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Citation

Faber, R. A., Meijer, R. P. J., Droogh, D. H. M., Jongbloed, J. J., Bijlstra, O. D., Boersma, F., ... Hilling, D. E. (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(10), 924-934. doi:10.1016/S2468-1253(24)00198-5

Version: Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).



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

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Summary

Background Anastomotic leakage is a severe postoperative complication in colorectal surgery and compromised bowel perfusion is considered a major contributing factor. Conventional methods to assess bowel perfusion have a low predictive value for anastomotic leakage. We therefore aimed to evaluate the efficacy of real-time assessment with near-infrared (NIR) fluorescence imaging with indocyanine green (ICG) in the prevention of anastomotic leakage.

Methods This multicentre, randomised, controlled, phase 3 trial was done in eight hospitals in the Netherlands. We included adults (aged >18 years) who were scheduled for laparoscopic or robotic colorectal surgery (with planned primary anastomosis) for benign and malignant diseases. Preoperatively, patients were randomly assigned (1:1) to fluorescence-guided bowel anastomosis (FGBA) or conventional bowel anastomosis (CBA) by variable block randomisation (block sizes 4, 6, and 8) and stratified by site. The operating surgeon and investigators analysing the data were not masked to group assignment. Patients were unmasked after the surgical procedure or after study end. In the FGBA group, surgeons marked anastomosis levels per conventional perfusion assessment and then administered 5 mg of ICG by 2 mL intravenous bolus. They assessed bowel perfusion using NIR fluorescence imaging and adjusted (or kept) transection lines accordingly. Only conventional methods for bowel perfusion assessment were used in the CBA group. The primary outcome was the difference in the rate of clinically relevant anastomotic leakage (ie, requiring active therapeutic intervention but manageable without reoperation [grade B] or requiring reoperation [grade C], per the International Study Group of Rectal Cancer) between the FGBA group and the CBA group within 90 days post-surgery. The primary outcome and safety were assessed in the intention-to-treat population. This study was registered with ToetsingOnline.nl (NL7502) and ClinicalTrials.gov (NCT04712032) and is complete.

Findings Between July 2, 2020, and Feb 21, 2023, 982 patients were enrolled, of whom 490 were assigned to FGBA and 492 were assigned to CBA. After excluding 51 patients, the intention-to-treat population comprised 931 (463 assigned FGBA and 468 assigned CBA). Patients had a median age of 68.0 years (IQR 59.0–75.0) and 485 (52%) were male and 446 (48%) were female. Ethnicity data were not available. The overall 90-day rate of clinically relevant anastomotic leakage was not significantly different between the FGBA group (32 [7%] of 463 patients) and the CBA group (42 [9%] of 468 patients; relative risk 0.77 [95% CI 0.50–1.20]; $p=0.24$). No adverse events related to ICG use were observed. 313 serious adverse events in 229 (25%) patients were at 90-day follow-up (159 serious adverse events in 113 [24%] patients in the FGBA group and 154 serious adverse events in 116 [25%] patients in the CBA group). 18 (2%) people died by 90 days (ten in the FGBA group and eight in the CBA group).

Interpretation ICG NIR fluorescence imaging did not reduce 90-day anastomotic leakage rates in this trial across all types of colorectal surgeries. Further research should be done in subgroups, such as rectosigmoid resections, for which evidence suggests ICG NIR might be beneficial.

Funding Olympus Medical, Diagnostic Green, and Intuitive Foundation.

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Introduction

Anastomotic leakage is a severe postoperative complication in colorectal surgery with an incidence of 1–8% after colon

resections and up to 20% after rectal resections.^{1–3} It is associated with increased morbidity, mortality, and health-care costs, and prolonged hospital stays.^{4,5} The risk factors

Lancet Gastroenterol Hepatol
2024; 9: 924–34

Published Online

August 13, 2024

[https://doi.org/10.1016/S2468-1253\(24\)00198-5](https://doi.org/10.1016/S2468-1253(24)00198-5)

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Research in context

Evidence before this study

We searched PubMed for all studies published in English from database inception to March 26, 2020 (ie, the study start date), comparing indocyanine green (ICG) near-infrared (NIR) fluorescence bowel perfusion assessment with conventional perfusion assessment methods. Search terms included “(indocyanine green OR ICG)” AND “(colorectal OR rectal)” AND “(anastomotic leakage OR anastomotic leak)”. This search resulted in 1041 full text articles, including clinical trials, meta-analyses, randomised controlled trials, reviews, and systematic reviews. Several prospective and retrospective studies have suggested the benefit of ICG NIR fluorescence bowel perfusion assessment in reducing the rate of anastomotic leakage after colorectal resections. However, efficacy was shown in only one of the three randomised controlled trials that had been conducted before study start and two of these trials were underpowered. Recently, the randomised controlled Essential trial showed clinical benefit of ICG NIR fluorescence bowel perfusion assessment in patients having minimally invasive rectal cancer surgery, reporting a significantly lower 30-day anastomotic leakage rate in the experimental group.

Added value of this study

The scope of most previous randomised controlled trials was primarily limited to sigmoid and rectal surgeries. To our

knowledge, the AVOID trial is the first published multicentre, randomised, controlled, phase 3 trial to evaluate the efficacy of ICG NIR fluorescence imaging in enhancing intraoperative bowel perfusion assessment and its subsequent effect on 90-day anastomotic leakage rates across all types of colorectal surgeries. Although we found no significant difference in the overall rate of 90-day clinically relevant (grade B or C) anastomotic leakage between the conventional and ICG NIR fluorescence groups, we did find significant reductions with fluorescence in left-sided and rectosigmoid surgeries. No adverse events related to ICG use were observed.

