tables and figures in the included studies were reviewed for completeness.

Risk of Bias

The methodological quality and risk of bias for each study were assessed using the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB2) [23]. To evaluate the quality of evidence for each outcome, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [24] approach was used, categorizing the evidence level for each endpoint as 'very low,' 'low,' 'moderate,' or 'high.' The quality of the studies was either downgraded or upgraded based on criteria such as risk of bias, inconsistency, indirectness, imprecision, publication bias, large magnitude, dose-response, or the effect of all plausible confounding factors. Authors FB and LB performed the GRADE assessment.

Outcomes

All prespecified outcomes were classified as primary or secondary. Primary outcomes were:

- Overall anastomotic leak (AL) rate in colorectal surgery, compared between the ICG and non-ICG groups, expressed as risk ratio (RR)
- AL rate in rectal surgery with low colorectal or coloanal anastomoses, compared between the ICG and non-ICG groups in terms of RR, as previously defined
- Severity of AL, classified according to ISREC criteria into Grade A and Grades B + C. Two analyses were performed:
    1. Comparison between groups for Grade A and Grades B + C AL in the overall study population.
    2. Comparison between groups restricted to patients who experienced an AL.

Secondary outcomes were:

- Operative time (minutes from skin incision to closure)
- Postoperative complication rate (Clavien–Dindo classification)
- Reoperation rate within 30 days
- Length of hospital stay.

Statistical Analysis

Continuous variables were analyzed using the mean difference (MD) and 95% confidence interval (CI). Categorical variables were evaluated using the natural logarithm of the risk ratio [log(RR)] and 95% CI. Final pooled estimates were exponentiated and presented as standard risk ratios (RR) with 95% confidence intervals for clarity and clinical interpretability. When variables were reported as median and range, they were converted to mean and standard deviation (SD) according to Wan et al. [25]. The log (RR) was calculated using random-effects models. The Q statistic and I2 statistic were used to test heterogeneity. Low, moderate, and high degrees of heterogeneity corresponded to I2 values of 25%, 50%, and 75%, respectively. When high heterogeneity was detected, a sensitivity analysis was performed to assess the robustness of the findings by systematically excluding individual studies or subgroups to determine their impact on pooled effect estimates. Statistical analyses were conducted using Python (Python Software Foundation, available at http://www.python.org). Trial Sequential Analysis (TSA) was used to evaluate the type I error risk and calculate the required information size [26, 27]. The Lan–DeMets approach was applied to construct monitoring boundaries and adjust thresholds for statistical significance. The information size was determined using an alpha level of 0.05 and a statistical power of 80%. A z-curve was created based on consecutive z-values derived from two-sided significance testing. Monitoring boundaries were generated using conventional testing methods and the O'Brien–Fleming alpha-spending function. The accrued information size (AIS) was defined as the total number of observed patients included in the cumulative meta-analysis. TSA analyses were performed using the Trial Sequential Analysis software (version 0.9 beta, available at http://www.ctu.dk/tsa) [28].

Results

Study selection and quality assessment

The systematic literature search identified 211 papers on PubMed, 200 on Scopus, 55 on Cochrane, and 1497 on Embase, totaling 1963 papers. After removing duplicates, 1587 papers remained for screening. Following the review of title and abstract, 1507 papers were excluded due to irrelevance to the study's objectives. A total of 80 papers

underwent full-text screening, 73 of which were excluded for the following reasons: 8 of them involved the wrong population, 63 of them had the wrong study design, and 2 of them were abstracts or poster presentations only. Ultimately, seven randomized controlled trials (RCTs) [14–16, 29–32] involving 4636 patients met the inclusion criteria and were included in the review (Figure 1). These studies were published between 2020 and 2025 and conducted in Russia [31], Italy [30], the Netherlands [14], the United States [32], Japan [29], UK [15] and Finland [16]. A summary of the included studies is presented in Table 1. The risk of bias assessment for these studies is depicted in Figure 2s of the Supplementary Materials, and the GRADE [24] evaluation is provided in Table 4s of the Supplementary Materials. All studies were determined to have a low risk of bias, with the quality of evidence rated as high.

Baseline patients characteristics

A total of 4636 patients were included in the study, with 2318 in the ICG group and 2318 in the non-ICG group, all undergoing colorectal resections with anastomosis. Detailed information about the patients and procedures are provided in Tables 1s, 2s and 3s of the Supplementary Materials. The mean age was 66 ± 9.74 years in the ICG group and 66 ± 9.6 years in the control group. In the ICG group, there were 1343 men (57.9%) and 976 women (42.1%), compared to 1311 men (56.6%) and 1006 women (43.4%) in the control group. The mean BMI was 25.97 ± 4.55 in the ICG group and 26.04 ± 4.52 in the control group. Neoadjuvant treatment was administered to 443 patients (25.32%) in the ICG group and 429 patients (24.5%) in the control group. The anastomosis distance from the anal verge was reported by three studies only, all of which included left-sided colorectal resections exclusively in their series [29, 31, 32]. The mean distance of the anastomosis from the anal verge was 6.15 ± 2.88 cm in the ICG group and 6.32 ± 3.07 cm in the control group. Five studies [14–16, 29, 31] reported data on changes to the operative plan in the ICG group. In 180 out of 2022 cases (8.9%), ICG influenced the surgeon's decision to modify the transection line.

Meta-analysis and Trial Sequential Analysis

Anastomotic leak

All [14–16, 29–32] included studies reported the rate of AL. The cumulative AL rate was 7.9% (183/2318) in the ICG group and 11.56% (268/2318) in the control group. The random-effects model analysis of seven RCTs demonstrated a significant reduction in the risk of AL in the ICG group compared to the non-ICG group, with a RR of 0.69 (log(RR) -0.37; 95% CI: 0.58–0.82, $p < 0.001$) (Fig. 2). The heterogeneity was negligible (I^2=0%; p=0.742).

The trial sequential analysis (TSA) shows the cumulative z-curve crossing the benefit boundary curve (Fig. 3), indicating that the required information size has been reached for the overall analysis, supporting the robustness of the observed protective effect.

The subgroup analysis of patients undergoing LAR showed that three studies [14, 29, 31] reported specific data on anastomotic leaks. The AL rate was 9.66% (60/621) in the ICG group and 15.4% (95/617) in the control group. The random-effects model analysis of three RCTs demonstrated a significant reduction in the risk of AL in the ICG group compared to the non-ICG group, with a RR of 0.63 (log(RR) of -0.46 (95% CI: 0.16–0.76, p = 0.002). These findings indicate that fluorescence angiography significantly reduces the risk of leak in LAR (Fig. 4). The heterogeneity was negligible (I2=0%; p=0.87). The TSA shows a cumulative z-curve crossing the benefit boundary curve (Fig. 5), but the required information size has not yet been reached.

