

Indocyanine Green Fluorescence Angiography Versus Standard Visual Assessment for Prevention of Anastomotic Leakage in Colorectal Surgery: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

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Abstract

Background: Anastomotic leakage is one of the most serious complications of colorectal surgery, and poor perfusion of the bowel ends is an important cause. Indocyanine green (ICG) fluorescence angiography allows the surgeon to see bowel perfusion during the operation. This review pooled randomised trials published before 2023 that compared ICG angiography with standard visual assessment.

Methods: PubMed was searched for randomised controlled trials published up to 31 December 2022 in adults undergoing colorectal resection with a colorectal or coloanal anastomosis. The primary outcome was anastomotic leakage. Risk ratios (RR) were pooled with a DerSimonian-Laird random-effects model, and the Hartung-Knapp-Sidik-Jonkman method was used as a sensitivity analysis because of the small number of trials. Risk of bias was assessed with the RoB 2 tool, and certainty of evidence with GRADE.

Results: Of 56 records screened, three randomised trials with 964 patients were included. Anastomotic leakage occurred in 39 of 483 patients (8.1%) with ICG angiography and in 58 of 481 (12.1%) with visual assessment. ICG angiography reduced the risk of leakage (RR 0.67, 95% CI 0.46-0.99; $p = 0.045$; $I^2 = 0\%$), which corresponds to about 40 fewer leaks per 1000 patients. The Hartung-Knapp-Sidik-Jonkman interval was wider and crossed 1 (95% CI 0.31-1.45). The result depended on the single-centre trial; excluding it gave RR 0.80 (95% CI 0.47-1.38). ICG angiography led to a change in the planned level of bowel division in 16% of patients in the two trials that reported it.

Conclusion: ICG fluorescence angiography probably reduces anastomotic leakage after colorectal resection, but the evidence from randomised trials published before 2023 is limited to three trials and is of low certainty. The benefit seems most relevant for low anastomoses. Larger multicentre trials are needed before routine use can be firmly recommended.

Keywords: Indocyanine Green; Fluorescence Angiography; Anastomotic Leakage; Colorectal Surgery; Anterior Resection; Bowel Perfusion; Meta-Analysis.

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Introduction

Anastomotic leakage is a feared complication after colorectal resection. Its reported frequency ranges from 1% to 19%, and it is more common after low rectal anastomoses [1,2]. An international group has defined leakage as a defect of the bowel wall at the anastomosis that leads to communication between the intraluminal and extraluminal spaces and graded it by its effect on management [3].

Leakage increases the length of hospital stay, readmissions and costs [4]. In cancer surgery it is associated with a higher risk of local recurrence and cancer-specific death [5]. After low anterior resection, more than half of patients with a symptomatic leak ended up with a permanent stoma, compared with 11% of those without a leak [6].

Many risk factors for leakage cannot be changed, but an adequate blood supply to both bowel ends is under the surgeon's control [1,2]. In practice, surgeons judge perfusion by the colour of the bowel, bleeding from the cut edge and pulsation of the mesenteric vessels. This clinical judgement is unreliable; in a prospective study, surgeons predicted leakage with low sensitivity and specificity [7].

Indocyanine green (ICG) is a fluorescent dye that binds to plasma proteins and can be seen with a near-infrared camera a few seconds after intravenous injection [8]. ICG angiography shows the perfusion of the bowel in real time and may lead the surgeon to move the level of bowel division to a better-perfused segment. Early studies

reported fewer revisions for leakage with fluorescence angiography [9], and a multicentre phase II trial reported a change in the site of bowel division in 5.8% of patients and a low leak rate [10]. Meta-analyses of non-randomised studies suggested that ICG angiography reduced leakage [11,12], but these studies were open to selection bias, and the first randomised trials were published only from 2019 onwards. This systematic review and meta-analysis therefore compared ICG fluorescence angiography with standard visual assessment for prevention of anastomotic leakage in colorectal surgery, using randomised controlled trials published before 2023.

Materials and Methods

Protocol and Reporting: The review was reported according to the PRISMA 2020 statement [13]. The protocol was not registered in advance. Ethics committee approval was not required because only published data were used.

