Intraoperative fluorescence angiography with indocyanine green to prevent anastomotic leak in rectal cancer surgery (IntAct): an unblinded randomised controlled trial

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Summary

Background Data are mixed on whether indocyanine green (ICG) fluorescence angiography can reduce the high rate of anastomotic leaks in patients undergoing surgery for rectal cancer. Therefore, we aimed to investigate the safety and efficacy of ICG fluorescence angiography in reducing the rate of clinical anastomotic leaks in these patients.

Methods IntAct was an unblinded randomised controlled trial conducted at 28 specialist rectal cancer centres across eight European countries. Adults (≥18 years) with rectal cancer (lower margin of cancer ≤15 cm from the anal verge) medically fit for elective, curative, laparoscopic or robotic high or low anterior resection were eligible. Patients not undergoing colorectal or anal anastomosis and those with synchronous colonic tumours or recurrent or locally advanced rectal cancer requiring extended or multi-visceral excision were excluded. Eligible participants were randomly assigned (1:1) by use of minimisation with a random element to undergo surgery with or without ICG (standard care). Resections and anastomoses were done per surgeon preference. In the ICG group, surgeons first marked proximal transection levels via standard white-light laparoscopy and then administered an intravenous bolus of 0·1 mg/kg of ICG for perfusion assessment. A second 0·1 mg/kg ICG assessment was done following anastomosis. In the standard care group, only a white-light assessment of bowel perfusion was performed. The primary endpoint was the rate of clinical anastomotic leak (grades B or C, per the International Study Group of Rectal Cancer) within 90 postoperative days. Analyses were done in the intention-to-treat population for complete cases. This trial is registered with the ISRCTN registry (ISRCTN13334746) and is now complete.

Findings Between Oct 20, 2017, and Aug 15, 2023, 2534 patients were assessed for eligibility and 766 participants were randomly assigned (383 to the ICG group and 383 to the standard care group). 501 (65%) of 766 participants were male, 726 (95%) were of White ethnicity, and the median age was 64·0 years (IQR 56·0–72·0). 343 patients in the ICG group and 355 in the standard care group were included in the intention-to-treat analysis. The rates of anastomotic leak were 11 (3%) of 343 in the ICG group and 20 (6%) in the standard care group for grade A, 11 (3%) and 31 (9%) for grade B, and 25 (7%) and 23 (6%) for grade C. Within 90 days, a clinical anastomotic leak occurred in 90 (13%) of 698 participants: 36 (10%) of 343 in the ICG group and 54 (15%) of 355 in the standard care group (adjusted odds ratio 0·667 [95% CI 0·419–1·060]; p=0·087). There were no serious adverse events related to ICG.

Interpretation Although IntAct did not show a significant benefit for ICG fluorescence angiography, a signal towards a reduction in clinical anastomotic leak rate was observed. The benefit of ICG could be in preventing grade A or B leaks, given similar rates of grade C leaks between groups. Future research is needed to standardise ICG fluorescence assessment and understand its relevance to anastomotic leak.

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Introduction

Anastomotic leak is one of the most serious complications of rectal cancer surgery, reported in 5–20% of cases regardless of whether the operation is performed open, laparoscopically, or with robotics.[1–4] Around 5% of patients who have an anastomotic leak will not survive,[2] while those who survive often have to live with long-term physical, mental, and financial consequences.[5] Anastomotic leak is a burden on health-care resources, more than tripling the average length of hospital stay and the cost of care.[6] Despite advances in surgical care, the rate of anastomotic leak has not improved.

An adequate blood supply is crucial to anastomotic healing and is traditionally assessed by the bowel colour, pulsation in the arterial blood supply, and bleeding. More recently, indocyanine green (ICG) fluorescence angiography has been used for assessment of anastomotic blood supply. The first multicentre study to evaluate ICG in colorectal surgery was the PILLAR II trial, which reported an anastomotic leak rate of 1·4%

Research in context

Evidence before this study

We searched PubMed between Jan 1, 2016, and Nov 1, 2024, for articles published in the English language using the search terms "indocyanine green" OR "rectal cancer" OR "perfusion assessment". We identified several observational studies, propensity-matched studies, systematic reviews, and meta-analyses reporting on the use of indocyanine green (ICG) to reduce anastomotic leak in colorectal surgery. Four randomised controlled trials were identified, of which only one, the Japanese EssentiAL trial, restricted inclusion to participants with rectal cancer. Results from non-randomised studies were generally favourable for the use of ICG in reducing anastomotic leak but these studies were limited by the inclusion of patients with benign and malignant disease and cancers of the right colon, left colon, and rectum. Three of the four randomised studies were similarly limited by the inclusion of mixed cohorts of participants. The EssentiAL study enrolled 850 patients scheduled for minimally invasive sphincter-preserving surgery for rectal cancer and found that ICG fluorescence angiography significantly reduced the rate of anastomotic leak (all grades) compared with white light laparoscopy, but did not prove its hypothesis that ICG would result in a reduction in anastomotic leak rate of 6 percentage points (actual reduction 4·2 percentage points). Additionally, rectal contrast enema to check anastomotic integrity was not mandatory and follow-up was restricted to 30 days, meaning that leak rates might have been under-reported. We also searched for registered trials on ClinicalTrials.gov between Jan 1, 2016, and Dec 31, 2024, using search terms including "indocyanine green", "colorectal", and "anastomotic leak", and found only one trial (NCT05153954), a prospective cohort study (QUANTICO) that recruited 115 patients and restricted inclusion to those with rectal cancer undergoing surgery. This study sought to evaluate the use of external software to quantify intraoperative ICG fluorescence. A Finnish study (ICG-COLORAL) has recruited patients with cancers of the upper rectum along with colon cancers and has recently finished recruiting participants. Consequently, there are insufficient data to support or reject the use of ICG to prevent anastomotic leak in a European population with rectal cancer.

Added value of this study

To the best of our knowledge, this randomised trial is the first to assess the use of ICG to prevent all grades of anastomotic leak in patients with the highest burden of leak after surgery: those with rectal cancer. There was no difference in the rate of clinical (grade B or C) anastomotic leaks (the primary endpoint) by 90 days post-operation between perfusion assessment with ICG fluorescence angiography (10%) versus white-light laparoscopy standard of care (15%). Although we did not show a significant benefit for ICG in preventing clinical anastomotic leaks, a signal towards a reduction was observed, with the 95% CI narrowly failing to exclude an odds ratio of no difference, and a significant reduction was observed for ICG for any anastomotic leak (grades A, B, or C). The benefit of ICG fluorescence angiography might be in preventing grade A or B leaks, with similar rates of grade C leaks in the ICG and standard care groups, indicating that mechanisms other than bowel perfusion might be more influential in grade C leaks. The effect of ICG appeared to be largely driven by more frequent changes in proximal bowel transection level and more frequent permanent stoma formation than when ICG was not used. No differences were observed in Global Health Status score or Low Anterior Resection Syndrome score at 90 days.