A further subgroup analysis was conducted based on the severity of AL, as reported by four studies [15, 29–31] that classified leak rates (Supplementary materials Fig. 3a-3b). The random-effects model analysis showed a significant difference in the risk of grade A anastomotic leak in the ICG group compared to the non-ICG group (RR = 0.54; CI 95%: 0.32-0.92, p=0.006; I2=0%), and the same result for grade B+C anastomotic leak (RR = 0.67; ln(RR) -0.40; CI 95%: 0.11-0.68, p=0.006; I2=0%).

Operative time

Four studies [14, 16, 29, 31] reported data on operative time (Fig. 6a). The mean operative time was 194.8 ± 79.2 minutes in the ICG group and 193.4 ± 86.5 minutes in the control group. The random-effects model analysis demonstrated no significant difference in operative time between the ICG and non-ICG groups, with a mean difference (MD) of −1.1 minutes (95% CI: −16.0 to 13.8; p = 0.89). Substantial heterogeneity was observed across studies (I^2 = 98%).

Postoperative complications

All included studies [14–16, 29–32] reported the rate of postoperative complications (Fig.6b). The rate was 29.2% in the ICG group (678/2318) and 32.6% (754/2318) in the control group. The random-effects model analysis of seven RCTs demonstrated a modest but statistically significant reduction in the rate of postoperative complications between ICG and non-ICG groups, with a RR of 0.9 (ln(RR) of -0.1; 95% CI: 0.82–0.99, p = 0.035). The heterogeneity was low (I2=13%).

Reoperations

Six included studies [14, 15, 29–31] reported the rate of reoperations (Fig.6c). The rate was 8% in the ICG group (186/2318) and 8.3% (192/2318) in the control group. The random-effects model analysis of six RCTs demonstrated a non-significant difference in the rate of reoperations between the ICG and non-ICG groups, with a RR of 0.99 (log (RR) of -0.01; 95% CI: -0.27–0.25, p = 0.96). The heterogeneity was moderate (I2=31.8%).

Length of Hospital Stay

Six studies [14, 15, 29–31] reported data on length of hospital stay (LOS) (Fig. 6d). The mean LOS was 7.72 ± 8.71 days in the ICG group and 7.68 ± 5.82 days in the control group. The random-effects model analysis showed a non-significant difference in the LOS between the ICG and non-ICG groups, with a MD of -0.01 days (95% CI: -0.05 – 0.05, p = 0.975). The heterogeneity was negligible (I2=0%).

Discussion

This systematic review and meta-analysis provides a comprehensive evaluation of the effectiveness of fluorescence angiography in reducing AL in colorectal surgery, including seven RCTs [14–16, 29–32], incorporating the recently published AVOID trial [14], IntAct trial [15] and ICG-COLORAL trial [16]. The results indicate that FA significantly lowers the overall AL rate from 11.56% to 7.9% (p<0.001). Particularly, for low anastomoses, the leak rate decreases from 15.4% to 9.66% (p=0.0023). Moreover, according to our results, FA is associated with a significant reduction of both subclinical (grade A, p=0.006) and clinical (grade B + C, p=0.006) AL. The TSA performed on the primary

outcome confirms that the required information size has been reached for the overall analysis, supporting the robustness of the observed protective effect. However, the TSA for the subgroup of low anastomoses has not yet reached the required information size, indicating that further trials targeting this specific subgroup are still warranted.

In their 2022 meta-analysis, Meyer et al. [11] noted that while individual RCTs investigating the protective effect of FA on ALs in colorectal surgery did not show statistically significant results, a significant protective effect became apparent in the pooled analysis. Similarly, Keller and Hompes, commenting on the prematurely closed PILLAR III trial [32], observed that its early termination, after recruiting 347 patients instead of the planned 800, prevented the trial from reaching an adequate sample size to conclusively demonstrate the effect of fluorescence angiography on AL [33]. Similar observations also apply to the recently published AVOID trial [14] and IntAct trial [15], both of which did not reach statistical significance for the primary outcome when analyzed independently. A further limitation of the AVOID trial [14] was the inclusion of right-sided colon resections, as well as resection performed for benign conditions. These are characterized by a lower prevalence of AL compared to the percentages used for the sample size calculation (12% for the control group *vs* 6% for the study group) and a lower prevalence of AL resulting from perfusion impairment. Even the IntAct trial [15], which included only rectal resections, failed to demonstrate a significant benefit of fluorescence angiography in decreasing the AL rate within 90 days after surgery. However, when combined with other RCTs, the overall results reinforce the protective effect of FA. The inclusion of the large ICG-COLORAL trial [16]– the most recent and one of the largest RCTs to date – further strengthens the evidence. Even though this trial alone did not reach statistical significance for the overall population, its addition to the pooled analysis maintains a highly significant protective effect of fluorescence angiography. The trial confirms a possible benefit restricted to left-sided colectomies, consistent with the subgroup findings of the other studies.

Several statistical and clinical considerations may account for these findings. In the EssentiAL [29] and IntAct [15] trials—both limited to rectal resections—sample size calculations assumed a reduction in AL from 13% and 12% in control group to 7% and 6% in study group, respectively. Indeed, AL is a multifactorial complication and the proportion of events directly attributable to impaired perfusion within these total rates is unknown. This uncertainty might have biased sample size estimates, leaving the trials underpowered. Furthermore, a single AL may result from multiple concurrent factors. Adequate serosal perfusion on ICG imaging does not exclude mucosal ischemia, which may act in synergy with other risks to complication development. Despite the expertise of participating centers, no consensus exists on standardized fluorescence protocols or objective criteria for defining the ICG transection line, potentially limiting the technology's impact. Under these conditions, demonstrating a statistically significant reduction in AL as a primary outcome in a RCT remains inherently challenging and, if perfusion and tissue oxygenation are recognized factors influencing tissue healings, the simple evidence of adequate perfusion should be considered enough for evaluating the benefit of such technology.

Studies by Alekseev et al. [31] and Watanabe et al. [29] suggest that fluorescence angiography is particularly effective in preventing AL in lower anastomoses, where the risk of leak is higher. Our study further builds on these findings by incorporating trial sequential analysis (TSA), which confirms that the protective effect of FA is unlikely to be disproven by future trials. However, despite the significant protective effect of fluorescence angiography, the required information size for this subgroup analysis has not yet been reached. The main limitation of this analysis is the impossibility of including data from the IntAct trial [15] , as it does not differentiate between high and low anastomoses.