Eligibility Criteria: Studies were included if they met all of the following criteria. (1) Design: randomised controlled trial. (2) Population: adults undergoing elective colorectal resection with a colorectal or coloanal anastomosis, by any approach. (3) Intervention: intraoperative ICG fluorescence angiography to assess perfusion of the bowel before or after construction of the anastomosis. (4) Comparator: standard visual and clinical assessment of perfusion without ICG. (5) Outcome: anastomotic leakage. (6) Publication: full report in a PubMed-indexed journal published up to 31 December 2022. Non-randomised studies, randomised trials that used ICG in both arms or compared other interventions, trial protocols without results, reviews and conference abstracts were excluded.

Information Sources and Search: PubMed was searched on 20 October 2026 for publications from 1 January 2000 to 31 December 2022. The search combined indocyanine green, ICG, fluorescence angiography, fluorescence imaging and near-infrared with anastomosis, with colorectal, rectal, colon, colonic, rectum and left-sided, and with the term random or the randomised controlled trial publication type. Reference lists of included trials and of earlier reviews were searched by hand [11,12].

Study Selection and Data Extraction: Titles and abstracts were screened, and full texts of potentially eligible reports were assessed against the criteria.

The following data were extracted: country, number of centres, period, type of resection and

approach, level of anastomosis, number randomised and analysed, ICG protocol, definition of leakage, number of leaks in each group, change in the level of bowel division and other complications.

Risk of Bias Assessment: Risk of bias was assessed with the revised Cochrane tool for randomised trials (RoB 2), covering the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result [14]. Each domain and the overall risk were judged as low, some concerns or high.

Statistical Analysis: The effect measure was the risk ratio (RR) with its 95% confidence interval (CI). Estimates were pooled with the inverse-variance method and a DerSimonian-Laird random-effects model [15]. Heterogeneity was assessed with Cochran's Q test and the I² statistic [16]. Because the DerSimonian-Laird method can give confidence intervals that are too narrow when few trials are pooled, the Hartung-Knapp-Sidik-Jonkman method was applied as a sensitivity analysis [17].

Further sensitivity analyses used a fixed-effect model, removed each trial in turn and restricted the analysis to multicentre trials. Funnel plots and tests for small-study effects were not used because fewer than ten trials were available [18]. Absolute effects were calculated from the pooled control-group risk. Certainty of evidence was rated with GRADE [19]. Analyses were performed in Review Manager (RevMan) version 5.4 (The Cochrane Collaboration, 2020), and the Hartung-Knapp-Sidik-Jonkman analysis was run in R version 4.2 with the meta package. A two-sided $p < 0.05$ was taken as significant.

Results

Study Selection: The search returned 56 records. After screening of titles and abstracts, 48 were excluded, and eight full-text reports were assessed (Figure 1). Five were excluded: one non-randomised study [20], two randomised trials that used ICG to compare other interventions rather than ICG against visual assessment [21,22], and two protocols of trials without published results [23,24]. Three randomised trials were included [25-27].