Implications of all the available evidence

The absence of a significant effect of ICG NIR fluorescence imaging on the overall 90-day anastomotic leakage rate could be due to the inclusion of right-sided colon resections, which might have a lower risk of anastomotic leakage than left-sided surgeries because of better blood supply and differences in the microbiome, potentially skewing efficacy results. However, based on the results of this trial and those of previous studies, including Essential, we would advocate for the integration of ICG NIR fluorescence imaging into surgical guidelines for patients undergoing rectosigmoid resections for cancer.

of anastomotic leakage include male sex, comorbidity, malnutrition, neoadjuvant treatment, short distance from the tumour to the anorectal junction, and poor vascularisation of the bowel tissue. The latter is considered an important modifiable risk factor.⁶

Conventional methods to assess bowel perfusion intraoperatively rely on subjective measures such as tissue colour, peristaltic movements, bleeding from marginal arteries, and palpation of mesenteric arterial pulsations.⁷ Other tests include the air leak test, intraoperative endoscopy, and doughnut inspection in transanal stapling. However, these clinical indicators have low predictive value for anastomotic leakage, highlighting the need for more accurate intraoperative diagnostic tests.^{8,9}

Near-infrared (NIR) fluorescence imaging with indocyanine green (ICG) offers a real-time, non-invasive assessment of bowel perfusion. ICG can be visualised in the NIR light spectrum (700–900 nm) by capturing the light emitted from ICG after excitation with an external NIR light source.¹⁰ ICG is an effective fluorescent contrast agent for NIR fluorescence perfusion assessment as it binds to serum albumin and is rapidly cleared from the blood by the liver and solely excreted via the biliary tract after intravenous administration.^{11–13}

Multiple cohort studies suggest that ICG NIR fluorescence bowel perfusion assessment might reduce the occurrence of anastomotic leakage.^{11,14–17} However, its

efficacy has been shown in only one of three randomised controlled trials that had been published before the study start. The 30-day anastomotic leakage rate was significantly reduced with ICG assessment in one of the studies¹⁸ whereas the two others did not show significant benefits due to having insufficient power.^{19,20} Larger phase 3 randomised controlled trials, such as the Intact trial,²¹ ICG-COLORAL (NCT03602677), and Essential trial,²² have been initiated around the same time as the start of this study to better evaluate the technique's efficacy. The Essential trial recently showed that ICG NIR fluorescence significantly reduced 30-day anastomotic leakage rates in patients having minimally invasive rectal cancer surgery.²²

Most randomised trials have been focused on sigmoid and rectal surgeries, whereas our study broadens this scope. This study aims to evaluate the efficacy of ICG NIR fluorescence imaging in enhancing intraoperative bowel perfusion assessment and the effect on 90-day anastomotic leakage rates across colorectal surgeries.

Methods

Study design and participants

This multicentre, randomised, controlled, phase 3 trial started on March 26, 2020, and was conducted at eight hospitals in the Netherlands according to the Declaration of Helsinki (appendix p 2). All participating hospitals had extensive experience with colorectal

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See Online for appendix

surgery, with a mean number of 240 (SD 65) colorectal surgical procedures per year. Medical ethics approval was obtained from the ethics committee Leiden-Den Haag-Delft (MEC-2021–0876). This study is registered with ToetsingOnline.nl (NL7502) and ClinicalTrials.gov (NCT04712032).

Eligible patients were older than 18 years, scheduled for laparoscopic or robotic colorectal surgery (with planned primary anastomosis) for malignant or benign diseases, able to communicate in Dutch, and had signed informed consent before any study-related procedure. We excluded patients with contraindications for ICG (allergy; history of an adverse reaction to ICG, iodine, or iodine dyes; or use of medication that could affect tissue absorption of ICG, such as phenobarbital, phenylbutazone, primidone, phenytoin, haloperidol, nitrofurantoin, and probenecid); severe liver or kidney insufficiency; hyperthyroidism or a benign thyroid tumour; were pregnant or breastfeeding; scheduled for emergency surgery, palliative surgery (or who were terminally ill), or planned for a diverting stoma before surgery; and those with any condition deemed by the investigator to be potentially jeopardising to patient wellbeing or study objectives. Patients for whom the surgeon decided to create a diverting stoma perioperatively (ie, not planned beforehand) were included in the analyses, as a diverting stoma does not prevent an anastomotic leakage but only mitigates the severity of clinical symptoms. Patients were recruited during their preoperative visit to the surgical outpatient clinic. They received information about the study during this visit and were given at least 1 week to consider before providing informed consent. The study protocol can be found in the appendix (pp 10–37).

Randomisation and masking

Patients were preoperatively randomly assigned (1:1) to fluorescence-guided bowel anastomosis (FGBA) or conventional bowel anastomosis (CBA) by variable block randomisation with block sizes of 4, 6, and 8, as standard in the Castor EDC online database, and stratified by participating hospital. Patients were enrolled by the coordinating investigator or the local principal investigator who created a patient identification in the Castor EDC database. The operating surgeon and those analysing the data were not masked to group assignment. For all participants, treatment allocation was unblinded either after the surgical procedure (to prevent premature dropout due to randomisation assignment) or after the end of the study period.

Procedures

Before patient recruitment, all relevant medical personnel at each participating hospital were briefed on the study protocol during a site initiation visit by the principal or coordinating investigator, or both. The coordinating investigator, experienced in fluorescence-guided surgery, trained all surgeons in using intraoperative NIR

fluorescence imaging and interpreting the fluorescence signal for bowel perfusion assessment. To guarantee procedural consistency, the coordinating investigator supported each surgeon through at least two guided procedures as part of the study. This study used specific fluorescence camera systems: Visera Elite II (Olympus Medical, Hoofddorp, the Netherlands) and da Vinci Firefly (Intuitive Surgical, Sunnyvale, CA, USA). For surgeons inexperienced with these systems, additional training was provided by the respective manufacturers. This training covered the operation and maintenance of the equipment as well as hands-on practice.

