INNOVATIONS JOURNALS

Review Article

Are We Overestimating the Effect of Indocyanine Green on Leaks Following Colorectal Surgery: A Systematic Review and Meta-Analysis

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Source of Support: None. Conflict of Interest: None.

Received: Dec 22, 2021; Revision Received: Apr 10, 2022; Accepted: Apr 12, 2022

Verhoeff K, Mocanu V, Fang B, et al. Are we overestimating the effect of indocyanine green on leaks following colorectal surgery: a systematic review and meta-analysis. *Innov Surg Interv Med*. 2022; 2:1–14. DOI: 10.36401/ISIM-21-05.

ABSTRACT

Introduction: Systematic reviews of retrospective studies suggest that indocyanine green (ICG) angiography reduces anastomotic leak (AL) and improves postoperative outcomes. This systematic review and meta-analysis evaluates colorectal surgery outcomes following ICG use with comparison of results found in randomized controlled trials (RCTs) and retrospective studies. **Methods:** A systematic search was conducted of studies evaluating ICG in colorectal surgery with more than five patients. Systematic search of MEDLINE, Embase, Scopus, and Web of Science was conducted in August 2021 and this study followed PRISMA and MOOSE guidelines. Primary outcome was AL. Meta-analysis was conducted with RevMan 5.4. **Results:** Overall, 2403 studies were retrieved with 28 total studies including three RCTs meeting criteria. RCTs included 964 patients, whereas other studies comprised 7327 patients with 44.6% receiving ICG. The ICG and non-ICG cohorts were similar with respect to age (62.6 vs 63.1 years), sex (45.1% vs 43.1% female), smoking (22.4% vs 25.3% smokers), and diabetes (13.4% vs 14.2%), respectively. Anastomotic height (6.5 vs 6.8 cm) and technique (78.7% vs 74.8% stapled) were also comparable. With retrospective studies included, ICG was associated with AL reduction (odds ratio [OR] 0.41; 95% CI, 0.32–0.53; $p < 0.001$) and reoperation for AL (OR 0.64; 95% CI, 0.43–0.95; $p = 0.03$), with pronounced effects for rectal anastomoses (OR 0.31; 95% CI, 0.21–0.44; $p < 0.001$). RCT evidence suggests a much smaller effect size (OR 0.64; 95% CI, 0.42–0.99; $p = 0.04$), and no reduction in AL reoperation (OR 0.72; 95% CI, 0.29–1.80; $p = 0.48$) or length of stay (LOS). **Conclusion:** Retrospective studies suggest reduced AL, reoperation for AL, and LOS with ICG angiography. However, RCTs suggest a smaller effect size and do not demonstrate reduced reoperation or LOS. Additional RCTs are required before widespread ICG uptake.

Keywords: indocyanine-green (ICG), colorectal surgery, anastomotic leak

INTRODUCTION

Anastomotic leaks (ALs) are amongst the most feared complications following colorectal surgery. Despite improvements in perioperative care, surgical techniques, and technology, ALs still occur in 10–20% of colorectal resections,[1,2] with up to 11% of patients requiring reoperation.[3] Several key factors, including anastomotic location, tissue tension, and anatomic collateral vascularization, influence AL through anastomotic perfusion effects.[4–7] Careful examination of transected bowel ends for pulsatile blood flow is currently the primary method to evaluate anastomotic perfusion. However, this approach is limited in its ability to accurately assess tissue viability particularly for low anastomoses performed in a narrow pelvis.[8,9]

Near-infrared fluorescence angiography (FA) is a cost-effective, safe, and readily available technology enabling

intraoperative assessment of anastomotic perfusion, which is thought to improve AL rates after colorectal surgery. FA involves injecting a fluorophore intravenously and illuminating it within tissue of interest at its absorption wavelength.[9,10] Indocyanine green (ICG) is the most common fluorophore used for FA; with light absorption at 700–800 nm and emittance at 700–900 nm.[9,11] Before bowel transection, ICG is used to evaluate for compromised bowel perfusion, allowing anastomoses to be formed in optimally perfused locations. Although promising, current reviews have disproportionately emphasized results from pooled findings of cohort studies without inclusion and comparison of recently conducted high-quality randomized trials. This may potentially overestimate the ICG effect size and preclude routine adoption of ICG FA.[12–18]