Implications of all the available evidence

Although our study did not demonstrate a significant reduction in clinical anastomotic leaks, the finding of a significant reduction in all leaks, which was most apparent for grade A and B leaks, provides some evidence of efficacy and concurs with the findings of a recent meta-analysis by Safiejko and colleagues. When considered along with the findings of the AVOID and EssentiAL studies, which showed reductions in leaks with ICG in left-sided colorectal resections (prespecified subgroup analysis) and rectal cancer surgeries (main analysis), respectively, as well as ICG's potential cost-effectiveness, there is now more evidence for ICG to become the standard of care in patients undergoing surgery for rectal cancer. Future research needs to concentrate on the standardisation and quantification of ICG fluorescence assessment and its relevance to anastomotic leak.

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(n=2) in 139 patients after laparoscopic left-sided colectomy or anterior resection for benign or malignant disease.[7] Several observational studies and meta-analyses have shown a reduction in anastomotic leak rate with ICG.[8–10] However, reports from randomised trials present a mixed picture. The single-centre FLAG trial randomly assigned 380 patients undergoing sigmoid or rectal resection for benign or malignant disease to perfusion assessment with ICG fluorescence angiography or white-light laparoscopy and found a significant reduction in anastomotic leak (all grades) in the ICG group (9·1% *vs* 16·3%).[11] By contrast, an Italian multicentre randomised trial, enrolling 252 patients undergoing laparoscopic left-sided colon or rectal resection, did not show a significant reduction in clinical leaks with ICG fluorescence angiography compared with white-light laparoscopy.[12] The results of two large randomised trials have recently been published. The Japanese multicentre EssentiAL trial enrolled 850 patients scheduled for minimally invasive sphincter-preserving surgery for rectal cancer and found that ICG fluorescence angiography significantly reduced the rate of clinical leaks compared with white-light laparoscopy, but did not prove the hypothesis that ICG would result in a reduction in anastomotic leak rate of 6 percentage points (actual reduction 4·2 percentage points).[13] The Dutch

AVOID study, which enrolled 982 patients, did not show a significant reduction in the primary outcome of the rate of clinically relevant anastomotic leakage (grades B or C) at 90 days with ICG fluorescence-guided bowel anastomosis versus conventional bowel anastomosis but enrolled patients scheduled for any laparoscopic or robotic colorectal resection for benign and malignant disease.[14] A subgroup analysis of only left-sided resections did suggest a significant reduction in 90-day clinically relevant anastomotic leakage rate with ICG.

The IntAct study aimed to investigate the safety, efficacy, and cost-effectiveness of ICG fluorescence angiography in patients with rectal cancer, who have the highest rate of anastomotic leakage after surgery and present the greatest health-care burden.

Methods

Study design and participants

IntAct was an unblinded, parallel-group, randomised controlled trial conducted in 28 hospitals across eight European countries (Belgium, Germany, Ireland, Italy, the Netherlands, Slovenia, Sweden, and the UK; appendix p 4). Participating centres had to be specialist rectal cancer centres able to perform laparoscopic or robotic rectal cancer surgery with ICG. The study was designed to compare surgery with ICG against standard care (white-light laparoscopy; no ICG) to assess the effect on anastomotic leakage in patients undergoing elective anterior resection for rectal cancer. Participating surgeons had to have performed a minimum of three rectal cancer resections with ICG before involvement in the study.

See Online for appendix

Patients were eligible if they had a diagnosis of rectal cancer (defined as the lower margin of the cancer ≤15 cm from the anal verge on endoscopy or radiology), were aged 18 years or older, and were medically fit (American Society of Anesthesiologists [ASA] physical status score ≤3) for elective, curative, laparoscopic or robotic high or low anterior resection. Patients not undergoing colorectal or anal anastomosis, and those with synchronous colonic tumours needing synchronous resections, recurrent rectal cancer, emergency presentation, locally advanced rectal cancer requiring extended or multivisceral excision, or coexistent colorectal pathology were ineligible. Other exclusion criteria were previous pelvic radiotherapy unrelated to rectal cancer, hepatic or renal dysfunction, known allergy to ICG, iodine, or iodine dyes, or taking drugs known to interact with ICG, being pregnant or likely to become pregnant within 3 months of surgery, and immunosuppression. The protocol was amended on Sept 28, 2020, to add an exclusion criterion (immunocompromised patients) and remove one (use of oral antibiotics within 8 weeks before randomisation). All participants provided written informed consent before entering the trial. The trial received UK ethical approval (reference 17/NW/0193) and either national or local ethical approval at international centres. Two independent oversight committees (Trial Steering Committee and Data Monitoring and Ethics Committee) oversaw the trial conduct. The trial was prospectively registered on the ISRCTN registry (ISRCTN13334746) and is now complete. The full trial protocol[15] has been published.

Randomisation and masking

Participants were enrolled by clinical research teams at each centre and underwent central randomisation by use of computer-generated minimisation, incorporating a random element (80:20 bias in favour of the minimised allocation), on a 1:1 basis, to receive surgery with or without ICG. The minimisation factors were intended treating surgeon, sex (male or female), ASA grade (I–III), radiological T-stage (T1–3), neoadjuvant therapy (none, short-course with no delay, short-course with delay, long-course), and tumour position (above, at, or below peritoneal reflection). Participants, surgeons, centres, and those analysing the trial data were not masked to treatment allocation.

Procedures

Bowel preparation and the use of preoperative antibiotic regimens were not stipulated. All resections were performed according to the surgeon's usual technique, with a laparoscopic or robotic approach. High anterior resection was defined as an anastomosis level above the peritoneal reflection and low anterior resection was defined as an anastomosis level at or below the peritoneal reflection. Colorectal or anal anastomosis was done according to the surgeon's preference, with creation of a defunctioning stoma at the surgeon's discretion.

In the standard care (no ICG) group, a white-light assessment of bowel perfusion was performed, assessing the colour of the bowel, pulsatile flow in the feeding artery, and bleeding from the cut bowel ends, to determine the level of optimal bowel transection.

In the ICG group, two assessments were required, each involving an intravenous bolus of 0·1 mg/kg of ICG (sourced from a local supplier). Before ICG assessment, the proximal colon was assessed by white-light laparoscopy and the point of planned proximal transection marked with a surgical clip. Additional aides to perfusion assessment, such as evaluation of marginal artery supply, were allowed. Then, after mobilisation of the colon and division of the rectum, followed by white-light laparoscopy, the first ICG perfusion assessment was performed, either extracorporeally or intracorporeally. Any change in the level of proximal bowel transection following the first ICG perfusion assessment was at the surgeon's discretion and was recorded. Colorectal or anal anastomosis was then performed. The second ICG assessment was done following anastomosis to assess perfusion at the anastomotic site and in the proximal colon and rectum, with any revision of the anastomosis as a result of ICG assessment recorded.

A third ICG assessment was allowed and done at the surgeon's discretion (eg, endoluminal assessment of anastomosis). Any deviations from the pre-planned operation (eg, use of a defunctioning stoma) were recorded. For each ICG assessment, a subjective assessment of fluorescence intensity (no fluorescence, borderline fluorescence, or clear fluorescence) was done with the near-infrared laparoscopic system available onsite (Pinpoint [now owned by Stryker], Firefly [Intuitive Surgical; Sunnyvale, CA, USA], Stryker [Kalamazoo, MI, USA], or Storz [Tagerwilen, Switzerland]). The time from intravenous administration of ICG to first observed fluorescence was also captured at each assessment.