Patients assigned to the FGBA group had laparoscopic or robotic colorectal surgery according to standard of care. In addition to intraoperative conventional bowel perfusion assessment (eg, inspection of tissue colour and palpation of mesenteric arteries), ICG NIR fluorescence imaging was applied using a standardised imaging protocol (appendix pp 1, 4). The method used for conventional bowel perfusion assessment was per surgeon preference without restrictions. Bowel perfusion assessment using ICG NIR fluorescence imaging was performed intracorporeally or extracorporeally, depending on the surgical procedure. For extracorporeal imaging, surgeons were instructed to turn off the ambient light in the operating theatre to avoid interference from external light sources. After dissection of the vascular branch, surgeons marked the chosen anastomosis levels on the proximal and distal bowel using a suture or electrocoagulation, based on conventional bowel perfusion assessment. ICG (Verdye, Diagnostic Green, Aschheim, Germany) was prepared by adding 10 mL of water for injections to a vial containing 25 mg of the active substance, resulting in a concentration of 2.5 mg/mL. Before bowel transection, an intravenous bolus injection of 2 mL, totalling 5 mg of ICG, was administered followed by a 10 mL saline flush. Within 1 min, bowel perfusion was assessed using the NIR overlay channel and compared with the pre-marked transection lines. Differentiation between poorly and sufficiently perfused bowel tissue was assessed by the operating surgeon and based on the subjective interpretation of the fluorescence signal intensity. If no fluorescence signal was detected at these lines, surgeons could change the surgical plan and adjust the transection line. If the fluorescence signal extended beyond the marked transection line, the initial plan remained unchanged. Subsequently, the anastomosis was created per the surgeon's discretion (eg, hand-sewn, stapled, side-to-side, or side-to-end). ICG NIR fluorescence imaging after completion of the anastomosis was not mandatory. Although assessment of the fluorescence signal before bowel transection was preferred, some patients required bowel resection before ICG NIR fluorescence imaging to improve the surgical overview. During the surgical procedure, up to three ICG bolus injections were allowed if both marked transection lines could not be captured in

one optical field or if the surgeon was uncertain about the adequacy of perfusion after the anastomosis was finalised. A 15-min washout period was maintained between each administration. A period of 15 min was chosen on the basis of ICG pharmacokinetics and our experience with ICG to ensure a good signal-to-background ratio. Endoscopic assessment of the fluorescence signal was not recommended.

Patients assigned to the CBA group had laparoscopic or robotic colorectal surgery according to standard of care. Conventional methods were used to assess the integrity and validity of the anastomosis. The method used for conventional bowel perfusion assessment was at the surgeon's discretion, and there were no limitations on the approaches used. No additional tools were used to assess bowel perfusion.

The indications for neoadjuvant treatment were based on Dutch guidelines.²³ Neoadjuvant systemic therapy was recommended for cT4bN0–2M0 colon carcinoma, neoadjuvant short-course radiotherapy (5 Gy/day for 5 days) for intermediate-stage rectal carcinoma (cT3cdN0 or cT1–3 mesorectal fascia–N1), and a combination of radiotherapy (2 Gy/day for 25 days or 1.8 Gy/day for 28 days) and capecitabine (825 mg/m² twice a day, administered orally for the duration of the radiotherapy) for locally advanced rectal cancer (cT4, mesorectal fascia positive, cN2, extramesorectal pathological lymph nodes, extramural vascular invasion, and M0).

The detection of clinically relevant anastomotic leakages was per local hospital protocols and clinical judgement and based on a combination of postoperative clinical symptoms and C-reactive protein (CRP) concentrations (ie, a CRP cutoff value of ≥ 170 mg/L on day 3 after surgery was used according to the meta-analysis of Singh and colleagues²⁴), leading to a diagnostic CT scan with contrast enema (appendix p 29). Follow-up was 90 days.

Data were collected by the coordinating investigator and trained local research staff. Baseline data we collected included sociodemographics, hospital information, neoadjuvant therapy, comorbidities, medical history, blood tests, smoking status, and surgical indication. Data on sex were extracted from the electronic patient dossier. Patient sex was automatically linked to their citizen service number on hospital registration. Additionally, data on surgical characteristics, such as type, duration, and type of procedure (ie, laparoscopic or robotic surgery) used, and 90-day postoperative complications were collected using an electronic case report form in the online database Castor EDC.

Outcomes

The primary outcome was the difference in the rate of clinically relevant anastomotic leakage between the FGBA group and the CBA group within 90 days post-surgery. Clinically relevant anastomotic leakage was defined as an anastomotic leakage that required active therapeutic intervention but was manageable without

reoperation (grade B) or an anastomotic leakage that required reoperation (grade C) according to the definition of the International Study Group of Rectal Cancer.^{25,26} Intra-abdominal abscesses related to the anastomosis were classified as grade B anastomotic leakages. Intra-abdominal abscesses not related to the anastomosis were not considered anastomotic leakages. The primary outcome was locally assessed by the treating surgeon and subsequently centrally reviewed and confirmed by the coordinating investigator (RAF) or principal investigator (DEH). Secondary outcomes were changes in the surgical plan based on the fluorescence signal and differences between the FGBA group and CBA group in: 30-day clinically relevant anastomotic leakage; 30-day and 90-day mortality; 30-day and 90-day complication rate; 30-day and 90-day reintervention rate (defined as radiological intervention [eg, CT-guided or ultrasound-guided drainage] or reoperation); 30-day and 90-day readmission rate (added after patient enrolment began to better capture overall patient recovery); length of in-hospital stay; and operation time. Length of in-hospital stay after readmission was added as a post-hoc outcome. Adverse events related to ICG use and all serious adverse events that occurred within 90 days after surgery were registered. Complications were scored using the Clavien–Dindo classification.²⁷

Statistical analysis

A total of 978 patients was deemed necessary to assess the benefit of ICG NIR fluorescence imaging to decrease the 90-day rate of anastomotic leakage from 7% (national average according to the Dutch Colorectal Audit)²⁸ to 3%, including an 80% power, a two-sided alpha level of 0.0492 (adjusted for the interim analysis using O'Brien–Fleming), a 5% drop-out rate, and a 1:1 ratio of control and intervention (489 patients vs 489 patients). The hypothesised reduction in anastomotic leakage was based on a review of studies by Mizrahi and Wexner.²⁹ In the largest case–control study they reviewed, which included laparoscopic and open right and left colectomy and low anterior resection, a reduction of 4.6 percentage points in anastomotic leakages was observed with the use of intraoperative NIR fluorescence imaging (experimental group 3.1% vs control group 7.7%; $p=0.04$).¹⁵ An interim analysis was performed after 489 patients (half the number required) had completed the 90-day follow-up. Results of the interim analysis showed neither benefit nor harm of the study intervention, providing no reason to stop the study prematurely.