Our study found a statistically significant lower AL rate in the ICG group, even when stratified by AL severity into both grade A and grades B and C. These results differ from those of Elmajdub et al. [12], who demonstrated a protective effect of fluorescence angiography on grade A ALs but not on grades B and C, as well as from those of Trastulli et al. [34], who reported a protective effect on grades B and C but not on grade A ALs. These discrepancies can likely be attributed to methodological differences: Elmajdub et al. [12] had a relatively small sample size, while Trastulli et al. [34] included around 15 studies with varying designs, including retrospective and prospective analyses, which may limit the reliability of the evidence. Once again, the strength of this study was its large sample size, even for the subgroup analyses.

Fluorescence angiography influenced the surgeon's decision to modify the transection line in 180 out of 2022 cases (8.9%). Among the included studies, only Faber et al. [14] reported the 90-day AL rate in patients whose transection line was adjusted based on FA guidance. Notably, the AL rate in these patients was 10% (4/41). The authors attributed this finding to a higher proportion of left-sided colorectal procedures (80% vs. 57%) and, specifically, low anterior resections (34% vs. 20%) in the surgical changes group compared to the overall ICG group. Furthermore, the surgical changes group exhibited higher comorbidity rates (90% vs. 86%), suggesting that these patients had an elevated baseline risk of postoperative complications. As previously noted, anastomotic leakage is multifactorial, influenced not only by insufficient vascular perfusion but also by patient-related factors and technical surgical aspects [35–37].

The use of ICG during colorectal surgery did not significantly increase operative time, in line with the 2023 EAES consensus by Cassinotti et al. [38]. By contrast, Elmajdub et al. [12] reported a significant increase in operative time with fluorescence angiography, although only after exclusion of the RCT by Wu et al. [39]. Overall, our findings do not support the hypothesis that FA meaningfully affects operative duration [12].

The 30-day postoperative complication rate was modestly but significantly lower in the ICG group. Most included RCTs [15, 16, 29–32] showed a trend toward reduced overall morbidity with fluorescence angiography, although effect sizes varied. The AVOID trial [14] reported a neutral result, possibly due to differences in patient selection, indications, and methodology. Overall, the pooled analysis supports a reduction in postoperative complications with FA, suggesting that the decrease in anastomotic leakage may translate into a broader, albeit modest, clinical benefit.

No statistically significant difference was observed in reoperation rates. Although this may appear counterintuitive, considering that anastomotic leakage is a major cause of reoperation in colorectal surgery [40], several factors may explain this finding. Lower anastomoses are both more prone to leakage and more often manageable conservatively, especially in the presence of a protective stoma [41, 42]. In addition, endoscopic and transanal techniques may further reduce the need for reoperation [43–45]. Along with the low overall event rate, these factors likely contributed to heterogeneity across studies. This finding is consistent with the meta-analyses by Tang et al. [46] and Elmajdub et al. [12], but differs from Liu et al. [47], who suggested a possible beneficial effect.

No statistically significant difference was found in length of hospital stay. This contrasts with Cassinotti et al. [38], who reported shorter hospitalization in the ICG group. Moreover, both Elmajdub et al. [12] and Trastulli et al. [34] emphasized the uncertainty surrounding this outcome, limiting the strength of any firm conclusion.

While statistical heterogeneity was negligible for the primary endpoint (I^2=0%), it is important to acknowledge the considerable clinical heterogeneity across the included trials. These differed substantially in terms of surgical indications (both benign and malignant disease), anastomotic level (ranging from right-sided colectomies to ultra-low anterior resections), ICG dosing protocols (from fixed 5 mg doses to weight-based 0.1–0.3 mg/kg), fluorescence imaging platforms (at least six different systems were used across the seven trials), and criteria for intraoperative modification of the transection line. Notably, neoadjuvant treatment rates varied across trials, the distance of the anastomosis from the anal verge was reported in only three studies, and changes to the operative plan were not documented in all trials. The absence of statistical heterogeneity should therefore not be interpreted as clinical homogeneity, and the pooled effect estimate should be contextualized within this variability. These considerations highlight that the overall protective effect of FA may not be uniformly applicable across all clinical scenarios, and that future studies should aim to identify which patient subgroups and surgical settings benefit most from this technology.
Several limitations inherent to the included studies warrant consideration. Firstly, the studies utilized different fluorescence imaging platforms. Secondly, as aforementioned, substantial variability existed in the protocols for ICG administration, including dosage and timing, with each study adopting a unique approach. This lack of standardization highlights the need for further research to establish uniform guidelines, as emphasized in recent consensus recommendations [38, 48, 49]. Moreover, the interpretation of fluorescence angiography remains operator-dependent, posing a challenge for providing consistent and objective assessments of anastomotic perfusion. Current evaluations have predominantly relied on subjective criteria, rather than well-defined fluorescence parameters. Lütken et al. [50] identified key metrics, such as time-to-peak fluorescence, fluorescence slope, and t1/2max, as reliable predictors of AL, suggesting that more objective parameters could enhance future applications of FA. Building on these insights, we recommend that future trials focus on refining the procedural protocols for FA, aiming to develop a more objective framework for perfusion assessment by incorporating fluorescence curves and standardized criteria to guide surgical decisions. Finally, the classification of all LAR anastomoses as ‘low’ was adopted for analytical consistency; however, this may have introduced misclassification, limiting the comparability of this subgroup across studies. Moreover, the subgroup analysis of AL severity was limited to four studies, and only three studies provided specific data for low anastomoses, restricting the strength of evidence for these secondary analyses.

In conclusion, this meta-analysis provides strong evidence that fluorescence angiography has a protective effect on AL in colorectal surgery, with a reduction in leakage rates of approximately 3% overall and 6% in low anastomoses. This corresponds to a number needed to treat of about 27 patients to prevent one anastomotic leak. TSA confirms that the required information size has been reached for the overall analysis, supporting the robustness of this finding. However, the benefit appears most pronounced in left-sided colectomies and low anterior resections, while the evidence for right-sided resections and benign disease remains less compelling. Although the overall protective effect is robust, the clinical heterogeneity across the included trials — in terms of indications, anastomotic level, ICG protocols, and imaging systems — warrants caution in generalizing these findings to all colorectal procedures. Routine use of FA appears justified, particularly in centers where the technology is already available and surgeons are familiar with its use. In this

setting, its integration into colorectal anastomotic assessment may represent a pragmatic and clinically valuable strategy, especially for high-risk anastomoses. Future research should focus on standardizing protocols, identifying the patient subgroups most likely to benefit, exploring advanced metrics such as time-to-peak and slope, and moving from subjective to objective fluorescence assessment in order to further optimize its protective effect.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

COI/Disclosure

Luigi Boni has received honoraria for Diagnostic Green. For the remaining authors none were declared.