Clinical research teams at each site were responsible for perioperative and postoperative data collection. Participants' sex was self-reported as male or female. Data collected at baseline were patient demographics, disease characteristics, EQ-5D-5L, the European Organisation for Research and Treatment of Cancer (EORTC) questionnaires QLQ-C30 and QLQ-CR29, Low Anterior Resection Syndrome (LARS) score, and health resource use (UK sites only). Data collected during participants' hospital stay included operation details (eg, operating surgeon and operation performed), intraoperative and postoperative complications (including anastomotic leaks), re-interventions, and length of hospital stay. Participants were followed up at 30 days and 90 days, with data collected on clinical record forms about complications (including anastomotic leaks), re-interventions, and re-admissions following clinical review. Data on quality of life, LARS score, and health resource use (UK only) were captured by questionnaires completed in clinic or by post at 30 days and 90 days after surgery. 12-month follow-up data on quality of life, complications, re-interventions, and re-admissions were collected for UK patients.

The severity of anastomotic leak was defined according to the International Study Group of Rectal Cancer[16] as follows: grade A corresponds to an anastomotic leak not requiring invasive treatment; grade B corresponds to an anastomotic leak requiring invasive treatment but without a return to the operating theatre; and grade C corresponds to an anastomotic leak requiring a return to the operating theatre. Clinical anastomotic leak (grade B and C) was diagnosed according to local practice, including assessment of the patient's condition and supplemented by CT scan as required. A rectal contrast enema was mandated between 4 weeks and 6 weeks after the surgical procedure in all participants who did not have a clinical anastomotic leak to detect the presence of an asymptomatic leak (grade A). The first five contrast enemas from each centre were subject to central review at the coordinating site in Leeds, UK.

Outcomes

The primary endpoint was locally assessed clinical anastomotic leak (grade B or C) rate within 90 days of the operation. An abscess close to the anastomosis was considered as arising from a leak. Secondary endpoints included any anastomotic leak (grades A–C) within 90 days of the operation; change in planned anastomosis (surgeon-reported, intraoperative changes to the planned anastomosis, including the transection level of the proximal colon and rectum and defunctioning stoma); stoma formation (no stoma, defunctioning stoma, or permanent stoma at operation, and 30 days and 90 days after the operation); incidence of intraoperative complications; and incidence and severity of postoperative complications within 90 days of the operation. The severity of complications was assessed with the Clavien–Dindo Classification.[17] Total postoperative complication burden was measured with the Comprehensive Complication Indicator (CCI),[18] scored from 0–100, for which higher scores indicate a higher complication burden. Other secondary endpoints were length of postoperative hospital stay; any re-intervention occurring by 90 days (plus 12-month data for UK participants); death within 90 days of the operation; quality of life (EORTC QLQ-C30,[19] QLQ-CR29,[20] and EQ-5D-5L[21]) at 30 days, 90 days, and 12 months (UK participants); LARS score[22] in patients without a defunctioning stoma assessed at 30 days and 90 days after the operation; health resource utilisation (UK sites only) at 30 days, 90 days, and 12 months; and changes in the rectal microbiome and correlation with anastomotic leak (mechanistic sub-study; will be reported separately to allow for comprehensive analysis). Full data for stoma formation at operation and 30 days, any re-intervention within 12 months, and EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D-5L, and health resource utilisation at 30 days, 90 days, and 12 months are not presented in this manuscript and will be reported in full in future publications. Health resource utilisation data were used for the analysis of cost-effectiveness (cost per clinical leak avoided) and cost-utility (cost per quality-adjusted life-year [QALY]) for all leaks.

Statistical analysis

The original target sample size was 880 patients, and included an interim analysis once primary endpoint data were available for 554 patients, which would have allowed the trial to stop early due to efficacy in the primary endpoint given sufficient evidence. This sample size provided 80% power at the 5% (two-sided) level of significance to detect a reduction in the clinical anastomotic leak rate from the assumed 12% in the no ICG group to 6% in the ICG group,[23,24] allowing for 10% attrition. At the interim analysis, the target sample size was reduced from 880 to 766 participants, partly driven by an updated conservative assumption that the true clinical anastomotic leak rate in the no ICG group was no less than 13·63% (based on the greater than anticipated observed clinical anastomotic leak rate of 16·43%). It was also partly driven by the observed difference between the groups, as the recalculation was

based on conditional power. The target difference, expressed as an odds ratio (OR), used for the recalculation was defined to be consistent with the original calculation. The independent Data Monitoring and Ethics Committee recommended and verified the recalculation.

To control type I error, the O'Brien–Fleming α spending function was used to set the nominal significance thresholds for interim and final analyses. The nominal p value thresholds used to determine efficacy were 0·0139 and 0·0477 at the interim and final analyses, respectively.

All analyses were prespecified and conducted with intention-to-treat principles, in which participants were analysed according to their randomised allocation, unless otherwise stated. Complete case analyses were performed for all prespecified endpoints. Analyses were done in SAS statistical software (version 9.4).

Hypothesis testing for the primary endpoint used the O'Brien–Fleming α spending function to maintain an overall 5% significance level across the two tests. Hypothesis testing on all secondary endpoints was only performed at the final analysis and conducted at the 5% significance level. All hypothesis tests were two-sided.

Adjusted treatment effect estimates (ORs and difference in means) and corresponding 95% CIs are reported. Variance component estimates and SEs, and estimated intra-class correlation coefficients (ICCs), are also reported for models of anastomotic leak outcomes.

All models incorporated a random effect with respect to intended operating surgeon and were adjusted for the other minimisation factors as fixed effects. Binary endpoints (clinical anastomotic leak, any anastomotic leak, change in planned anastomosis, intraoperative complications, postoperative complications, re-interventions, and death within 90 days) used multi-level logistic regression to estimate the ORs.

Continuous endpoints (postoperative CCI score, length of postoperative stay, EORTC Global Health Status, and LARS score) used multi-level generalised linear models to estimate the difference in mean outcome between the treatment groups. In all cases, normal errors and an identity link were the preliminary approach taken, with alternatives considered based on model diagnostics, where appropriate. Initial poor fit of the prespecified model for length of postoperative stay meant that a log-link model was used instead, and the non-normal distribution of the postoperative CCI scores also led to the use of an alternative hurdle model. For quality of life outcomes, participants were included as a random effect, timepoints were included as fixed effects, and the treatment by timepoint interaction estimated. Multi-level ordinal logistic regression was used to estimate the ORs for stoma formation.

A hurdle model comprising a multi-level logistic regression and multi-level generalised linear model was used to estimate the ORs for having at least one postoperative complication with ICG versus without ICG and the difference in expected severity between the treatment groups in those patients who had at least one complication. A hurdle model was chosen over a zero-inflated model as it is not possible for the CCI to generate a score of 0 once a postoperative complication has occurred, and therefore the data-generating mechanism of a zero-inflated model was inappropriate in this case.