Patient characteristics are described using summary statistics. The distribution of all continuous variables was assessed using histograms and verified with the Shapiro–Wilk test. Normally distributed variables are reported as mean (SD) and skewed continuous variables are reported as median (IQR). Continuous variables were compared using the independent *t* test or the Mann–Whitney *U* test, depending on distribution. Categorical variables

were compared using the χ^2 test after confirming that no more than 20% of expected cell counts were less than five and all individual expected cell counts were one or greater. Fisher's exact test was used if more than 20% of the expected cell counts were less than five. The Mantel–Haenszel test, stratified by centre, was prespecified as the main analysis method for the primary outcome but was later changed to χ^2 to simplify the analysis and ensure robustness. This was changed before data unblinding to the individuals analysing the data. In prespecified analyses, the primary outcome was assessed in the overall FGBA and CBA groups and in the right-sided surgery subgroup, left-sided surgery subgroup, and other surgeries subgroup. The other surgeries subgroup comprised transverse colectomies and subtotal colectomies (appendix pp 17, 45–46). The assessment of the primary outcome in rectosigmoid resections was added post hoc based on the results of the Essential trial²² and for a more detailed examination of the left-sided surgery subgroup. We calculated 95% CIs for relative risk using SPSS version 29.0.

A univariate logistic regression analysis was performed to assess the association of various factors with 90-day clinically relevant anastomotic leakage overall, in left-sided surgeries, in rectosigmoid surgeries (post-hoc), and in low anterior resections. These factors were selected based on available data in our database and their documented effect on anastomotic leakage in the

literature. Factors analysed overall were ICG fluorescence, age 70 years and older, male sex, BMI of 25 kg/m² and higher, diabetes, former or current smoker, neoadjuvant therapy, malignancy, diverting stoma, and left-sided colorectal surgery. For patients who had left-sided colorectal surgery and, specifically, rectosigmoid resections, the same variables (excluding left-sided colorectal surgery) were assessed. We assessed the same variables (excluding left-sided surgery and malignancy, as all low anterior resections were performed for malignancy) for patients having low anterior resection, as well as the effect of tumour stage T3 or worse and distance from the tumour to the anorectal junction of less than 5 cm. Variables with a p value of less than 0.20 in the univariate analysis were subsequently included in the multivariable logistic regression analysis to calculate the odds ratio (OR) of each variable on anastomotic leakage occurrence. Factors independently associated with anastomotic leakage were thus identified. The use of fluorescence was always included in multivariable regression analyses, irrespective of statistical significance, because it reflected the primary research question. Regarding the left-sided analysis, malignancy (p=0.20) was included in the multivariable analysis due to rounding (the actual p value was <0.20), whereas smoking status (p=0.20) for the rectosigmoid group was not included since the actual p value was just above 0.20. Regression analysis was not done in right-sided surgeries or other surgeries as these factors did not affect the significant difference in anastomotic leakage between the CBA group and FGBA group.

Due to the low risks associated with participation in this study (appendix p 30), no data monitoring committee was assigned. Local monitoring ensured data collection and documentation accuracy. All statistical analyses were performed using SPSS version 29.0. An intention-to-treat analysis was performed for all randomised patients who underwent surgery. The statistical outcomes were considered significant if the p value was less than 0.0492, adjusted for the interim analysis using the O'Brien–Fleming approach.³⁰

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between July 2, 2020, and Feb 21, 2023, 982 patients were enrolled (figure; appendix p 2). 36 experienced colorectal surgeons performed surgery in the study. 51 patients were excluded because the surgical procedure was non-compliant with the study protocol (n=5), they had no bowel resection (n=9), cancellation of surgery due to medical reasons, such as complete response to neoadjuvant therapy or peritoneal metastases (n=17), no primary anastomosis formation (n=17), and emergency

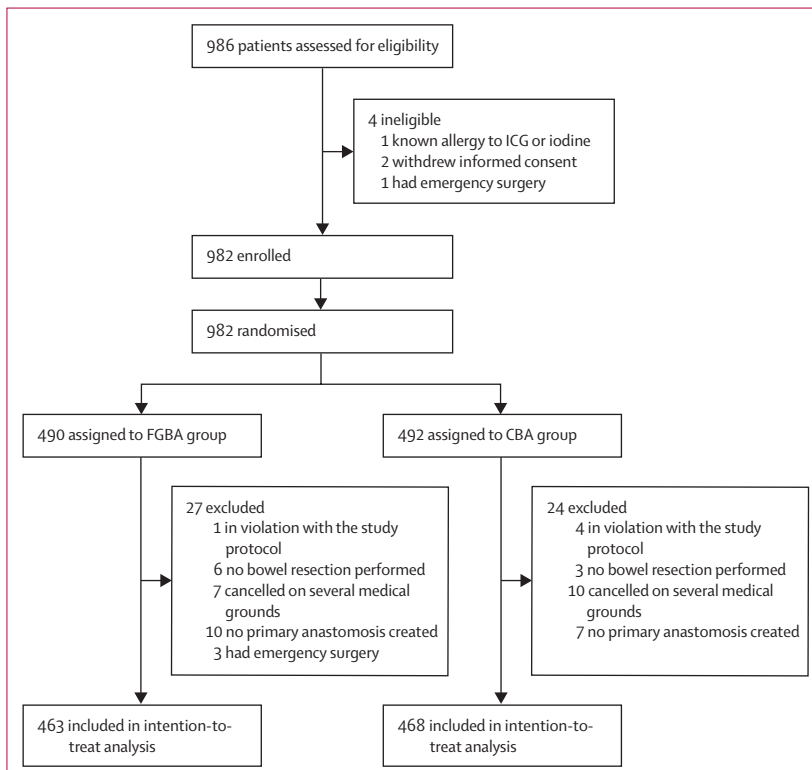


Figure: Trial profile

CBA=conventional bowel anastomosis. FGBA=fluorescence-guided bowel anastomosis. ICG=indocyanine green.