Funding/Support

None

Acknowledgements

None

Contributors: FB conceived the study, designed the protocol, did the literature search, data extraction, statistical analysis, and drafted the first version of the manuscript. SL contributed substantially to study design, data acquisition, statistical analysis, and drafting of the manuscript. LBa contributed to literature screening, data verification, statistical analysis, and critical revision of the manuscript. LB provided senior surgical input, contributed to interpretation of the data, and critically revised the manuscript for important intellectual content. RS, GD, GT, IM, and EC contributed to data interpretation, provided clinical expertise, and revised the manuscript for intellectual content. FB and SL accessed and verified the underlying data. All authors had full access to all the data in the study, reviewed and approved the final version of the manuscript, and had final responsibility for the decision to submit for publication.

Data sharing statement

No individual participant data were collected for this study. All data used in the analyses are extracted from published articles, which are fully referenced in the manuscript. The search strategies, extracted datasets, and statistical analysis code are available from the corresponding author on reasonable request.

REFERENCES

1. Davis B, Rivadeneira DE (2013) Complications of Colorectal Anastomoses. Surgical Clinics of North America 93:61–87. https://doi.org/10.1016/j.suc.2012.09.014

2. Paun BC, Cassie S, MacLean AR, Dixon E, Buie WD (2010) Postoperative Complications Following Surgery for Rectal Cancer. Annals of Surgery 251:807–818. https://doi.org/10.1097/SLA.0b013e3181dae4ed

3. Thomas M, Margolin D (2016) Management of Colorectal Anastomotic Leak. Clinics in Colon and Rectal Surgery 29:138–144. https://doi.org/10.1055/s-0036-1580630

4. Ha GW, Kim JH, Lee MR (2017) Oncologic Impact of Anastomotic Leakage Following Colorectal Cancer Surgery: A Systematic Review and Meta-Analysis. Ann Surg Oncol 24:3289–3299. https://doi.org/10.1245/s10434-017-5881-8

5. Kim IY, Kim BR, Kim YW (2015) The impact of anastomotic leakage on oncologic outcomes and the receipt and timing of adjuvant chemotherapy after colorectal cancer surgery. International Journal of Surgery 22:3–9. https://doi.org/10.1016/j.ijsu.2015.08.017

6. Degiuli M, Elmore U, De Luca R, De Nardi P, Tomatis M, Biondi A, Persiani R, Solaini L, Rizzo G, Soriero D, Cianflocca D, Milone M, Turri G, Rega D, Delrio P, Pedrazzani C, De Palma GD, Borghi F, Scabini S, Coco C, Cavaliere D, Simone M, Rosati R, Reddavid R, and collaborators from the Italian Society of Surgical Oncology Colorectal Cancer Network Collaborative Group (2022) Risk factors for anastomotic leakage after anterior resection for rectal cancer (RALAR study): A nationwide retrospective study of the Italian Society of Surgical Oncology Colorectal Cancer Network Collaborative Group. Colorectal Disease 24:264–276. https://doi.org/10.1111/codi.15997

7. Meyer J, Naiken S, Christou N, Liot E, Toso C, Buchs NC, Ris F (2019) Reducing anastomotic leak in colorectal surgery: The old dogmas and the new challenges. WJG 25:5017–5025. https://doi.org/10.3748/wjg.v25.i34.5017

8. Chan DKH, Lee SKF, Ang JJ (2020) Indocyanine green fluorescence angiography decreases the risk of colorectal anastomotic leakage: Systematic review and meta-analysis. Surgery 168:1128–1137. https://doi.org/10.1016/j.surg.2020.08.024

9. Wojcik M, Doussot A, Manfredelli S, Duclos C, Paquette B, Turco C, Heyd B, Lakkis Z (2020) Intra-operative fluorescence angiography is reproducible and reduces the rate of anastomotic leak after colorectal resection for cancer: a prospective case-matched study. Colorectal Disease 22:1263–1270. https://doi.org/10.1111/codi.15076

10. Lucarini A, Guida AM, Orville M, Panis Y (2024) 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 Disease 26:408–416. https://doi.org/10.1111/codi.16868

11. Meyer J, Joshi H, Buchs NC, Ris F, Davies J (2022) Fluorescence angiography likely protects against anastomotic leak in colorectal surgery: a systematic review and meta-analysis of randomised controlled trials. Surg Endosc 36:7775–7780. https://doi.org/10.1007/s00464-022-09255-1

12. Elmajdub A, Brebesh N, Maatough A, Willeke F, Weiss C, Darwich I (2024) Does indocyanine green fluorescence angiography reduce the risk of anastomotic leaks in colorectal resections? A

systematic review and meta-analysis of randomized controlled trials. Updates Surg. https://doi.org/10.1007/s13304-024-02036-6

13. Maroli A, Paoluzzi Tomada E, Foppa C, Carvello M, Ris F, Hompes R, Arezzo A, Wexner S, Spinelli A (2026) Indocyanine green fluorescence to prevent anastomotic leak in colorectal surgery: an updated systematic review and meta-analysis on randomized controlled trials. Surg Endosc 40:1815–1827. https://doi.org/10.1007/s00464-026-12592-0

14. Faber RA, Meijer RPJ, Droogh DHM, Jongbloed JJ, Bijlstra OD, Boersma F, Braak JPBM, Meershoek-Klein Kranenbarg E, Putter H, Holman FA, Mieog JSD, Neijenhuis PA, Van Staveren E, Bloemen JG, Burger JWA, Aukema TS, Brouwers MAM, Marinelli AWKS, Westerterp M, Doornebosch PG, Van Der Weijde A, Bosscha K, Handgraaf HJM, Consten ECJ, Sikkenk DJ, Burggraaf J, Keereweer S, Van Der Vorst JR, Hutteman M, Peeters KCMJ, Vahrmeijer AL, Hilling DE (2024) Indocyanine green near-infrared fluorescence bowel perfusion assessment to prevent anastomotic leakage in minimally invasive colorectal surgery (AVOID): a multicentre, randomised, controlled, phase 3 trial. The Lancet Gastroenterology & Hepatology 9:924–934. https://doi.org/10.1016/S2468-1253(24)00198-5