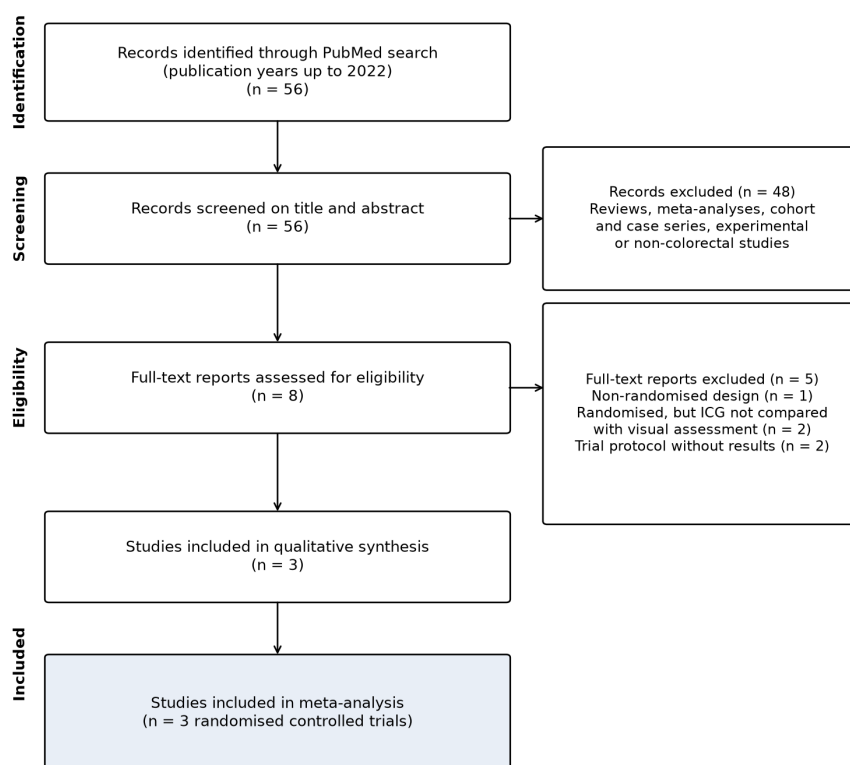


Figure 1: PRISMA 2020 flow diagram of study selection

Characteristics of included trials: The three trials were carried out in Italy [25], Russia [26] and the United States [27], and were published from 2020 to 2021 (Table 1). Together they included 964 patients: 483 had ICG angiography and 481 visual assessment. The Italian trial enrolled patients having laparoscopic left-sided colon or rectal

resection in a multicentre setting [25]. The Russian trial was a single-centre study of patients having sigmoid or rectal resection with a stapled colorectal anastomosis [26]. The American trial enrolled patients with an anastomosis within 10 cm of the anal verge at 25 centres and was stopped early because of slow recruitment [27].

Table 1: Characteristics of the included trials

Trial	Country and centres	Population	Anastomosis	Patients analysed (ICG/visual)	Change in bowel division with ICG	Leak, ICG vs visual
De Nardi 2020 [25]	Italy; multicentre	Laparoscopic left-sided colon or rectal resection	Colorectal	118/122	13 (11%)	6 (5%) vs 11 (9%)
Alekseev 2020 [26]	Russia; single centre	Sigmoid and rectal resection	Stapled colorectal, 4-15 cm from anal verge	187/190	36 (19%)	17 (9.1%) vs 31 (16.3%)
Jafari 2021 [27]	United States; 25 centres	Low anterior resection	Within 10 cm of anal verge	178/169	Not reported in abstract	16 (9.0%) vs 16 (9.6%)

ICG: indocyanine green.

Risk of Bias: All three trials were judged to have some concerns about risk of bias (Table 2). Surgeons could not be blinded to the intervention, and the outcome assessors were not described as blinded in the abstracts. In the Italian trial, 12

patients were excluded after randomisation [25]. The Russian trial counted grade A leaks, which do not change management, and so may have been more sensitive to detection bias [26]. The American trial did not reach its planned sample size [27].

Table 2: Risk of bias in the included trials (RoB 2)

Trial	Randomisation	Deviations from intended interventions	Missing outcome data	Outcome measurement	Selection of reported result	Overall
De Nardi 2020	Some concerns	Low	Some concerns (12 excluded after randomisation)	Some concerns	Low (registered)	Some concerns
Alekseev 2020	Some concerns	Low	Low (3 excluded)	Some concerns (grade A leaks counted)	Some concerns	Some concerns
Jafari 2021	Some concerns	Low	Low	Some concerns	Low	Some concerns (stopped early)

Judgements are based on the published trial reports.

Anastomotic leakage: Anastomotic leakage occurred in 39 of 483 patients (8.1%) with ICG angiography and in 58 of 481 (12.1%) with visual assessment. ICG angiography reduced the risk of leakage (RR 0.67, 95% CI 0.46-0.99; $p = 0.045$), without heterogeneity ($Q = 1.62$, $df = 2$, $p = 0.45$;

$I^2 = 0\%$) (Figure 2). At the pooled control-group risk of 121 per 1000, this corresponds to 40 fewer leaks per 1000 patients (95% CI 1 to 66 fewer). The individual trials gave RR 0.56 (95% CI 0.22-1.48) [25], 0.56 (95% CI 0.32-0.97) [26] and 0.95 (95% CI 0.49-1.84) [27].