A potential unintended consequence of the use of ICG might be a decrease in the use of defunctioning stoma, which in turn might increase the incidence of anastomotic leak in the ICG group. A prespecified mediation analysis was done to explore the strength of the association between treatment allocation and the decision to form a defunctioning stoma in a multi-level logistic regression model. If a sufficiently strong association existed, the mediating effect of defunctioning stoma would be estimated with causal inference, such as with the counterfactual approach for causal mediation analysis method described by Valeri and Vanderwheele.[25] In the event that a sufficiently strong association was not observed, the interaction effect of treatment with defunctioning stoma would be explored as described below in a moderator subgroup analysis.

Prespecified moderator subgroup analyses explored any potential interactions between ICG and minimisation factor effects (with the exception of intended treating surgeon) on clinical anastomotic leak rate. Each minimisation factor was tested by comparing the primary analysis model with and without the inclusion of the interaction effect of treatment by subgroup indicators, and by performing a test of the type III effects.

In a post-hoc sensitivity analysis, the clinical and any anastomotic leak models were refitted using the corrected minimisation factors, actual operating surgeon, and the treatment actually received to assess the robustness of the analysis conclusions.

An economic evaluation was conducted alongside the clinical trial over a 3-month time horizon and from the perspective of the health and personal social services, consisting of a cost-effectiveness analysis (cost per clinical leak avoided) and cost-utility analysis (cost per QALY for all leaks). The base case evaluation used multiple imputation with chained equations to impute the missing cost or EQ-5D-5L datapoints. A supplementary complete case analysis included only those patients with complete EQ-5D-5L and cost data across all timepoints in the analysis. Further details of the economic evaluation methods are provided in the appendix (pp 31–44).

Role of the funding source

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

Results

Between Oct 20, 2017, and Aug 15, 2023, 2534 patients were assessed for eligibility across all participating sites,

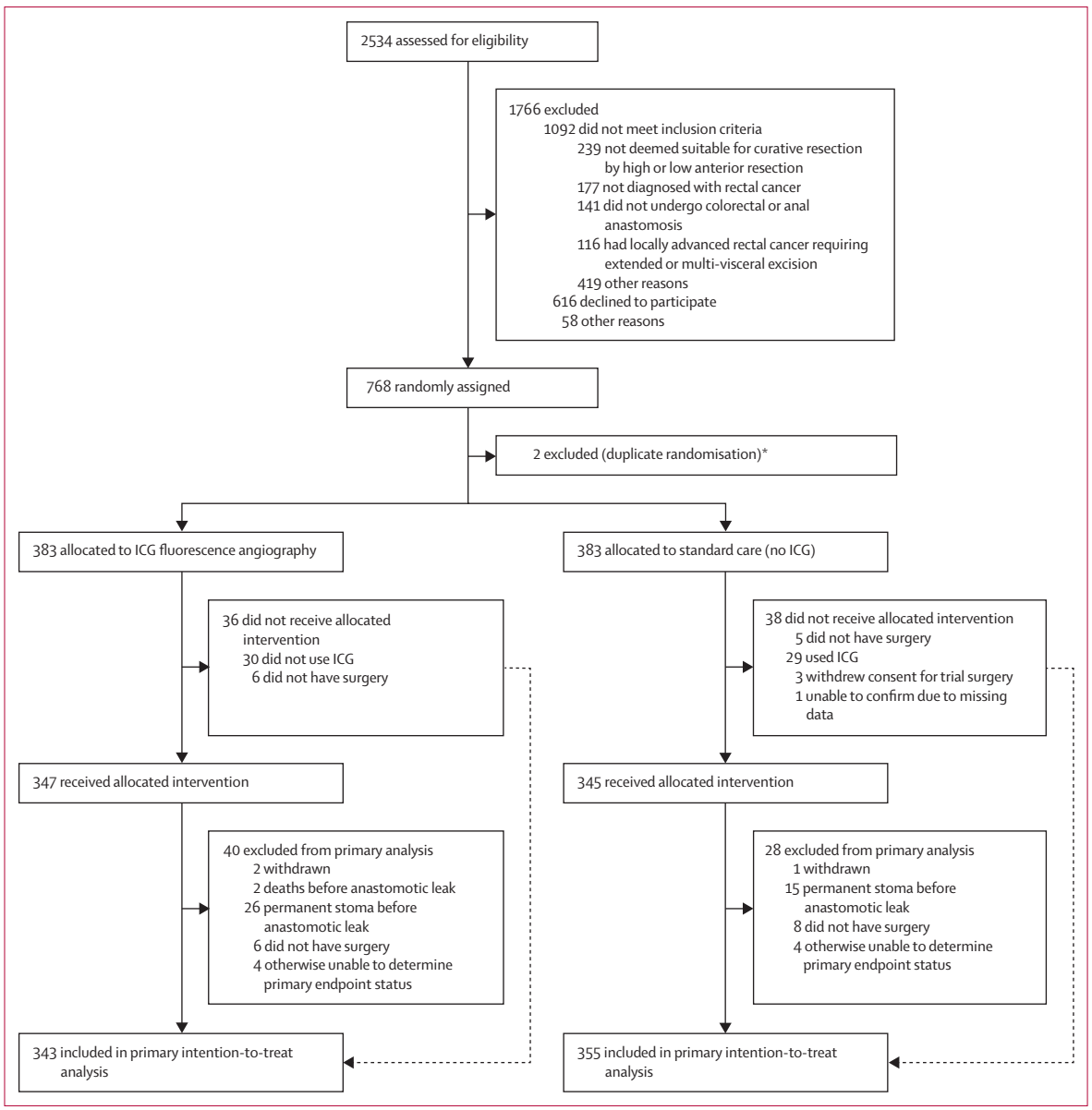

Figure 1: **Trial profile**
ICG=indocyanine green. *Two participants were mistakenly enrolled twice under different trial numbers; the duplicate participant numbers were removed from the trial.

with 1766 subsequently excluded (figure 1). Of the 766 participants recruited by 78 surgeons (appendix p 4), 383 were randomly assigned to each of the ICG and standard care groups. 68 (9%) of 766 patients were not evaluable for primary analysis: 28 (7%) of 383 in the standard care group and 40 (10%) of 383 in the ICG group. Recruitment by centre and the treatment allocation by intended surgeon at randomisation are provided in the appendix (pp 4, 19–20). Recruitment into the trial was affected by the COVID-19 pandemic due to reduced research capacity at centres, particularly in the UK.

Baseline characteristics are presented in table 1. Most participants were male (501 [65%] of 766) and of White ethnicity (726 [95%] of 766). The median age was 64·0 years (IQR 56·0–72·0), with a median BMI of 26·2 kg/m² (23·3–29·1). Participants were predominantly ASA grade II. Tumour stage and use of neoadjuvant therapy were similar between the groups. Tumours located below the peritoneal reflection accounted for 155 (40%) cases in the standard care group and for 158 (41%) cases in the ICG group. Summary data of performed procedures are provided in the appendix (pp 1–3).