15. Jayne D, Croft J, Corrigan N, Quirke P, Cahill RA, Ainsworth G, Meads DM, Kirby A, Tolan D, Gordon K, Hompes R, Spinelli A, Foppa C, Wolthuis AM, D'Hoore A, Vignali A, Tilney HS, Moriarty C, Vargas-Palacios A, Young C, Kelly R, Stocken D, Aryal K, Bajwa A, Baker R, Baker K, Bemelman W, Bislenghi G, Blind N, Bostrom P, Boyce S, Buczaki S, Cahill R, Chand M, Chitsabesan P, Coimbra Marques C, Cornish J, Courtney E, Coyne P, Cunningham C, Dalton S, Decker E, D'Hoore A, Di Benedetto G, Elmore U, Evans C, Foppa C, Forssell J, Gerdin A, Griffith J, Griffiths B, Grosek J, Gudgeon M, Guy R, Hance J, Harris D, Hompes R, Horwood J, Hussain T, James D, Jayne D, Jones O, Jourdan I, Juvan R, Kreis ME, Lauscher J, Leong K, Liao C, Lim M, Lindsey I, Maslekar S, Miskovic D, Nizar A, Norcic G, Paraoan M, Peristerakis I, Phillips S, Quyn A, Read J, Rockall T, Rosati R, Rutegard M, Sagar P, Saunders R, Scala A, Selvasekar C, Shaban M, Smith R, Smolarek S, Spinelli A, Symons N, Tanis P, Thaha MA, Tiernan J, Tilney H, Tomazic A, Torkington J, Tuynman J, Velchuru V, Vignali A, Wolthuis A (2025) Intraoperative fluorescence angiography with indocyanine green to prevent anastomotic leak in rectal cancer surgery (IntAct): an unblinded randomised controlled trial. The Lancet Gastroenterology & Hepatology 10:806–817. https://doi.org/10.1016/S2468-1253(25)00101-3

16. Rinne JKA, Huhta H, Pinta T, Turunen A, Mattila A, Tahkola K, Helminen O, Ohtonen P, Rautio T, Kössi J (2025) Indocyanine Green Fluorescence Imaging in Prevention of Colorectal Anastomotic Leakage: A Randomized Clinical Trial. JAMA Surg 160:486. https://doi.org/10.1001/jamasurg.2025.0006

17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ n71. https://doi.org/10.1136/bmj.n71

18. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A (2016) Rayyan—a web and mobile app for systematic reviews. Syst Rev 5:210. https://doi.org/10.1186/s13643-016-0384-4

19. Al Asari S, Cho MS, Kim NK (2015) Safe anastomosis in laparoscopic and robotic low anterior resection for rectal cancer: A narrative review and outcomes study from an expert tertiary center. European Journal of Surgical Oncology (EJSO) 41:175–185. https://doi.org/10.1016/j.ejso.2014.10.060

20. Slieker JC, Daams F, Mulder IM, Jeekel J, Lange JF (2013) Systematic Review of the Technique of Colorectal Anastomosis. JAMA Surg 148:190. https://doi.org/10.1001/2013.jamasurg.33

21. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, Holm T, Wong WD, Tiret E, Moriya Y, Laurberg S, Den Dulk M, Van De Velde C, Büchler MW (2010) Definition and grading of anastomotic leakage following anterior resection of the rectum: A proposal by the International Study Group of Rectal Cancer. Surgery 147:339–351. https://doi.org/10.1016/j.surg.2009.10.012

22. Clavien PA, Barkun J, De Oliveira ML, Vauthey JN, Dindo D, Schulick RD, De Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M (2009) The Clavien-Dindo Classification of Surgical Complications: Five-Year Experience. Annals of Surgery 250:187–196. https://doi.org/10.1097/SLA.0b013e3181b13ca2

23. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT (2019) RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ l4898. https://doi.org/10.1136/bmj.l4898

24. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336:924–926. https://doi.org/10.1136/bmj.39489.470347.AD

25. Wan X, Wang W, Liu J, Tong T (2014) Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 14:135. https://doi.org/10.1186/1471-2288-14-135

26. Claire R, Gluud C, Berlin I, Coleman T, Leonardi-Bee J (2020) Using Trial Sequential Analysis for estimating the sample sizes of further trials: example using smoking cessation intervention. BMC Med Res Methodol 20:284. https://doi.org/10.1186/s12874-020-01169-7

27. Miladinovic B, Mhaskar R, Hozo I, Kumar A, Mahony H, Djulbegovic B (2013) Optimal information size in trial sequential analysis of time-to-event outcomes reveals potentially inconclusive results because of the risk of random error. Journal of Clinical Epidemiology 66:654–659. https://doi.org/10.1016/j.jclinepi.2012.11.007

28. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G,, Gluud C (2011) User Manual for Trial Sequential Analysis (TSA)

29. Watanabe J, Takemasa I, Kotake M, Noura S, Kimura K, Suwa H, Tei M, Takano Y, Munakata K, Matoba S, Yamagishi S, Yasui M, Kato T, Ishibe A, Shiozawa M, Ishii Y, Yabuno T, Nitta T, Saito S, Saigusa Y, Watanabe M, for the EssentiAL Trial Group (2023) Blood Perfusion Assessment by Indocyanine Green Fluorescence Imaging for Minimally Invasive Rectal Cancer Surgery (EssentiAL trial): A Randomized Clinical Trial. Annals of Surgery 278:e688–e694. https://doi.org/10.1097/SLA.0000000000005907

30. De Nardi P, Elmore U, Maggi G, Maggiore R, Boni L, Cassinotti E, Fumagalli U, Gardani M, De Pascale S, Parise P, Vignali A, Rosati R (2020) Intraoperative angiography with indocyanine green to assess anastomosis perfusion in patients undergoing laparoscopic colorectal resection: results of a multicenter randomized controlled trial. Surg Endosc 34:53–60. https://doi.org/10.1007/s00464-019-06730-0

31. Alekseev M, Rybakov E, Shelygin Y, Chernyshov S, Zarodnyuk I (2020) A study investigating the perfusion of colorectal anastomoses using fluorescence angiography: results of the FLAG randomized trial. Colorectal Disease 22:1147–1153. https://doi.org/10.1111/codi.15037

32. Jafari MD, Pigazzi A, McLemore EC, Mutch MG, Haas E, Rasheid SH, Wait AD, Paquette IM, Bardakcioglu O, Safar B, Landmann RG, Varma MG, Maron DJ, Martz J, Bauer JJ, George VV,

Fleshman JW, Steele SR, Stamos MJ (2021) 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. Diseases of the Colon & Rectum 64:995–1002. https://doi.org/10.1097/DCR.0000000000002007

33. Keller DS, Hompes R (2021) PILLAR of Surgical Decision-Making? Perhaps Not Without More Evidence. Diseases of the Colon & Rectum 64:921–922. https://doi.org/10.1097/DCR.0000000000002098

34. Trastulli S, Munzi G, Desiderio J, Cirocchi R, Rossi M, Parisi A (2021) Indocyanine green fluorescence angiography *versus* standard intraoperative methods for prevention of anastomotic leak in colorectal surgery: meta-analysis. British Journal of Surgery 108:359–372. https://doi.org/10.1093/bjs/znaa139