The aim of this study was to address this gap in literature and perform a comprehensive systematic review and meta-analysis evaluating all studies that assess the role of ICG in optimizing colorectal surgery outcomes with a focus on contrasting outcomes between randomized controlled trials (RCTs) and cohort studies. Primary outcomes of our study were evaluating AL rates between colorectal anastomoses with and without ICG use. Secondary outcomes included evaluating differences in postoperative complications, reoperations, and intraoperative differences between ICG and non-ICG groups.

MATERIALS AND METHODS

Study Design and Formulation of Research Question

We conducted a systematic review and meta-analysis in keeping with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-analysis of Observational Studies) guidelines.[19] The population consisted of subjects 18 years of age or older undergoing colorectal surgery with anastomoses. The intervention was ICG FA to assess anastomotic perfusion, compared to standard of care.[9] Outcomes of interest included AL, changes in anastomotic transection line, rate of diversion with ostomy formation, reoperation for AL, operative duration, LOS, ureteric injury, and mortality. This review was exempt from ethics board review.

Search Strategies

The medical librarian conducted comprehensive searches in MEDLINE, Embase, Scopus, Web of Science Core Collection, and Cochrane Library (Wiley) on July 24, 2020. The search was updated August 25, 2021. Search strategies identified all literature pertaining to ICG and colorectal surgery with relevant keywords and vocabulary limited to the English language (Supplemental Table S1, available online). In addition to subscription databases, we evaluated gray literature by using the first 200 results from Google Scholar, which has been demonstrated to be a reasonable number of results to screen.[20] Bibliographies from included studies were also reviewed.

Study Inclusion and Exclusion Criteria

Articles were systematically reviewed and selected on the basis of the following inclusion criteria: (1) evaluated the influence of ICG on AL, (2) included a comparison group, (3) enrolled patients 18 years or older undergoing general surgery procedures, (4) enrolled greater than five patients. All comparative study designs were included such as retrospective cohort studies, prospective cohort studies, and case-control studies to ensure complete, nonbiased, evaluation of all comparative studies. Non-English studies, animal studies, and abstracts were excluded. Two independent reviewers screened titles and abstracts, assessed full-text versions, and extracted data. Disagreements were resolved by re-extraction, or third-party adjudication.

Primary and Secondary Outcomes

The primary outcome of our study was AL rate for colorectal anastomoses with and without ICG use. Only ALs resulting in a change of clinical course (grade B and C) were included in data collection. This includes grade B and C AL as defined by the International Study Group of Rectal Cancer.[21] Secondary outcomes included evaluating differences in postoperative complications and intraoperative differences between ICG and non-ICG groups. Postoperative outcomes collected were ureteric injury, LOS, rate of changed transection lines, operative time, mortality, and reoperation due to AL. Patient demographics collected included age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) score, active smoking status, diabetes rates, American Joint Committee on Cancer (AJCC) malignancy stage, and neoadjuvant status. Technical factors captured were distance of the anastomosis from the anal verge (in cm), surgical indication, anastomosis type (staples versus hand-sewn), anastomotic location (rectal, left colon, or right colon), follow-up duration, and type of ICG technology.

Risk of Bias Assessment

Study bias assessment was completed independently by two authors, with disagreements resolved by a third party. Included nonrandomized studies were assessed for quality by using the Methodological Index for Non-Randomized Studies (MINORS), a validated index to assess nonrandomized comparative studies.[22,23] Randomized studies were evaluated with the revised Cochrane risk-of-bias tool for randomized studies (ROB2).[24] Both MINORS and ROB2 tools evaluate included studies on several factors of quality including their management of missing data.