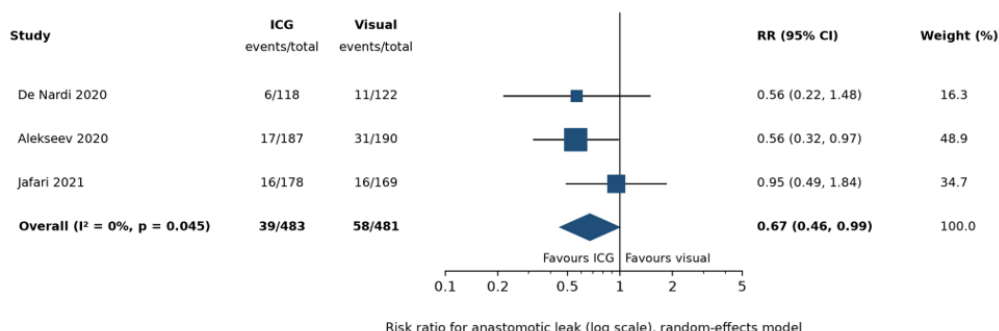


Figure 2: Forest plot of the effect of indocyanine green (ICG) fluorescence angiography compared with visual assessment on anastomotic leakage (random-effects model). Squares show trial risk ratios, with size proportional to weight; horizontal lines show 95% confidence intervals; the diamond shows the pooled estimate

Sensitivity Analyses: The fixed-effect model gave the same estimate (RR 0.67, 95% CI 0.46-0.99) (Table 3). With the Hartung-Knapp-Sidik-Jonkman method, the confidence interval was wider and crossed 1 (RR 0.67, 95% CI 0.31-1.45; $p = 0.16$). In the leave-one-out analysis, removal of the

Russian single-centre trial gave RR 0.80 (95% CI 0.47-1.38), and removal of either of the other trials left a significant result.

Restricting the analysis to the two multicentre trials gave RR 0.80 (95% CI 0.47-1.38).

Table 3: Sensitivity analyses for anastomotic leakage

Analysis	Trials (n)	Pooled RR (95% CI)	I^2 (%)
Random effects, DerSimonian-Laird (main analysis)	3	0.67 (0.46-0.99)	0
Fixed effect, inverse variance	3	0.67 (0.46-0.99)	0
Random effects, Hartung-Knapp-Sidik-Jonkman	3	0.67 (0.31-1.45)	0
Omitting De Nardi 2020	2	0.71 (0.42-1.18)	32
Omitting Alekseev 2020 (multicentre trials only)	2	0.80 (0.47-1.38)	0
Omitting Jafari 2021	2	0.56 (0.35-0.90)	0

RR: risk ratio.

Secondary Outcomes: ICG angiography showed inadequate perfusion and led to a more proximal

division of the bowel in 13 of 118 patients (11%) in the Italian trial [25] and in 36 of 187 (19%) in the

Russian trial [26], or 49 of 305 patients (16%) overall. In the American trial, perfusion could be seen adequately in 95.4% of patients in the ICG group, and abscess requiring surgical treatment occurred in 5.7% with ICG and 4.2% with standard assessment [27]. In the Russian trial, the benefit was limited to low anastomoses, 4 to 8 cm from the anal verge (leak rate 14.4% with ICG vs 25.7%

without), whereas the rate after high anastomoses was low in both groups (1.3% vs 4.6%) [26].

Certainty of Evidence: The certainty of evidence for anastomotic leakage was rated low, downgraded for risk of bias and for imprecision, because the confidence interval came close to no effect and the Hartung-Knapp-Sidik-Jonkman interval included it (Table 4).