35. Vignali A, Gianotti L, Braga M, Radaelli G, Malvezzi L, Carlo VD (2000) Altered microperfusion at the rectal stump is predictive for rectal anastomotic leak. Diseases of the Colon & Rectum 43:76–82. https://doi.org/10.1007/BF02237248

36. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC (2015) Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. British Journal of Surgery 102:462–479. https://doi.org/10.1002/bjs.9697

37. Penna M, Buchs NC, Bloemendaal AL, Hompes R (2016) Transanal total mesorectal excision for rectal cancer: the journey towards a new technique and its current status. Expert Review of Anticancer Therapy 16:1145–1153. https://doi.org/10.1080/14737140.2016.1240040

38. Cassinotti E, Al-Taher M, Antoniou SA, Arezzo A, Baldari L, Boni L, Bonino MA, Bouvy ND, Brodie R, Carus T, Chand M, Diana M, Eussen MMM, Francis N, Guida A, Gontero P, Haney CM, Jansen M, Mintz Y, Morales-Conde S, Muller-Stich BP, Nakajima K, Nickel F, Oderda M, Parise P, Rosati R, Schijven MP, Silecchia G, Soares AS, Urakawa S, Vettoretto N (2023) European Association for Endoscopic Surgery (EAES) consensus on Indocyanine Green (ICG) fluorescence-guided surgery. Surg Endosc 37:1629–1648. https://doi.org/10.1007/s00464-023-09928-5

39. Wu GLJ, Xu W, Guo C, Xu F. (2018) Application of indocyanine green imaging on preventing anastomotic leakage after laparoscopic colorectal cancer radical operation. 754–6

40. Boccola MA, Buettner PG, Rozen WM, Siu SK, Stevenson ARL, Stitz R, Ho Y (2011) Risk Factors and Outcomes for Anastomotic Leakage in Colorectal Surgery: A Single-Institution Analysis of 1576 Patients. World j surg 35:186–195. https://doi.org/10.1007/s00268-010-0831-7

41. Chiarello MM, Fransvea P, Cariati M, Adams NJ, Bianchi V, Brisinda G (2022) Anastomotic leakage in colorectal cancer surgery. Surgical Oncology 40:101708. https://doi.org/10.1016/j.suronc.2022.101708

42. Blumetti J, Chaudhry V, Cintron JR, Park JJ, Marecik S, Harrison JL, Prasad LM, Abcarian H (2014) Management of Anastomotic Leak: Lessons Learned from a Large Colon and Rectal Surgery Training Program. World j surg 38:985–991. https://doi.org/10.1007/s00268-013-2340-y

43. Chiarello MM, Bianchi V, Fransvea P, Brisinda G (2022) Endoluminal vacuum-assisted therapy as a treatment for anastomotic leakage in colorectal surgery. WJG 28:3747–3752. https://doi.org/10.3748/wjg.v28.i28.3747

44. Sirois-Giguère É, Boulanger-Gobeil C, Bouchard A, Gagné J-P, Grégoire RC, Thibault C, Bouchard P (2013) Transanal Drainage to Treat Anastomotic Leaks After Low Anterior Resection for Rectal

Cancer: A Valuable Option. Diseases of the Colon & Rectum 56:586–592. https://doi.org/10.1097/DCR.0b013e31827687a4

45. Jagielski M, Piątkowski J, Jarczyk G, Jackowski M (2022) Transrectal endoscopic drainage with vacuum-assisted therapy in patients with anastomotic leaks following rectal cancer resection. Surg Endosc 36:959–967. https://doi.org/10.1007/s00464-021-08359-4

46. Tang G, Du D, Tao J, Wei Z (2022) Effect of Indocyanine Green Fluorescence Angiography on Anastomotic Leakage in Patients Undergoing Colorectal Surgery: A Meta-Analysis of Randomized Controlled Trials and Propensity-Score-Matched Studies. Front Surg 9:815753. https://doi.org/10.3389/fsurg.2022.815753

47. Liu D, Liang L, Liu L, Zhu Z (2021) Does intraoperative indocyanine green fluorescence angiography decrease the incidence of anastomotic leakage in colorectal surgery? A systematic review and meta-analysis. Int J Colorectal Dis 36:57–66. https://doi.org/10.1007/s00384-020-03741-5

48. Dip F, Boni L, Bouvet M, Carus T, Diana M, Falco J, Gurtner GC, Ishizawa T, Kokudo N, Lo Menzo E, Low PS, Masia J, Muehrcke D, Papay FA, Pulitano C, Schneider-Koraith S, Sherwinter D, Spinoglio G, Stassen L, Urano Y, Vahrmeijer A, Vibert E, Warram J, Wexner SD, White K, Rosenthal RJ (2022) Consensus Conference Statement on the General Use of Near-infrared Fluorescence Imaging and Indocyanine Green Guided Surgery: Results of a Modified Delphi Study. Annals of Surgery 275:685–691. https://doi.org/10.1097/SLA.0000000000004412

49. Spota A, Al-Taher M, Felli E, Morales Conde S, Dal Dosso I, Moretto G, Spinoglio G, Baiocchi G, Vilallonga R, Impellizzeri H, Martin-Martin GP, Casali L, Franzini C, Silvestri M, De Manzini N, Castagnola M, Filauro M, Cosola D, Copaescu C, Garbarino GM, Pesce A, Calabrò M, De Nardi P, Anania G, Carus T, Boni L, Patané A, Santi C, Saadi A, Rollo A, Chautems R, Noguera J, Grosek J, D'Ambrosio G, Ferreira CM, Norcic G, Navarra G, Riva P, Quaresima S, Paganini A, Rosso N, De Paolis P, Balla A, Sauvain MO, Gialamas E, Bianchi G, La Greca G, Castoro C, Picchetto A, Franchello A, Tartamella L, Juvan R, Ioannidis O, Kosir JA, Bertani E, Stassen L, Marescaux J, Diana M (2021) Fluorescence-based bowel anastomosis perfusion evaluation: results from the IHU-IRCAD-EAES EURO-FIGS registry. Surg Endosc 35:7142–7153. https://doi.org/10.1007/s00464-020-08234-8

50. Lütken CD, Achiam MP, Svendsen MB, Boni L, Nerup N (2020) Optimizing quantitative fluorescence angiography for visceral perfusion assessment. Surg Endosc 34:5223–5233. https://doi.org/10.1007/s00464-020-07821-z