	FGBA group (n=463)	CBA group (n=468)
Age, years	69·0 (59·0–75·0)	67·5 (59·0–76·0)
Sex		
Male	249 (54%)	236 (50%)
Female	214 (46%)	232 (50%)
BMI, kg/m ²	25·8 (23·5–29·2)	25·9 (23·4–29·0)
Diabetes		
Yes	60 (13%)	62 (13%)
No	403 (87%)	406 (87%)
Smoking		
Current	49 (11%)	59 (13%)
Former	200 (43%)	216 (46%)
Never	212 (46%)	192 (41%)
Missing	2 (<1%)	1 (<1%)
History of abdominal surgery		
Yes	148 (32%)	175 (37%)
No	315 (68%)	293 (63%)
Surgery indication		
Malignant	405 (87%)	421 (90%)
Benign	58 (13%)	47 (10%)
Neoadjuvant therapy in the 3 months before surgery		
Yes	23 (5%)	25 (5%)
Radiotherapy	10 (2%)	14 (3%)
Chemotherapy	7 (2%)	5 (1%)
Chemoradiotherapy	6 (1%)	6 (1%)
No	440 (95%)	443 (95%)
Steroid use in the 3 months before surgery		
Yes	21 (5%)	31 (7%)
No	442 (95%)	437 (93%)
Type of surgery		
Ileocaecal resection	11 (2%)	15 (3%)
Right hemicolectomy	178 (38%)	193 (41%)
Transversectomy	4 (1%)	3 (1%)
Left hemicolectomy	42 (9%)	39 (8%)
Sigmoidectomy	132 (29%)	122 (26%)
Low anterior resection	88 (19%)	96 (21%)
Subtotal colectomy	6 (1%)	0
Transanal total mesorectal excision	2 (<1%)	0

(Table 1 continues in next column)

	FGBA group (n=463)	CBA group (n=468)
(Continued from previous column)		
Type of anastomosis		
Side-to-side isoperistaltic	184 (40%)	194 (41%)
Side-to-side antiperistaltic	55 (12%)	58 (12%)
Side-to-end	143 (31%)	140 (30%)
End-to-side	3 (<1%)	6 (1%)
End-to-end	54 (12%)	44 (9%)
Surgical platform		
Olympus Visera Elite II laparoscopic system*	359 (78%)	363 (78%)
Intuitive da Vinci Firefly	103 (22%)	104 (22%)
Other†	1 (<1%)	1 (<1%)
Converted to open procedure	33 (7%)	35 (7%)

Data are median (IQR) or n (%). Right-sided colon resection comprised ileocaecal resection and right hemicolectomy. Left-sided colorectal resection comprised left hemicolectomy, sigmoidectomy, low anterior resection, and transanal total mesorectal excision. Other resection comprised transversectomy and subtotal colectomy. FGBA=fluorescence-guided bowel anastomosis. CBA=conventional bowel anastomosis. *The Olympus camera system was used in eight patients who had primary open surgery. Among these patients, six had right hemicolectomy, two of whom received indocyanine green perioperatively, and two underwent transversectomy. †One surgical procedure in the CBA group was performed with the Storz camera system (Karl Storz SE, Tuttlingen, Germany) and one procedure in the FGBA group was performed with the Quest near-infrared fluorescence imaging system (Quest Medical Imaging BV, Wieringerwerf, Netherlands) because neither the Olympus fluorescence imaging system nor the Intuitive da Vinci Firefly were available at the time of surgery.

Table 1: Baseline and surgical characteristics

transversectomy or subtotal colectomy was performed. Conversion to an open procedure occurred in 68 (7%) patients (33 [7%] of 463 in the FGBA group and 35 [7%] of 468 in the CBA group).

Anastomotic leakage was diagnosed in 74 (8%) of 931 patients (see appendix p 3 for 90-day anastomotic leakage rate per type of surgery performed). The majority (70 [95%] of 74) of anastomotic leakages occurred within 30 days of surgery, with a median time to anastomotic leakage of 5 days (IQR 3–10). Overall, the 90-day rate of clinically relevant anastomotic leakage was not significantly different between the FGBA group (32 [7%] of 463 patients) and the CBA group (42 [9%] of 468 patients; relative risk [RR] 0·77 [95% CI 0·50–1·20]; $p=0·24$; table 2). The Mantel–Haenszel test, stratified by centre, showed a similar result (OR 0·76 [95% CI 0·47–1·23]; $p=0·25$). In patients who had left-sided colorectal surgery, the 90-day anastomotic leakage rate was lower in the FGBA group (20 [8%] of 264) than in the CBA group (33 [13%] of 257; RR 0·59 [95% CI 0·35–1·00]; $p=0·047$). Among the 521 patients who had left-sided surgery, the majority (440 [84%]) had rectosigmoid resection (ie, sigmoidectomy, low anterior resection, and transanal total mesorectal excision). Anastomotic leakages occurred in two (2%) of 81 patients undergoing left hemicolectomy, 19 (7%) of 254 patients undergoing sigmoidectomy, 31 (17%) of 184 patients undergoing

surgery (n=3). Consequently, 931 patients were included in the intention-to-treat analysis, with 463 (50%) in the FGBA group and 468 (50%) in the CBA group.

Baseline characteristics were similar across both groups (table 1). Patients had a median age of 68·0 years (IQR 59·0–75·0), and 485 (52%) of 931 patients were male and 446 (48%) were female. Data on ethnicity were unavailable. Most patients had colorectal resection for malignancy. 48 (5%) of 931 patients received neoadjuvant therapy in the 3 months before surgery. Right-sided colon resection was performed in 397 (43%) of 931 patients and left-sided colorectal resection in 521 (56%) patients. In the remaining 13 (1%) patients, a

	Total (n=931)	FGBA group (n=463)	CBA group (n=468)	p value*
90-day anastomotic leakage				
No	857 (92%)	431 (93%)	426 (91%)	0.24
Yes	74 (8%)	32 (7%)	42 (9%)	..
30-day anastomotic leakage				
No	861 (92%)	433 (94%)	428 (91%)	0.23
Yes	70 (8%)	30 (6%)	40 (9%)	..
Right-sided 90-day anastomotic leakage				
No	380/397 (96%)	181/189 (96%)	199/208 (96%)	0.96
Yes	17/397 (4%)	8/189 (4%)	9/208 (4%)	..
Left-sided 90-day anastomotic leakage				
No	468/521 (90%)	244/264 (92%)	224/257 (87%)	0.047
Yes	53/521 (10%)	20/264 (8%)	33/257 (13%)	..
Other 90-day anastomotic leakage				
No	9/13 (69%)	6/10 (60%)	3/3 (100%)	0.50
Yes	4/13 (31%)	4/10 (40%)	0/3 (0)	..