Table 4: Summary of findings and certainty of evidence (GRADE)

Outcome	Trials (patients)	Pooled RR (95% CI)	Absolute effect per 1000 patients*	Certainty and reasons
Anastomotic leakage	3 (964)	0.67 (0.46-0.99)	40 fewer (1 to 66 fewer)	Low; downgraded for risk of bias and imprecision
Change in level of bowel division (ICG arm only)	2 (305)	Not applicable	161 per 1000 patients	Low; downgraded for risk of bias and inconsistency

*Control-group risk 121 per 1000 (pooled visual-assessment groups).

Discussion

This meta-analysis of three randomised trials with 964 patients found that ICG fluorescence angiography reduced anastomotic leakage after colorectal resection by about one third, from 12.1% to 8.1%. In absolute terms, about one leak would be avoided for every 25 patients assessed with ICG. The finding was consistent across trials in direction, but it was imprecise and depended largely on one single-centre trial.

The size of the effect is smaller than that reported in non-randomised studies. Meta-analyses of cohort studies found odds ratios of 0.27 to 0.34 [11,12], which are likely to be exaggerated by selection bias and by comparison with historical controls. A case-matched study found no benefit at all [28]. A meta-analysis of the same three randomised trials published in 2022 reported an identical risk ratio of 0.67 and judged the effect to be real but possibly small [29]. The present review adds a Hartung-Knapp-Sidik-Jonkman sensitivity analysis, which shows that the evidence is fragile when only three trials are available [17].

ICG angiography works by changing surgical decisions. In the included trials, perfusion assessment led to a more proximal division of the bowel in 11% to 19% of patients [25,26], which is more than the 5.8% reported in a phase II study [10] and the 3.7% (4 of 107 patients) in a feasibility series [30]. If a change in the level of division is the mechanism of benefit, the effect of ICG will depend on how often the surgeon's visual judgement is wrong. That may explain why the American trial, done by experienced surgeons, showed no benefit [27]. Surgeons' clinical judgement of leak risk is known to be poor [7], so an objective measure of perfusion is attractive.

The benefit seems most relevant for low anastomoses, where leakage is most frequent [2]. In

the Russian trial, the reduction was confined to anastomoses 4 to 8 cm from the anal verge [26]. The American trial enrolled only patients with an anastomosis within 10 cm and did not show a significant effect, but it was stopped early and was underpowered [27]. Large multicentre trials in rectal cancer surgery were in progress at the end of 2022 and should give a clearer answer [23,24]. The method has practical advantages. ICG is inexpensive, has a long record of clinical use with a good safety profile, and can be repeated during the same operation [8]. The main cost is the near-infrared imaging system. For centres that already have a fluorescence-capable laparoscope, routine use in left-sided and rectal resections seems reasonable. For centres without one, the evidence available before 2023 is not strong enough to justify purchase on the basis of leak prevention alone.

Strengths and Limitations: This review included only randomised trials, used a conservative method for pooling a small number of trials and rated the certainty of evidence. Its limitations are important. Only PubMed was searched, and only reports published before 2023 were included, so larger trials published later were not considered. Only three trials were available, one of which was stopped early. The trials differed in the level of anastomosis, the definition of leakage and the inclusion of grade A leaks. Surgeons and in most cases outcome assessors were not blinded. Subgroup analysis by level of anastomosis could not be pooled because the data were not reported separately by all trials. Finally, ICG angiography was assessed qualitatively by the surgeon in all trials, and quantitative methods could not be evaluated.

Conclusion

In randomised trials published before 2023, ICG fluorescence angiography reduced anastomotic leakage after colorectal resection from about 12% to 8%. The certainty of evidence is low because only three trials were available and the result was imprecise. ICG angiography changed the planned level of bowel division in about one in six patients and appears safe. It may be used routinely where equipment is available, particularly for low anastomoses, while larger trials define the size of its benefit.

Declarations

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Conflict of Interest: The author declares no conflict of interest.

Ethical Approval: Not required, as the review used only published data.

Author Contribution: Dr. Mayur Pradip Gangwal conceived the review, performed the search, extracted and analysed the data, wrote the manuscript and approved the final version.

Data Availability: All data used in this review are available in the published reports of the included trials.

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