The planned interim analysis was done at a timepoint at which we anticipated that around 554 patients would be evaluable for the primary endpoint once the relevant

	ICG (n=383)	Standard care (no ICG; n=383)	Total (n=766)
Age, years			
Mean (SD)	62·9 (11·6)	63·3 (11·5)	63·1 (11·6)
Median (IQR; range)	64·0 (55·0–72·0; 23·0–89·0)	63·5 (56·0–72·0; 22·0–88·0)	64·0 (56·0–72·0; 22·0–89·0)
Data missing	0	1	1
Sex*			
Male	253 (66%)	248 (65%)	501 (65%)
Female	130 (34%)	135 (35%)	265 (35%)
Neoadjuvant therapy*			
None received	214 (56%)	217 (57%)	431 (56%)
Short course with no delay	12 (3%)	15 (4%)	27 (4%)
Short course with delay	20 (5%)	16 (4%)	36 (5%)
Long course	137 (36%)	135 (35%)	272 (36%)
T stage*			
T1	34 (9%)	30 (8%)	64 (8%)
T2	125 (33%)	127 (33%)	252 (33%)
T3	207 (54%)	206 (54%)	413 (54%)
T4	17 (4%)	20 (5%)	37 (5%)
Position of the rectal tumour*			
Above peritoneal reflection	116 (30%)	119 (31%)	235 (31%)
At peritoneal reflection	109 (28%)	109 (28%)	218 (28%)
Below peritoneal reflection	158 (41%)	155 (40%)	313 (41%)
ASA grade*			
Grade I	72 (19%)	75 (20%)	147 (19%)
Grade II	243 (63%)	246 (64%)	489 (64%)
Grade III	68 (18%)	62 (16%)	130 (17%)
Ethnicity			
White	357 (93%)	369 (96%)	726 (95%)
Mixed (White and Black Caribbean)	0	1 (<1%)	1 (<1%)
Other mixed background	1 (<1%)	0	1 (<1%)
Asian (Indian)	2 (1%)	1 (<1%)	3 (<1%)
Asian (Pakistani)	1 (<1%)	0	1 (<1%)
Asian (Bangladeshi)	1 (<1%)	0	1 (<1%)
Other Asian background	6 (2%)	1 (<1%)	7 (1%)
Black Caribbean	2 (1%)	1 (<1%)	3 (<1%)
Black African	0	2 (1%)	2 (<1%)
Chinese	1 (<1%)	0	1 (<1%)
Not stated	5 (1%)	5 (1%)	10 (1%)
Other ethnic group	5 (1%)	1 (<1%)	6 (1%)
Data missing	2 (1%)	2 (1%)	4 (1%)
(Table 1 continues in next column)			

	ICG (n=383)	Standard care (no ICG; n=383)	Total (n=766)
(Continued from previous column)			
BMI, kg/m²			
Mean (SD)	26·7 (4·7)	26·5 (4·8)	26·6 (4·7)
Median (IQR; range)	26·3 (23·6–29·3; 16·6–45·0)	26·2 (23·1–28·8; 17·0–48·7)	26·2 (23·3–29·1; 16·6–48·7)
Data missing	18	17	35
BMI classification			
Underweight or normal (0 kg/m² to <25 kg/m²)	140 (37%)	139 (36%)	279 (36%)
Overweight (≥25 kg/m² to <30 kg/m²)	147 (38%)	161 (42%)	308 (40%)
Obese class I (≥30 kg/m² to <35 kg/m²)	56 (15%)	39 (10%)	95 (12%)
Obese class II (≥35 kg/m² to <40 kg/m²)	10 (3%)	20 (5%)	30 (4%)
Obese class III (≥40 kg/m²)	9 (2%)	5 (1%)	14 (2%)
Data missing	21 (5%)	19 (5%)	40 (5%)
Smoking status			
Yes, current smoker (within the past month)	45 (12%)	49 (13%)	94 (12%)
No, never smoked	197 (51%)	206 (54%)	403 (53%)
No, ex-smoker	123 (32%)	117 (31%)	240 (31%)
Data missing	18 (5%)	11 (3%)	29 (4%)

Data are n (%), mean (SD), or median (IQR; range). ASA=American Society of Anesthesiologists. ICG=indocyanine green. *Minimisation factors at randomisation, alongside intended operating surgeon. Intended operating surgeon is summarised in the appendix (p 19).

Table 1: **Baseline characteristics of all randomised participants**

data cleaning had been performed. The choice of timepoint was approved by the independent oversight committees. The actual number of patients with evaluable primary endpoint data at the interim analysis was 546 patients. A clinical anastomotic leak (grades B and C) occurred in 75 (14%) of 546 patients overall: 28 (11%) of 260 in the ICG group and 47 (16%) of 286 in the standard care group. The estimated adjusted OR of clinical anastomotic leak rate with ICG compared with standard care was 0·623 (98·61% CI 0·327–1·187, p=0·071). This p value did not meet the interim prespecified level of significance (p≤0·0139), and so the trial continued as per the recommendation of the independent Data Monitoring and Ethics Committee.

Data were available for 698 participants for the intention-to-treat analyses (figure 1). Within 90 days, a clinical anastomotic leak (grades B and C) occurred in 90 (13%) of 698 patients overall: 36 (10%) of 343 in the ICG group and 54 (15%) of 355 in the standard care group (adjusted OR with ICG *vs* standard care 0·667 [95% CI 0·419–1·060]; p=0·087; table 2). This treatment effect estimate did not meet the prespecified significance threshold of 0·0477 required to conclude efficacy. Sensitivity analysis based on treatment actually received concluded similarly (appendix pp 7–8), with clinical anastomotic leaks in 39 (11%) of 356 patients in the ICG group and 51 (15%) of 342 in the standard care group, yielding an adjusted OR of 0·714 (95% CI 0·450–1·131; p=0·15). In the unadjusted summary, grade A and B leaks occurred less frequently in the ICG group than in the standard care group and the proportion of patients in each group with grade C leaks was similar (table 2).

Regarding the prespecified mediator analysis, defunctioning stomas were formed in 490 (70%) of

698 patients overall: 235 (69%) of 343 in the ICG group and 255 (72%) of 355 in the standard care group. The estimated adjusted OR of defunctioning stoma formation in the ICG group versus the standard care group was 0·857 (95% CI 0·560–1·313; p=0·48), ruling out defunctioning stoma as a potential mediator (appendix p 9). The prespecified moderator subgroup analyses found insufficient evidence of any interaction effects between treatment and subgroups (appendix pp 10, 21).

An anastomotic leak (grade A, B, or C) occurred within 90 days in 121 (17%) of 698 patients overall: 47 (14%) of 343 in the ICG group and 74 (21%) of 355 in the standard care group (ICG *vs* standard care adjusted OR 0·607 [95% CI 0·403–0·915]; p=0·017; table 2). Sensitivity analysis based on treatment actually received concluded similarly (appendix pp 7–8).

Change in planned anastomosis occurred in 73 (10%) of 751 patients overall: 47 (12%) of 377 in the ICG group and 26 (7%) of 374 in the standard care group (adjusted OR 2·152 [95% CI 1·251–3·699]; p=0·0057; table 3). At least one intraoperative complication occurred in 33 (4%) of 751 patients overall: 17 (5%) of 377 in the ICG group and 16 (4%) of 374 in the standard care group (adjusted OR 1·113 [95% CI 0·542–2·284]; p=0·77). In 31 of 33 patients there was one intraoperative complication; there were two intraoperative complications in each of the two other patients. Summary data of intraoperative complications by treatment actually received are provided in the appendix (p 11).