Data are n (%) or n/N (%). Right-sided colon resection comprised ileocaecal resection and right hemicolectomy. Left-sided colorectal resection comprised left hemicolectomy, sigmoidectomy, low anterior resection, and transanal total mesorectal excision. Other resection comprised transversectomy and subtotal colectomy. FGBA=fluorescence-guided bowel anastomosis. CBA=conventional bowel anastomosis. *Categorical variables were compared using χ^2 after confirming the assumption that no more than 20% of the expected cell counts were less than five and all individual expected cell counts were one or greater. Fisher's exact test was used for the other subgroup as more than 20% of the expected cell counts were less than five.

Table 2: Rates of clinically relevant anastomotic leakage

low anterior resection, and one (50%) of two patients undergoing transanal total mesorectal excision (appendix p 3). In a post-hoc analysis, patients who underwent rectosigmoid resection had a lower 90-day anastomotic leakage rate in the FGBA group (19 [9%] of 222) than in the CBA group (32 [15%] of 218; RR 0.58 [95% CI 0.34–1.00]; $p=0.045$). Conversely, the 90-day anastomotic leakage rate in patients who underwent right-sided colon surgery was similar in both groups (eight [4%] of 189 in the FGBA group and nine [4%] of 208 in the CBA group; RR 0.98 [0.39–2.48]; $p=0.96$). There was also no difference between groups in the 30-day rate of clinically relevant anastomotic leakage.

In the FGBA group, the surgical plan was changed in 43 (9%) of 463 patients. Specifically, in 41 (9%) patients, the surgical plan was changed based on the fluorescence signal (appendix pp 4–6). In the other two patients, the surgical plan was changed by alteration of the distal anastomosis level due to a stenosis at the distal side of the anastomosis ($n=1$) and bleeding of the rectal stump ($n=1$). Alterations to the level of anastomosis predominantly occurred on the proximal side ($n=30$), less frequently on the distal side ($n=10$), and occasionally on both ends ($n=3$), with a median shift of 2.0 cm (IQR 1.0–3.0). The median shift of 2.0 cm (1.0–3.0) for the 41 patients in which the surgical plan was changed based on fluorescence was similar to the median shift for all patients in which the surgical plan was changed. Of the 41 patients whose

	Total (n=931)	FGBA group (n=463)	CBA group (n=468)	p value*
90-day serious adverse events	313 in 229 patients (25%)	159 in 113 patients (24%)	154 in 116 patients (25%)	0.89
30-day serious adverse events	275 in 210 patients (23%)	137 in 101 patients (23%)	138 in 109 patients (23%)	0.59
Clavien–Dindo ≥ 3	138 in 113 patients (12%)	76 in 60 patients (13%)	62 in 53 patients (11%)	0.45
90-day reintervention	119 (13%)	66 (14%)	53 (11%)	0.18
30-day reintervention	107 (11%)	59 (13%)	48 (10%)	0.23
In-hospital stay, days	4 (3–5)	4 (3–6)	4 (3–5)	0.34
90-day readmission	122 (13%)	59 (13%)	63 (13%)	0.74
30-day readmission	92 (10%)	41 (9%)	51 (11%)	0.30
In-hospital stay after readmission, days	4 (2–7)	4 (2–8)	3 (3–7)	0.96
Operation time, min	135 (109–164)	141 (110–168)	130 (107–158)	0.0047
90-day mortality	18 (2%)	10 (2%)	8 (2%)	0.62
30-day mortality	15 (2%)	9 (2%)	6 (1%)	0.42

Data are n (%) or median (IQR) unless otherwise specified. FGBA=fluorescence-guided bowel anastomosis. CBA=conventional bowel anastomosis. *Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using the χ^2 test after confirming the assumption that no more than 20% of the expected cell counts were less than five and all individual expected cell counts were one or greater.

Table 3: Complications, hospital stay, and operation time

surgical plan was changed based on the fluorescence signal, eight (20%) underwent right-sided colon resections and 33 (80%) underwent left-sided colorectal resections. Anastomotic leakage occurred in four (10%) of these 41 patients, of whom three had low anterior resection (including two with tumours located less than 5 cm from the anorectal junction and one with postoperative haemorrhage and fatal COVID-19 infection) and one had sigmoidectomy during which fluorescence was improperly assessed due to low fluorescence signal intensity. No other instances of improper fluorescence assessment were reported in the study. Median operation time was 11 min longer for patients in the FGBA group (141 min [IQR 110–168]) than for patients in the CBA group (130 min [107–158]; $p=0.0047$; table 3). During surgery, a diverting stoma was created in 24 (3%) of 931 patients. In one patient, a diverting stoma was created specifically due to a weak fluorescence signal at the distal anastomosis site.

Univariate logistic regression analysis showed that the use of fluorescence, an age of 70 years or older, male sex, a BMI of 25 kg/m² or higher, diabetes, being a former or current smoker, malignancy, and having a diverting stoma did not affect the likelihood of 90-day clinically relevant anastomotic leakage overall ($p \geq 0.20$; appendix pp 7–8). However, neoadjuvant therapy and undergoing left-sided

colorectal resection were associated with an increased odds of anastomotic leakage and were, therefore, included in the multivariable logistic regression analysis. Multivariable logistic regression analysis showed that neoadjuvant therapy (OR 3.75 [95% CI 1.82–7.72]; $p=0.0003$) and left-sided colorectal surgery (2.24 [1.26–3.98]; $p=0.0058$; appendix pp 7–8) were associated with increased odds of anastomotic leakage.