Statistical Analysis

Two separate analyses were conducted in this study. The first analyzed only patients evaluated in RCT studies,

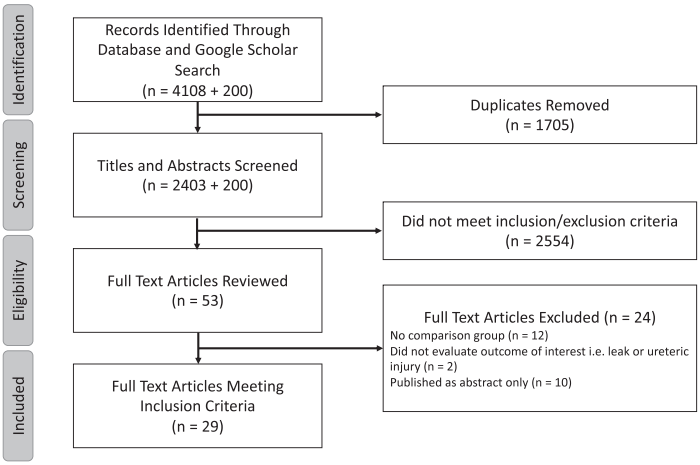

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) summary of systematic review study search and inclusion.

whereas the second analysis included all studies that met inclusion criteria. This was done to compare patient demographics and outcomes between RCTs and previously well-studied and collated cohort studies.

In scenarios where studies presented both matched data and unmatched data, only matched data were included. When data were presented as a median, means were estimated by applying the formula presented by Wan et al.[25] Patient characteristics and follow-up data were summarized and described as a weighted mean or percentages. Meta-analysis was used to evaluate AL, LOS, rate of changed transection line, operative time, and rate of diversion where appropriate. The estimated effects were calculated by using RevMan 5.4 software. The Mantel-Haenszel random-effects model was applied in our analysis, assuming the true effect estimates varied among studies. Included studies were tested for heterogeneity, with significance set at $p < 0.10$ and the heterogeneity quantified by the I^2 statistic as low (< 50%), moderate (50–75%), or high (> 75%).[26]

RESULTS

Study Selection

A total of 4108 results were retrieved and when duplicates were removed, 2403 unique results and 200 Google Scholar results remained for title and abstract screening. Following screening, 53 manuscripts underwent full-text review; of those, 28 texts met inclusion criteria (Fig. 1). Studies included three RCTs, two prospective cohort studies, 23 retrospective cohort studies, and one retrospective case control study (Table 1).[1–3,27–51]

Clinical Characteristics of Study Population

RCTs identified 964 patients with 483 (51.1%) receiving ICG. Groups were well balanced with regard to sex (46.0% female ICG vs 46.6% control), age (61.6 years ICG vs 61.4 control), and BMI (26.5 kg/m^2 ICG vs 26.9 control). Patients were also similar with regard to ASA score and rate of diabetes mellitus (11.2% ICG vs 12.3% control). Patients undergoing ICG evaluation were more likely to be smokers (27.5% ICG vs 18.3% control) but this was only reported in one study. Studies evaluated a mix of patients, with Alekseev et al[27] including left-sided colon cancers, De Nardi et al[28] studying mixed malignant and benign left colon disease, and Jafari et al[29] including only patients with rectal cancer. An equal number of patients in RCTs received neoadjuvant therapy (31.9% ICG vs 32.8% control), and cancer stage was similar but only reported by Alekseev et al.[27] RCT follow-up was 30 days for two studies, and 240 days in the study by Jafari et al.[29]

When all studies were included, 7327 patients were identified with 3269 (44.6%) evaluated with ICG. Patients primarily underwent colorectal surgery owing to malignancy, with 13 studies evaluating patients with rectal cancer, 4 studies including left-sided malignancies, and 11 studies assessing mixed benign and malignant resections as shown in Table 2. Most patients received colorectal or coloanal anastomoses (67.0% ICG vs 67.4% non-ICG), compared to left colon (23.5% ICG vs 23.3% non-ICG) or right colon (9.4% ICG vs 9.9% non-ICG). There were no differences between ICG and non-ICG patients with regard to AJCC stages or neoadjuvant treatment status (29.2% ICG vs 27.4% control) (Table 2).