Overall, 313 (42%) of 751 patients had at least one postoperative complication within 90 days: 145 (38%) of 377 in the ICG group and 168 (45%) of 374 in the standard care group (adjusted OR 0·738 [95% CI 0·539–1·011], p=0·059). The histogram of CCI scores in patients who had at least one postoperative complication and Kernal density plot of CCI scores split by treatment group are shown in figure 2. The estimated adjusted difference in mean CCI score (ICG *vs* standard care) was 1·167 (95% CI –2·376 to 4·710, p=0·52; table 3). Summary data of postoperative complications by Clavien–Dindo severity and by treatment actually received are provided in the appendix (pp 12–13).

Re-interventions occurred within 90 days of the procedure in 147 (20%) of 751 patients overall: 66 (18%) of 377 in the ICG group and 81 (22%) of 374 in the standard care group (adjusted OR 0·761 [95% CI 0·523–1·107]; p=0·15). Summary data of reasons for re-interventions at 30 days and 90 days by randomised allocation are provided in the appendix (pp 14–15).

Two patients in the ICG group and two in the standard care group died within 90 days of the operation. Both deaths in the standard care group were attributed to anastomotic leak. In the ICG group, one death was attributed to "cardiac arrest due to acute renal failure" and one death was attributed to "sepsis, aspiration pneumonia". The prespecified model was not fitted due to the low number of events. There were no serious adverse events related to ICG.

Stoma formation (defunctioning or permanent) at 90 days post-operation occurred in 474 (63%) of 751 patients overall: 238 (63%) of 377 in the ICG group and 236 (63%) of 374 in the standard care group (adjusted OR 1·163 [95% CI 0·848–1·595]; p=0·35). Due to the proportional odds assumption, the OR of permanent stoma presence versus no permanent stoma (defunctioning or no stoma) was not significant. The length of postoperative hospital stay was similar between the groups (mean 10·2 days [SD 17·9] for ICG *vs* 9·7 days [9·1] for standard care group; difference in means 0·990 [95% CI 0·911–1·077]; p=0·82).

The estimated adjusted difference in mean EORTC QLQ-C30 Global Health Status Score (ICG minus standard care) was 0·5240 (95% CI –3·1532 to 4·2013, p=0·78) at 30 days, –1·4955 (–4·6844 to 1·6934, p=0·36) at 90 days, and –0·5969 (–5·1179 to 3·9241, p=0·80) at 12 months post-operation. The general trend of the mean Global Health Status Score in both groups was a drop in quality of life at 30 days, with subsequent improvement at 90 days and 12 months post-operation (appendix pp 16, 22, 24). 12-month data were only collected for UK patients who reached this timepoint within the IntAct follow-up period.

The estimated adjusted difference in mean LARS score (ICG minus standard care) was 2·3022 (95% CI –1·8278 to 6·4323, p=0·27) at 30 days and 0·8671 (–2·2988 to 4·0329, p=0·56) at 90 days post-operation. In both groups, the LARS score was worse than baseline

	ICG (n=343)	Standard care (no ICG; n=355)	Estimate
Unadjusted summary of anastomotic leak grade			
No active therapeutic intervention (grade A)	11 (3%)	20 (6%)	..
Active therapeutic intervention but manageable without re-laparotomy (grade B)	11 (3%)	31 (9%)	..
Re-laparotomy (grade C)	25 (7%)	23 (6%)	..
No leak	296 (86%)	281 (79%)	..
Primary analysis model of participants with clinical (grade B or C) anastomotic leaks only			
Number with anastomotic leak (%)	36/343 (10%)	54/355 (15%)	0·667 (0·419–1·060), p=0·087
Planned surgeon at randomisation (random-effect variance component)	..	..	0·0609 (0·1978), ICC=0·0328
Secondary analysis model of participants with all (grade A, B, or C) anastomotic leaks			
Number with anastomotic leak (%)	47/343 (14%)	74/355 (21%)	0·607 (0·403–0·915), p=0·017
Planned surgeon at randomisation (random-effect variance component)	..	..	0·0046 (0·0727), ICC=0·0147

Estimate represents adjusted odds ratio (95% CI), p value, or random-effect variance component estimate (SE), ICC. The standard care (no ICG) group was the reference group (1 [ref]) for estimation of the odds ratios. The full model is presented in the appendix (pp 5–6). ICC=intra-class correlation coefficient.

Table 2: **Anastomotic leak outcomes by 90 days**

	ICG	Standard care (no ICG)	Adjusted odds ratio or model estimate (95% CI)	p value
Binary secondary outcomes				
Change in planned anastomosis	47/377 (12%)	26/374 (7%)	2·152 (1·251 to 3·699)*	0·0057
Permanent stoma formed rather than anastomosis	19/377 (5%)	9/374 (2%)	..	..
Planned proximal colon transection level changed	24/358 (7%)	11/365 (3%)	..	..
Planned site of rectal stump changed	4/358 (1%)	6/365 (2%)	..	..
Intraoperative complication (incidence)	17/377 (5%)	16/374 (4%)	1·113 (0·542 to 2·284)*	0·77
Postoperative complication within 90 days (incidence)†	145/377 (38%)	168/374 (45%)	0·738 (0·539 to 1·011)*	0·059
Any re-intervention within 90 days of trial operation	66/377 (18%)	81/374 (22%)	0·761 (0·523 to 1·107)*	0·15
Death within 90 days of trial operation	2/377 (1%)	2/374 (1%)	NA	NA
Ordinal secondary outcome				
Stoma formation at 90 days post-operation	238/377 (63%)	236/374 (63%)	1·163 (0·848 to 1·595)*	0·35
No stoma	130/377 (34%)	132/374 (35%)	..	..
Defunctioning stoma	208/377 (55%)	216/374 (58%)	..	..
Permanent stoma	30/377 (8%)	20/374 (5%)	..	..
Continuous secondary outcomes				
Postoperative complications (CCI score)†, mean (SD)	28·3 (17·2)	27·0 (16·0)	1·167 (−2·376 to 4·710)‡	0·52
Total number of patients (number missing)	139 (6)	163 (5)	..	..
Length of postoperative stay§, mean (SD), days	10·2 (17·9)	9·7 (9·1)	0·990 (0·911 to 1·077)‡	0·82
Median (IQR)	7 (5 to 10)	7 (5 to 10)	..	..
Total number of patients (number missing)	374 (9)	373 (10)	..	..

Data are n/N (%), mean (SD), or median (IQR), unless otherwise specified. CCI=Comprehensive Complication Index. ICG=indocyanine green. NA=not applicable. *Adjusted odds ratio. †See methods for full details of the modelling procedure for postoperative complications. CCI score was only modelled in patients who had at least one postoperative complication. ‡Model estimate. §Since a log-transformation was used, the exponentiated model estimate is presented for the length of postoperative stay endpoint.