For left-sided resections, neoadjuvant therapy was also associated with an increased odds of anastomotic leakage in multivariable analysis (OR 4.25 [95% CI 1.97–9.13]; $p=0.0002$); the use of fluorescence had no effect (0.56 [0.31–1.02]; $p=0.056$). Additionally, in the context of rectosigmoid resections, post-hoc multivariable logistic regression analysis showed that patients aged 70 years or older (OR 1.87 [95% CI 1.01–3.45]; $p=0.046$) and those who received neoadjuvant therapy (3.59 [1.66–7.80]; $p=0.0012$) were at higher odds for anastomotic leakage. The use of fluorescence was associated with an OR of 0.54 (95% CI 0.29–1.01; $p=0.052$), but this was not significant. For patients undergoing low anterior resection, multivariable logistic regression analysis showed that tumours located less than 5 cm from the anorectal junction were associated with higher odds of anastomotic leakage (3.98 [1.43–11.11]; $p=0.0083$); the use of fluorescence had no effect.

Overall, complication rates were similar in the FGBA group and CBA group (table 3). No adverse events related to ICG use were observed. Within 90 days, 159 serious adverse events occurred in 113 (24%) patients in the FGBA group and 154 occurred in 116 (25%) patients in the CBA group, with the majority (275 [88%] of 313 serious adverse events in 210 [23%] patients) occurring within 30 days of surgery. 138 severe complications (Clavien–Dindo ≥ 3) were observed in 113 (12%) of 931 patients overall, with similar rates occurring in both groups ($p=0.45$). There was also no difference in the duration of in-hospital stay. Within 90 days, reinterventions (ie, drainage and reoperation) were required in 119 (13%) of 931 patients, with no difference between groups. Furthermore, 122 (13%) of 931 patients required hospital readmission within 90 days due to postoperative complications, with a median in-hospital stay of 4 days (IQR 2–8) in the FGBA group and 3 days (3–7) in the CBA group following readmission. Within 90-day follow-up, 18 (2%) patients died (ten patients in the FGBA group and eight patients in the CBA group), most of whom (15 [83%]) died within 30 days of surgery (additional information about the causes of death is provided in the appendix p 9).

Discussion

The use of ICG NIR fluorescence imaging for bowel perfusion assessment did not significantly reduce 90-day anastomotic leakage in patients undergoing laparoscopic or robotic colorectal surgery. However, this multicentre, randomised, controlled, phase 3 trial provides evidence

of the advantages of using ICG NIR fluorescence imaging for assessing bowel perfusion intraoperatively during minimally invasive left-sided and, specifically, rectosigmoid cancer resections.

Several randomised controlled trials have investigated the efficacy of ICG NIR fluorescence imaging in reducing anastomotic leakage after colorectal surgery.^{18–20,22} Notably, only the FLAG trial¹⁸ and the EssentiAL trial²² observed a significant decrease in 30-day anastomotic leakage rates with the use of fluorescence. These trials specifically targeted rectosigmoid resections¹⁸ or rectal cancer surgeries²² and included all grades of anastomotic leakage, even grade A, which typically does not necessitate active therapeutic intervention. The EssentiAL trial reported a significant reduction in 30-day grade B and C anastomotic leakage rate with ICG fluorescence (4.7%) versus no ICG fluorescence (8.2%; $p=0.044$) in patients after minimally invasive rectal cancer surgery.²² By contrast, the FLAG trial showed no significant differences in grade B and grade C 30-day anastomotic leakages together, possibly due to an insufficient sample size.¹⁸ These outcomes suggest that ICG NIR fluorescence imaging could become standard practice for rectosigmoid resections.

The absence of significant effect from ICG NIR fluorescence imaging on the overall 90-day anastomotic leakage rate in this study could be due to the inclusion of right-sided colon resections (371 patients with right hemicolectomies). Ileocolic anastomoses have a lower risk of anastomotic leakage than distal colorectal, coloanal, and ileoanal anastomoses, potentially skewing efficacy results.^{31,32} This lower risk of anastomotic leakage might stem from better blood supply to the ileum and differences in the microbiome, with local bacterial activities, such as increased collagenase activity, in the colon impairing anastomotic healing there.^{2,33} For example, one study found that an abundance of *Enterococcus faecalis*, a common inhabitant of the colon, could lead to degradation of collagen IV at the anastomosis site through matrix metalloproteinase-9 activation.³⁴ However, most evidence on the effect of the microbiome on anastomotic leakage is from animal studies, necessitating further studies in humans.

In this study, 41 (9%) patients had their surgical plan altered based on the fluorescence signal, with anastomotic leakage occurring in four patients (one sigmoidectomy, three low anterior resections). This finding aligns with a meta-analysis that found surgical plan changes due to ICG NIR fluorescence imaging in 331 (9%) of 3614 patients in studies of colorectal surgeries.³⁵ A change in surgical plan was associated with a significantly higher odds of anastomotic leakage (unspecified days and grade; 13 [4%] of 331 patients with an alteration of the anastomosis level vs 106 [3%] of 3283 patients without changes of the surgical plan; OR 2.73 [95% CI 1.54–4.82]).³⁵ This increased risk of anastomotic leakage (90-day) with a change in surgical plan was also suggested by our study (four [10%] of 41 vs 28 [7%] of 422 in the FGBA group), but

numbers were small. The EssentiAL trial reported fewer intraoperative changes (ten [2%] of 422) based on the fluorescence signal.²² The higher rate of 90-day anastomotic leakage among patients in whom the surgical plan was changed based on the fluorescence signal in our study could have stemmed from the higher proportion of left-sided colorectal procedures (80% vs 57%) and, particularly, low anterior resections (34% vs 20%) in the group with surgical changes compared with the entire FGBA group, as well as higher comorbidity rates in the surgical changes group (90% vs 86%), implying that these patients were at higher risk of postoperative surgical complications beforehand (appendix pp 5–6). Surgical changes might also have been under-reported when fluorescence matched the pre-marked transection line, possibly causing surgeons to subconsciously place the stapler more proximal to this transition line without formally acknowledging these as plan changes. Such nuances could contribute to the underestimated effect of fluorescence-based adjustments. Additionally, factors other than bowel perfusion might contribute to anastomotic leakage. Among the four patients with anastomotic leakage after surgical plan changes, two underwent low anterior resection with tumours located less than 5 cm from the anorectal junction, one had postoperative bleeding and a fatal COVID-19 infection, and one patient had improper fluorescence assessment during sigmoidectomy. These factors underscore the multifaceted nature of anastomotic leakage risk beyond surgical adjustments.