Legends

Table 1: Characteristics of the included studies

Figure 1: Flowchart of study screening according to PRISMA guidelines

Figure 2: Effect of ICG on the overall anastomotic leak

Figure 3: Trial sequential analysis of 7 trials comparing ICG vs. non-ICG for AL rate. The cumulative Z-curve crossed the conventional boundary for benefit, required information size and the trial sequential monitoring boundary for benefit, suggesting that the current evidence is statistically significant and support a superiority of ICG and further trials will not change this conclusion. A diversity adjusted required information size of 2059 patients was calculated using an alpha = 0.05 (two sided) and a beta = 0.20 (power 80%), and empirical estimation from TSA software

Figure 4: Effect of ICG on the anastomotic leak in low anastomosis

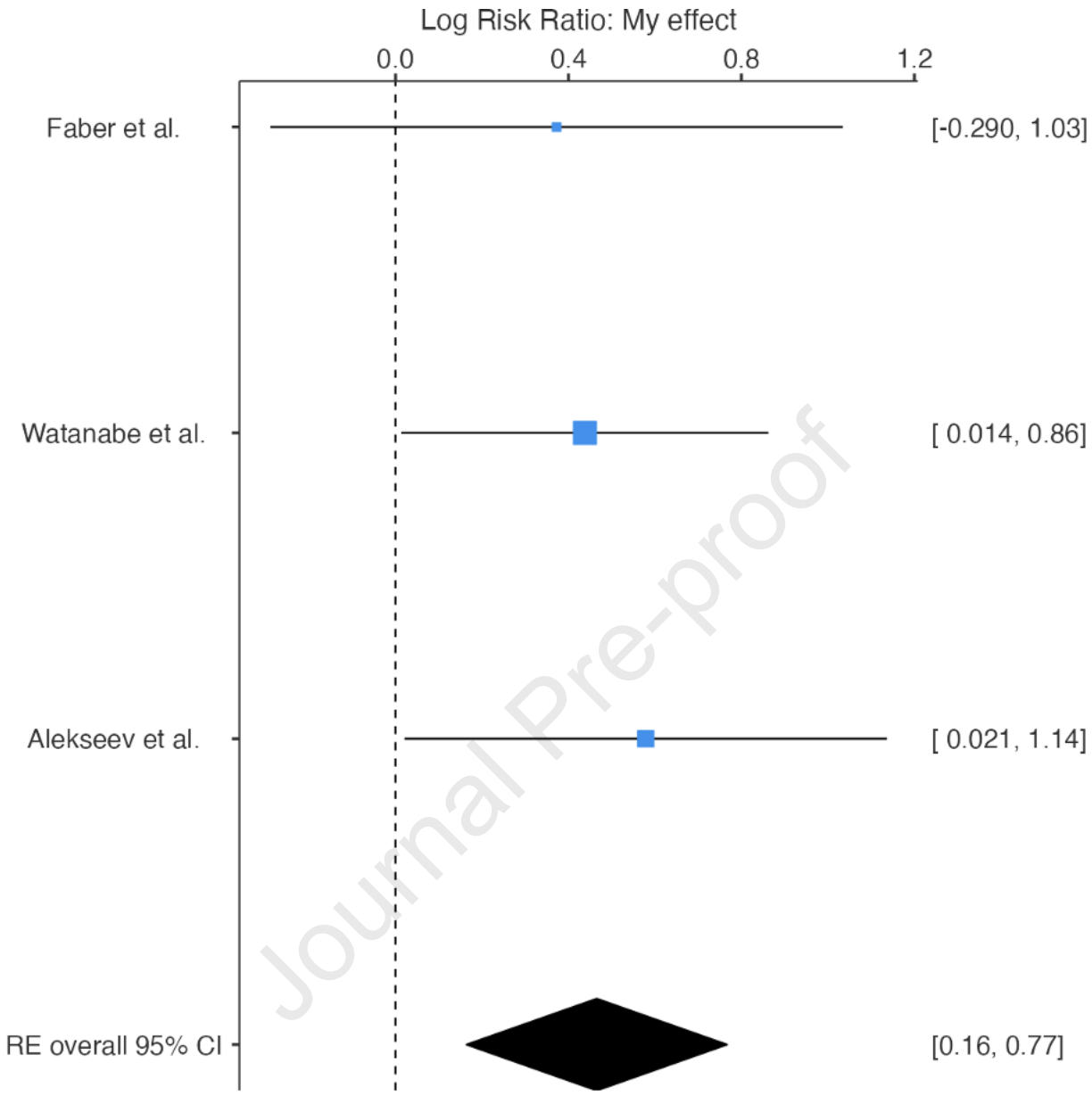
Figure 5: Trial sequential analysis of 3 trials comparing ICG vs. non-ICG for AL rate in low anastomoses. The cumulative Z-curve crossed the conventional boundary for benefit and the trial sequential monitoring boundary for benefit, but did not cross the required information size, suggesting that the current evidence is statistically significant and support a superiority of ICG but further trials could change this conclusion. A diversity adjusted required information size of 2464 patients was calculated using an alpha = 0.05 (two sided) and a beta = 0.20 (power 80%), and empirical estimation from TSA software