Table 3: **Main results from secondary outcome analyses**

at 30 days and 90 days post-operation (appendix pp 16–17, 23, 25).

The results of the multiple-imputed (base case) and complete-case (supplementary) cost-effectiveness analyses are shown in the appendix (p 18). ICG was cheaper than standard care (saving £73 per patient). QALYs were almost the same between groups but indicated a small loss for ICG (of 0·001). This loss is negligible, highly uncertain, and is outweighed by the cost savings. The incremental cost-effectiveness ratio for the multiple-imputed analysis was £77 383. Given the direction of incremental costs and QALYs, this figure represents the costs saved by losing 1 QALY (ie, the cost utility), and, as it is above the UK National Institute for Health and Care Excellence threshold (which values a QALY at £20 000–30 000), it indicates cost-effectiveness. The complete-case analysis indicated a cost saving (£140 per leak) and also a very small QALY gain, indicating that ICG is dominant. The cost-effectiveness acceptability curve and cost-effectiveness plane are shown in the appendix (pp 26–27). These figures indicate that there is substantial uncertainty around the results but that ICG is likely (around 60% chance) to be cost-effective. As ICG numerically reduced leaks and was cost-saving, it was not possible to calculate cost per clinical leak avoided.

Discussion

In the randomised IntAct study assessing the effect of ICG on anastomotic leakage in patients undergoing elective anterior resection for rectal cancer, the rate of clinical (grade B or C) anastomotic leaks (the primary endpoint) was no different between perfusion assessment with ICG fluorescence angiography (10%) versus white-light laparoscopy standard of care (15%). The overall anastomotic leak rate (grades A, B, and C) in the standard care group was 21%, illustrating that many leaks are subclinical. Although we did not show a significant benefit for ICG in preventing clinical anastomotic leaks, a signal towards a reduction was observed, with the 95% CI narrowly failing to exclude an OR of no difference. A significant reduction was observed for ICG for any anastomotic leak (grades A, B, or C). The benefit of ICG fluorescence angiography might be in preventing grade A or B leaks, with similar rates of grade C leaks in the ICG and standard care groups. Grade C leaks usually involve substantial disruption of the anastomosis. It is possible that these leaks result from mechanisms other than inadequate blood supply, such as technical problems with the anastomosis (eg, too much tissue in the anastomosis, excessive tension, or multiple stapler firings). The importance of preventing anastomotic leaks is clearly evidenced in the literature, with patients with anastomotic leak having poor functional results, impaired quality of life, and worse oncological outcomes.[26,27] Although we did not show a difference in Global Health Status Score and LARS score between the ICG and standard care groups, this probably reflects the relative difference in leak rates and analysis at the population, rather than patient, level.

A change in the planned anastomosis was observed in 12% of patients in the ICG group versus 7% in the standard care group, a difference predominantly driven by higher rates of change at the proximal colon transection level. The rate of permanent stoma formation was also higher in the ICG group, with a greater proportion of patients in the ICG group having intraoperative permanent stoma formation rather than an anastomosis. Such differences between groups might contribute to the lower rate of all anastomotic leaks with ICG. The rates of intraoperative and postoperative complications and re-interventions were similar in the two groups.

In a recent systematic review and meta-analysis of 32 studies and 11 047 patients undergoing colorectal

cancer surgery, ICG fluorescence angiography significantly reduced the rate of clinical leaks.[28] The effect was greater in non-randomised studies (3·1% with ICG *vs* 7·3% without ICG; relative risk [RR] 0·43 [95% CI 0·35–0·52], p<0·001) than in randomised controlled trials (8·1% with ICG *vs* 12·1% without ICG; RR 0·67 [95% CI 0·46–0·98], p=0·04). This meta-analysis also found a significant difference in grade A leaks, a strong indication of reduced grade B leaks, but no difference in grade C leaks, which is not dissimilar to our results.

Two multicentre randomised controlled trials of ICG fluorescence angiography versus white-light laparoscopy in colorectal cancer have recently been published. The AVOID trial[14] recruited 982 patients from eight centres in the Netherlands and included a mixed cohort of right and left colonic resections, and other surgeries, for benign and malignant disease. The primary outcome was the rate of grade B and C leaks at 90 days post-operation and was no different between the ICG and no ICG groups (7% with ICG *vs* 9% without ICG; RR 0·77 [95% CI 0·50–1·20], p=0·24). This non-significant finding probably reflects the inclusion of right-sided resections, which might have a lower risk of anastomotic leakage than left-sided surgeries and could have diluted any benefit in the ICG group. Subgroup analyses did show a significant benefit for ICG in left-sided and rectosigmoid resections, with 90-day anastomotic leak rates of 8% (*vs* 13%) and 9% (*vs* 15%), respectively; these leak rates with ICG are lower than those found in IntAct, which could be due to different populations. The EssentiAL trial[13] recruited 850 patients with rectal cancer scheduled for minimally invasive sphincter-preserving surgery from 41 centres in Japan. The primary outcome was the rate of all anastomotic leaks (grades A, B, and C) at 30 days following surgery. A rectal contrast enema was only stipulated within 30 days in patients with a defunctioning stoma, potentially leading to the underestimation of the number of grade A leaks in patients without a defunctioning stoma and missing those who developed a leak beyond 30 days. The modified intention-to-treat analysis showed a significant reduction in anastomotic leak in the ICG group versus the no ICG group (7·6% *vs* 11·8%; RR 0·645 [95% CI 0·422–0·987], p=0·041), but did not meet the hypothesised absolute reduction in leak rate of 6 percentage points. A significant reduction was also observed in the secondary endpoint of clinical anastomotic leak rate (grades B and C; 4·7% with ICG *vs* 8·2% without ICG). The lower leak rates in the EssentiAL study, compared with IntAct, might reflect the demographics of the populations (eg, participants in EssentiAL had a lower BMI than those in IntAct),[29] or differences between European and Japanese surgical practices such as the higher use of neoadjuvant therapy in Europe.

The strength of IntAct lies in its randomised and pragmatic design. Restricting recruitment to patients with rectal cancer was justified based on reported leak rates of 5–20% in colorectal anastomoses compared with 1–8% in ileo-colic anastomoses.[30,31] The consequences for patients and health-care systems are also greater when a leak occurs in colorectal anastomoses. By excluding patients with benign disease, the effect of inflammatory disease on anastomotic healing was removed, which has been a limitation in other studies. The ICG and standard care groups were well matched for patient demographics, tumour characteristics, use of neoadjuvant therapy, and operative technique. The study cohort was typical of a European rectal cancer population, reflecting the increased rate in men with the expected distribution of ASA grades and tumour T-stages. The study also included a broad surgeon population, increasing the generalisability of the results to wider surgical practice. The only part of the operation that was prespecified was assessment of anastomotic perfusion with or without ICG. Therefore, the results are more likely to be generalisable to surgical practices in Europe. Unlike the EssentiAL study, in IntAct a rectal contrast enema was mandated at 4–6 weeks post-operation and primary and secondary outcomes were reported at 90 days, rather than 30 days, post-operation. It is therefore unlikely that subclinical leaks were missed and the reported rate for all anastomotic leaks is likely to be accurate. Unlike other studies, we included a cost-effectiveness analysis in IntAct, which is important to inform wider adoption of ICG. There is substantial uncertainty around the results, but they appear to suggest equivalence between ICG and standard care in terms of QALYs. However, there appears to be a cost saving with ICG; this cost saving is small to moderate depending on the analyses but is a relatively robust finding. However, even a small cost saving could have a substantial positive impact on budgeting across large numbers of patients.