Multivariable logistic regression analysis showed that neoadjuvant therapy and left-sided colorectal surgeries were associated with an increased odds of anastomotic leakage in the overall group. Furthermore, patients receiving neoadjuvant therapy in the left-sided and rectosigmoid subgroups and those aged 70 years or older in the rectosigmoid subgroup had higher odds of anastomotic leakage. Although the χ^2 test for ICG NIR fluorescence imaging in the left-sided and rectosigmoid subgroups showed statistical significance, the multivariable logistic regression analysis did not, although ORs of 0.56 and 0.54, respectively, were observed. It is possible that the multivariable analysis was underpowered, considering the number of patients in these subgroups. Additionally, for low anterior resection, a tumour location of less than 5 cm from the anorectal junction was associated with significantly increased odds of anastomotic leakage. These results are in line with existing literature, further highlighting that anastomotic leakage arises from a complex interplay of factors, with compromised tissue perfusion being crucial but not the sole element affecting the onset of anastomotic leakage.⁶

The overall 90-day serious adverse event rate of 25% (24% in the FGBA group and 25% in the CBA group) in this study was higher than in international reports. For example, the EssentiAL trial²² had a 30-day complication rate of 20.4% (19.4% with ICG vs 21.3%

without ICG) and a meta-analysis of ICG in colorectal surgeries reported a rate of 21.7% (undefined timepoint and complications). However, the complication rate in the EssentiAL trial was reported at 30 days compared with 90 days in our study. This finding could help explain our higher complication rates. Moreover, the rate we report is similar to the rate reported in the Dutch Colorectal Audit, a nationwide registry of surgical outcomes of patients undergoing colorectal surgery, which recorded 30-day overall (surgical related and non-surgical related) complication rates of 28.6% for colon resections and 35.8% for rectal resections between 2011 and 2017.³⁶ No adverse events related to ICG use were observed, indicating that ICG fluorescence for bowel perfusion assessment is safe for routine use.

This study has some limitations. Enrolment began during the COVID-19 pandemic, which considerably affected the inclusion rate for an extended period. Although our study is a randomised controlled trial, which helps to control for confounders by balancing variables associated with the outcome and treatment groups across the study population, we acknowledge that this process cannot eliminate all potential for unmeasured or residual confounding. Specifically, measurement errors in confounders, such as smoking status, might still introduce some bias. The cause of anastomotic leakage was also not consistently documented in surgical reports. Therefore, we could not provide an accurate number of anastomotic leakages caused by ischaemia at the bowel end. Additionally, our power analysis was based on the overall anastomotic leakage rate, combining right-sided, left-sided, and other surgeries, rather than on specific subgroups. Therefore, although our study is adequately powered for the overall anastomotic leakage rate, it might not be sufficiently powered for individual subgroups, such as right-sided colon surgery, if their occurrence deviated from our initial expectations. This limitation underscores the need for further research specifically focused on ICG use in right-sided colon surgery. Furthermore, the majority of patients included in this study underwent colorectal resection for malignancy, so applicability to benign resections might be limited. Moreover, there is a potential for observational bias because the surgeons were not masked to the treatment group as they had to determine the location of the anastomosis based on the fluorescence signal. Furthermore, participation in this study might have increased the surgeon's attentiveness in creating a proper anastomosis, which might have affected surgical outcomes. Nevertheless, the observed anastomotic leakage rates align with existing literature. Another limitation is the subjective interpretation of the fluorescence signal, which could have led to misjudgement in bowel perfusion in the FGBA group, potentially underestimating the efficacy of ICG NIR fluorescence. Previous studies^{37–40} show poor-to-moderate inter-observer agreement in fluorescence signal interpretation. However, this variability in interpretation is

not necessarily correlated with adverse clinical outcomes, such as anastomotic leakage. Quantification of the ICG NIR fluorescence signal could improve objectivity and accuracy of bowel perfusion assessment. Finally, not all participating surgeons were experienced with ICG NIR fluorescence imaging, and, despite comprehensive training, a learning curve might have affected study outcomes.

In conclusion, although there was no effect on 90-day anastomotic leakage overall, this study provides evidence supporting the efficacy of ICG NIR fluorescence bowel perfusion assessment to prevent anastomotic leakage in patients undergoing minimally invasive left-sided and, specifically, rectosigmoid cancer resections. In alignment with current evidence, we recommend incorporating ICG NIR fluorescence imaging into surgical guidelines for patients undergoing rectosigmoid resections for cancer.

Contributors

RAF, RPJM, JPBMB, EM-KK, HP, JSMD, JB, KCMJP, ALV, and DEH designed the study. RAF, ALV, and DEH received funding for the study. RAF, RPJM, ODB, FAH, PAN, JPBMB, TSA, MAMB, AWKSM, MW, PGD, KB, ECJC, KCMJP, JGB, and JWAB carried out the study. RAF, RPJM, DHMD, JJJ, ODB, FB, EvS, JB, AvdW, HJMH, and DJS conducted the data curation activities. RAF, RPJM, DHMD, JPBMB, EM-KK, ALV, and DEH administered the project. RAF, RPJM, HP, and DEH analysed the data. RAF, RPJM, JB, EM-KK, HP, SK, JRvdV, MH, KCMJP, ALV, and DEH validated the data. RAF, JB, and EM-KK accessed and verified the data. RAF and DEH wrote the first draft of the manuscript. All authors provided a critical review and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The data for this study are available to other researchers for scientific research purposes on request and after the proposed analysis plan has been approved. A data transfer agreement must be signed, which defines obligations that the data requester must adhere to regarding privacy and data handling. For data access, please contact the corresponding author (d.e.hilling@lumc.nl).

Acknowledgments

This study was supported by funding from Olympus Medical, Diagnostic Green, and the Intuitive Foundation. We used AI-assisted technologies in the writing process only to enhance the readability and language of the text. We carefully reviewed and edited the AI-generated content and are responsible and accountable for the originality, accuracy, and integrity of the work.

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