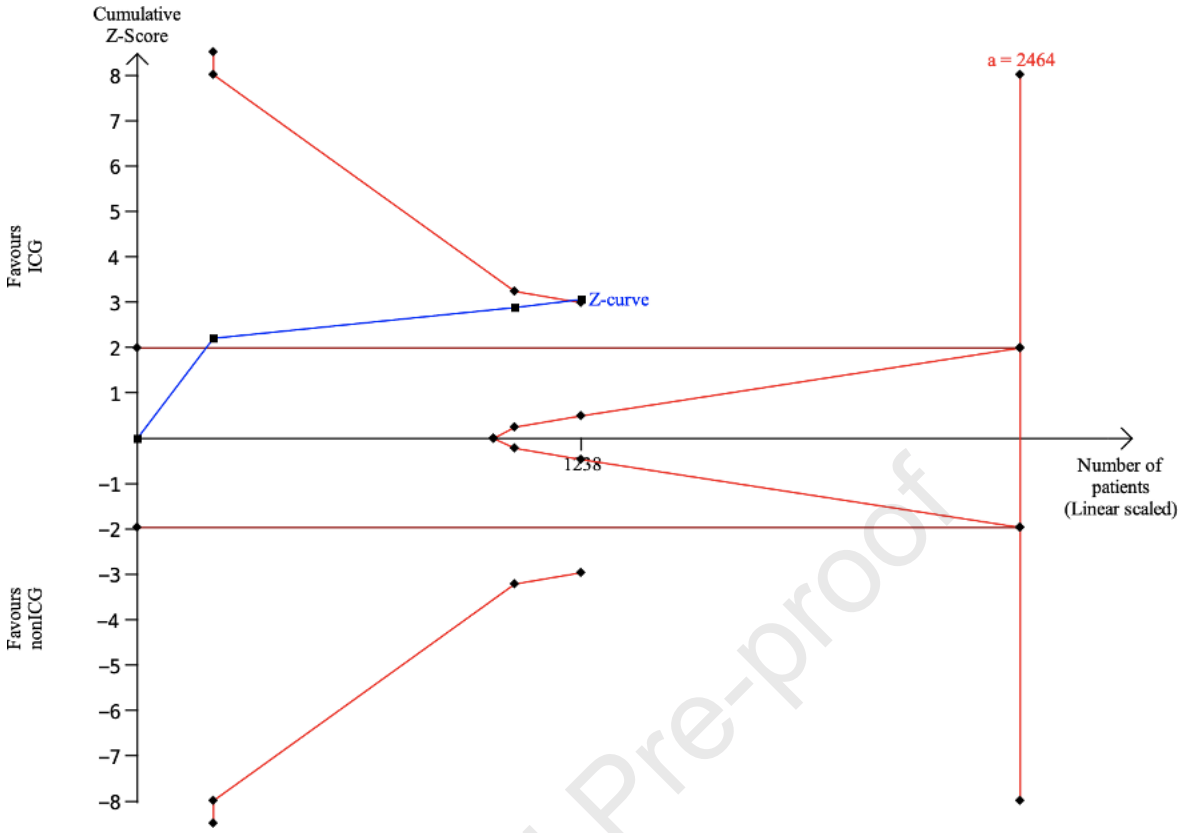
Figure 6: a) Effect of ICG on operative time; b) Effect of ICG on postoperative complications; c) Effect of ICG on 30-day reoperation rate; d) Effect of ICG on length of hospital stay

Figures and Table

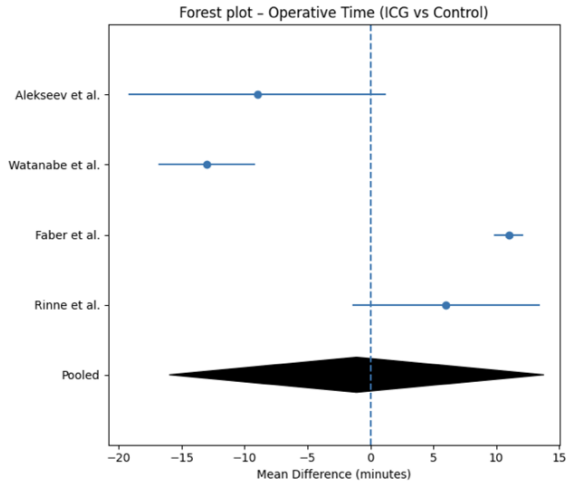
Table 1

Study	Country and year	Period of study	ICG platform	ICG dose	Total number of patients	ICG group	non-ICG group
Rinne et al.	Finland, 2025	Sep 2018 – Dec 2023	Stryker 1688 4K camera with advanced imaging modality and Pinpoint camera (Stryker), EinsteinVision 3.0 fluorescence imaging (Aesculap), OlympusEndoeye10mm,Endoeye10mmExeraIII,Medtronic EleVision IR Platform, and DaVinci Xi.	total of 5 mg of ICG	1136	567	569
Jayne et al.	UK, 2025	Oct 2017 - Aug 2023	Pinpoint [Stryker], Firefly [Intuitive Surgical; Sunnyvale, CA, USA], Stryker [Kalamazoo, MI, USA], or Storz [Tagerwilen, Switzerland]	0·1 mg/kg	766	383	383
Faber et al.	Netherlands, 2024	Jul 2020 - Feb 2023	Olympus Visera Elite II/Intuitive da Vinci Firefly/Storz camera	2 mL, total of 5 mg of ICG	931	463	468
Watanabe et al.	Japan, 2023	Dec 2018– Feb 2021	Stryker	5 mL of a 2.5 mg mL−1 solution	839	422	417
Jafari et al.	USA, 2021	Mar 2015– Feb 2017	Stryker	3 ± 1 mL of a 2.5 mg mL−1 solution	347	178	169
Alekseev et al.	Russia, 2020	Nov 2017– Aug 2019	Karl Storz	0.2 mg kg−1	377	187	190
De Nardi et al.	Italy, 2020	Jan 2016– Nov 2017	Karl Storz	0.3 mg kg−1	240	118	122

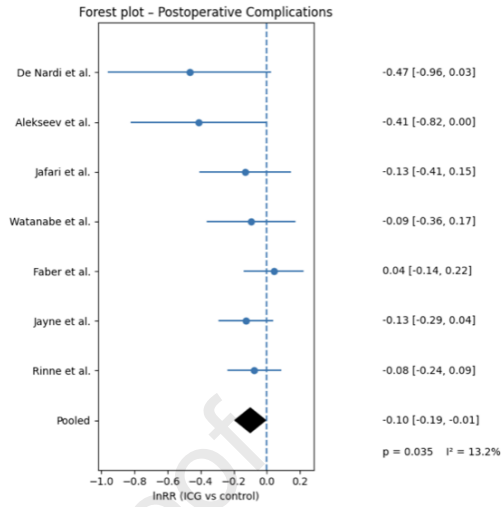




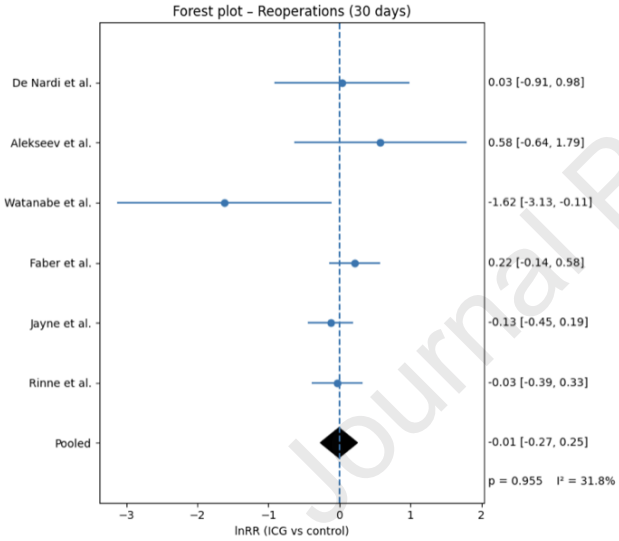
A) Operative time (ICG + vs. ICG -)



B) 30-day Postoperative complications (ICG + vs. ICG -)



C) 30-day Reoperation (ICG + vs. ICG -)



D) Length of stay (ICG + vs. ICG -)