The limitations of IntAct include the non-masking of surgeons and data collectors, which might have

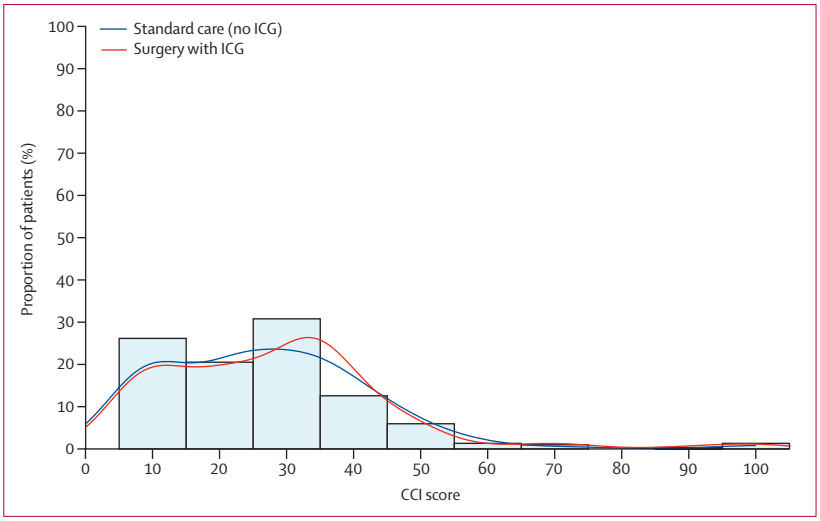

Figure 2: **Histogram and kernel density plot of CCI data for patients who had at least one postoperative complication**
CCI=Comprehensive Complication Index. ICG=indocyanine green.

introduced an observational bias. Most participants (95%) were of White ethnicity, the reason for which is unclear but warrants further investigation. It was not practical to standardise the use of ICG in terms of the laparoscopic system used, which might have introduced variability between centres. Although we attempted to eliminate the learning curve for using ICG by specifying a minimum of three previous rectal cancer resections with ICG, it is possible that a learning curve effect was present and diluted the benefit seen in the ICG group. A planned central review of randomly selected intraoperative videos proved to be impractical due to logistics around file sizes for data transfer. Additional work on the contrast enema studies, a full economic evaluation, an evaluation of surgeon learning and experience, and microbiome analysis are planned in future publications.

The evidence in favour of using ICG to prevent anastomotic leak in colorectal cancer surgeries is growing. Although the results are not so clear-cut in colon cancer, due to studies with small sample sizes and mixed cohorts of benign and malignant disease, together, the EssentiAL, AVOID, and IntAct studies, lend support to the benefits of ICG in preventing anastomotic leak in patients undergoing surgery for rectal cancer. Given the overall burden of anastomotic leak for health-care providers and patients, we believe that the argument against using ICG is probably no longer justified. We would advocate for ICG usage becoming standard of care in all patients undergoing rectal cancer resection.

The IntAct Collaborative Group

The following institutions and surgeons participated in the trial and form the IntAct Collaborative Group: AMC Amsterdam, the Netherlands: Roel Hompes, Willem Bemelman, Pieter Tanis, Jurriaan Tuynman; Bradford Royal Infirmary, UK: John Griffith; Charité – Universitätsmedizin Berlin, Germany: Martin E Kreis, Johannes Lauscher; Churchill Hospital, UK: Chris Cunningham, Oliver Jones, Stephen Boyce, Richard Guy, Ian Lindsey, Nicholas Symons, David James, Kat Baker, Simon Buczaki; Derriford Hospital, UK: Sebastian Smolarek; Frimley Park Hospital, UK: Henry Tilney, Mark Gudgeon, Ahmed Nizar, Ralph Smith; IRCCS San Raffaele Hospital, Italy: Andrea Vignali, Ugo Elmore, Riccardo Rosati; Istituto Clinico Humanitas, Italy: Antonino Spinelli, Caterina Foppa; James Paget Hospital, UK: Christopher Liao, Kamal Aryal, Vamsi Velchuru; Liège University Hospital, Belgium: Carla Coimbra Marques, Emmanuel Decker; Mater Misericordiae University Hospital, Ireland: Ronan Cahill; Morriston Hospital, UK: Dean Harris; Royal Albert Edward Infirmary, UK: Marius Paraoan, Tasadooq Hussain; Royal Preston Hospital, UK: Ioannis Peristerakis; Royal Surrey County Hospital, UK: Tim Rockall, Iain Jourdan, Andrea Scala, James Read; Royal United Hospital Bath, UK: Stephen Dalton, Edward Courtney; Royal Victoria Infirmary, UK: Peter Coyne, Ben Griffiths, Mohamed Shaban; St James' University Hospital, UK: David Jayne, Sushil Maslekar, Julian Hance, Richard Baker, Aaron Quyn, Peter Sagar, Rick Saunders, Jim Tiernan; St Mark's Hospital, UK: Danilo Miskovic, James Read; The Christie Hospital, UK: Chelliah Selvasekar; The Royal London Hospital, UK: Mohamed A Thaha; UMC Ljubljana, Slovenia: Ales Tomazic, Robert Juvan, Gregor Norcic, Jan Grosek; University College London Hospitals, UK: Manish Chand; Umeå University Hospital, Sweden: Martin Rutegård, Anders Gerdin, Petrus Bostrom, Jannice Forssell, Niillas Blind; University Hospital Coventry, UK: Charles Evans, Adeel Bajwa, Kai Leong; University Hospital Leuven, Belgium: Albert Wolthuis, André D'Hoore, Gabriele Bislenghi; University Hospital of Wales, UK: James Horwood, Jared Torkington, Simon Phillips, Julie Cornish; York Hospital, UK: Praminthra Chitsabesan, Michael Lim, Gabriele Di Benedetto.

Contributors

DJ, JC, NC, DT, RAC, PQ, and AK conceptualised the trial, obtained funding, and wrote the trial protocol. NC and GA did the statistical analysis. JC, NC, GA, and DJ wrote the first draft of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication. All authors contributed to the writing and review of this report. DJ and NC have directly accessed and verified the underlying data reported in the manuscript.

Declaration of interests

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Data sharing

Individual participant data (with any relevant supporting material, eg, data dictionary, protocol, and statistical analysis plan) for all trial participants (excluding any trial-specific participant opt-outs) will be made available upon reasonable request for secondary research purposes at the end of the trial (ie, usually when all primary and secondary endpoints have been analysed and all key analyses are complete and published). Requests to access trial data should be made to CTRU-DataAccess@leeds.ac.uk in the first instance. Requests will be reviewed by relevant stakeholders. No data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention requirements, which will usually stipulate that data recipients must delete their copy of the data at the end of the planned project.

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