ICG and non-ICG cohorts were similar with regard to age (62.6 years ICG vs 63.1 non-ICG), sex (45.1% female ICG vs 43.1% non-ICG), and ASA score (Table 2). Groups were also similar with regard to AL risk factors including BMI (25.2 kg/m^2 ICG vs 25.2 non-ICG), smoking (22.4% ICG vs 25.3% non-ICG), and diabetes (13.4% ICG vs 14.2% non-ICG) (Table 2). Follow-up was 30 days in most studies ($n = 14$) with an average of 47.4 days, excluding two studies with outcomes extending beyond 6 months (Table 1).

Technical Factors of Study Population

RCTs had anastomoses that occurred 6.8 cm and 7.1 cm above the anal verge for ICG and control groups, respectively. All patients underwent anterior or low anterior resection and received rectal anastomoses, and over half were treated laparoscopically (65.4% ICG vs 63.5% control).

For other studies, anastomotic distance from the anal verge (5.8 cm ICG vs 6.3 non-ICG), and anastomotic technique (84.7% stapled ICG vs 86.4% non-ICG) were similar between groups (Table 3). Most patients underwent laparoscopic surgery, with 91.9% of ICG patients treated laparoscopically compared to 87.2% of the non-ICG group.

ICG techniques and dosing varied tremendously. Timing of ICG assessment ranged from 30 seconds[30] to 3 minutes.[27] Most authors reported perfusion assessment after 1 minute ($n = 6$) or did not report timing of their FA assessment ($n = 17$). ICG doses used

Table 1. Summary of key characteristics for included studies

Study	Publication Year	Study Type	No. of Patients	Total MINORS Score	Follow-up (days)	Surgical Indication	ICG Technology Used	ICG Dose Used (mg/kg)
Alekseev et al[27]	2020	Randomized controlled trial	ICG: 187 Control: 190	N/A	ICG: 30 Control: 30	Left colorectal cancers	KARL STORZ GmbH & Co. KG, Tuttlingen, Germany, (SPIES) with a light source (D-LIGHT P SCB; KARL STORZ)	0.2
Bonadio et al[1]	2020	Retrospective cohort	ICG: 33 Control: 33	18	ICG: 30 Control: 30	Rectal cancer	KARL STORZ GmbH & Co. KG, Tuttlingen, Germany, (SPIES) with a light source (D-LIGHT P SCB; KARL STORZ)	0.2
Boni et al[35]	2017	Retrospective cohort	ICG: 42 Control: 38	15	N/A	Rectal cancer	KARL STORZ GmbH & Co. KG, Tuttlingen, Germany, (SPIES) with a light source (D-LIGHT P SCB; KARL STORZ)	0.2
Brescia et al[36]	2018	Retrospective cohort	ICG: 75 Control: 107	15	N/A	Mixed	KARL STORZ GmbH & Co. KG, Tuttlingen, Germany, (SPIES) with a light source (D-LIGHT P SCB; KARL STORZ)	0.25
Chivé et al[37]	2021	Retrospective cohort	ICG: 158 Control: 677	17	30	Mixed	SPY Elite Intraoperative Perfusion Assessment System (Novadaq Technologies Inc., Bonita Springs, FL)	N/A
De Nardi et al[28]	2020	Randomized controlled trial	ICG: 118 Control: 122	N/A	ICG: 30 Control: 30	Mixed benign and malignant	N/A	0.3
Dinallo et al[33]	2019	Retrospective cohort	ICG: 234 Control: 320	17	N/A	Mixed benign and malignant	SPY Elite Intraoperative Perfusion Assessment System (Novadaq Technologies Inc., Bonita Springs, FL)	N/A
Foo et al[38]	2020	Retrospective cohort*	ICG: 253 Control: 253	22	ICG: > 9 months‡	Rectal cancer	SPY Elite System (Stryker, Kalamazoo, MI), Pinpoint System (Stryker), and the Da Vinci Xi (Firefly, Intuitive Surgical, Sunnyvale, CA)	7.5 mg
Hasegawa et al[39]	2020	Retrospective cohort*	ICG: 141 Control: 279	18	ICG: 30 Control: 30	Rectal cancer	IMAGE1 S system (Karl Storz SE & Co. KG, Tuttlingen, Germany), 1588 Advanced Imaging Modalities (AIM) Platform and SPY Fluorescence technology (Stryker, Kalamazoo, MI), or HyperEye Medical System Handy (Mizuho Medical Co. Ltd., Tokyo, Japan).	5 mg
Impellizzeri et al[40]	2020	Retrospective cohort	ICG: 98 Control: 98	19	N/A	Mixed	SPIES system (KARL STORZ GmbH & Co.)	12.5 mg
Ishii et al[41]	2020	Retrospective cohort*	ICG: 87 Control: 87	18	ICG: 30 Control: 30	Rectal cancer	N/A	5 mg
Jafari et al[29]	2021	Randomized controlled trial	ICG: 178 Control: 169	N/A	8 wk	Rectal cancer	N/A	7.5 mg
Jafari et al[42]	2013	Retrospective cohort	ICG: 16 Control: 22	9	ICG: 60 Control: 60	Rectal cancer	The da Vinci Si Surgical System (Intuitive Surgical, Sunnyvale, CA)	3.75–7.5 mg
Kim et al[43]	2019	Retrospective cohort	ICG: 310 Control: 347	16	N/A	Rectal cancer	DaVinci Xi robot (Intuitive Surgical) or Firefly	10 mg
Kin et al[44]	2015	Retrospective cohort†	ICG: 173 Control: 173	16	ICG: 60 Control: 60	Mixed benign and malignant	SPY Imaging System (Novadaq Technologies Inc., Bonita Springs, FL)	N/A
Kojima et al[45]	2020	Retrospective cohort*	ICG: 27 Control: 27	18	ICG: 30 Control: 30	Left colorectal cancers	N/A	N/A
Kudszus et al[46]	2010	Retrospective cohort†	ICG: 201 Control: 201	10	N/A	Mixed benign and malignant	(IC-View, PulsionMedical Systems AG, Munich, Germany).	0.2–0.5
Mizrahi et al[31]	2018	Retrospective cohort*	ICG: 30 Control: 30	20	ICG: 60 Control: 60	Rectal cancer	PINPOINT Endoscopic Fluorescence Imaging System (Novadaq, Toronto, Ontario, Canada)	N/A
Otero-Pineiro et al[3]	2020	Retrospective cohort	ICG: 80 Control: 204	17	ICG: 30 Control: 30	Rectal cancer	The PINPOINT Endoscopic Fluorescence Imaging System from Novadaq Technologies Inc.	2.5 mg
Shapera and Hsiung[47]	2019	Retrospective cohort	ICG: 74 Control: 30	15	ICG: 30 Control: 30	Mixed benign and malignant	DaVinci Xi robot (Intuitive Surgical)	25 mg
Skrovina et al[48]	2020	Retrospective cohort	ICG: 50 Control: 50	20	ICG: 30 Control: 30	Rectal cancer	SPIES system (KARL STORZ GmbH & Co.)	0.2

Table 1 continues on next page

Table 1. Continued

Study	Publication Year	Study Type	No. of Patients	Total MINORS Score	Follow-up (days)	Surgical Indication	ICG Technology Used	ICG Dose Used (mg/kg)
Spinelli et al[30]	2019	Retrospective cohort*	ICG: 32 Control: 32	17	ICG: 9.5 mo‡ Control: 39.5 mo‡	Benign	PINPOINT endoscopic fluorescence imaging system (Stryker, Kalamazoo, MI), and laparoscopic Spies system (KARL STORZ GmbH, Tuttlingen, Germany)	0.1–0.2
Starker and Chinn[49]	2018	Retrospective cohort	ICG: 238 Control: 109	14	ICG: 30 Control: 30	Mixed benign and malignant	DaVinci Xi (Intuitive Surgical)	N/A
Su et al[50]	2020	Retrospective cohort	ICG: 84 Control: 105	18	ICG: 60 Control: 60	Mixed malignant	opto-cam2100 (Optomedic, Guangdong, China)	7.5 mg
Tsang et al[51]	2020	Prospective cohort	ICG: 63 Control: 68	20	ICG: 30 Control: 30	Mixed benign and malignant	Firefly high-definition vision system or DaVinci Xi robotic surgical system (Intuitive Surgical, Sunnyvale, CA) or Olympus laparoscopic camera system OTV-S300 with IR light source CLV-S200-IR (Olympus, Tokyo, Japan).	10 mg
Wada et al[54]	2019	Retrospective cohort*	ICG: 34 Control: 34	17	N/A	Rectal cancer	PDE-neo System (Hamamatsu Photonics K.K., Hamamatsu, Japan)	5 mg
Watanabe et al[55]	2020	Retrospective cohort*	ICG: 211 Control: 211	17	ICG: 30 Control: 30	Rectal cancer	Karl Storz (D-Light P; Tuttlingen, Germany) and the Stryker Corporation (1588 AIM Platform; Kalamazoo, MI).	0.25
Wojcik et al[2]	2020	Prospective cohort*	ICG: 42 Control: 42	18	ICG: 30 Control: 30	Left colorectal cancers	PINPOINT (Stryker, Kalamazoo, MI)	0.1
Total or average:			ICG: 3269 Control: 4058	16.8	ICG: 47.4 Control: 47.4	13 rectal cancers, 3 left colorectal cancers, 13 mixed		

*Only propensity-matched data included.
†Only matched pairs data included.
‡Excluded from calculation of follow-up.
ICG: indocyanine green; MINORS: Methodological Index for Non-Randomized Studies; N/A: Not available.

Table 2. Patient demographics

Study	Age, mean (SD), y	Female Patients (*n*, %)	BMI (mean ± SD), kg/m^2	ASA Status, I/II/ >II (*n*, %)	Active Smokers (*n*, %)	Diabetes (*n*, %)	Cancer Stage (AJCC 0/1/2/3/ 4)	Neoadjuvant Therapy (%)
Alekseev et al[27]	ICG: 63 (10.8)	ICG: 95 (51)	N/A	ICG: 18 (10)/145 (78)/24 (13)	N/A	ICG: 15 (8)	ICG: 3 (2)/7 (4)/ 49 (26)/77 (41)/ 17 (9)	ICG: 20 (11)
	Control: 63 (11.0)	Control: 98 (52)		Control: 3 (2)/143 (75)/25 (7)		Control: 17 (9)	Control: 7 (4)/25 (13)/46 (24)/87 (46)/19 (10)	Control: 19 (10)
Bonadio et al[1]	ICG: 71.9 (11.1)	ICG: 12 (36)	ICG: 25.6 (4)	ICG: 0 (0)/19 (58)/14 (42)	N/A	ICG: 6 (18)	ICG: 4 (12)/17 (52)/6 (18)/3 (9)/3 (9)	ICG: 16 (48)
	Control: 69.0 (12)	Control: 18 (55)	Control: 25.7 (4.1)	Control: 4 (12)/22 (67)/7 (21)		Control: 2 (6)	Control: 4 (12)/15 (46)/2 (6)/9 (27)/3 (9)	Control: 14 (42)
Boni et al[35]	ICG: 69 (8)	ICG: 14 (33)	ICG: 27 (11)	N/A	ICG: 18 (42.9)	N/A	N/A	ICG: 33 (79)
	Control: 67 (7)	Control: 16 (42)	Control: 29 (15)		Control: 23 (60.5)			Control: 23 (61)
Brescia et al[36]	ICG: 67.1 (6)	ICG: 32 (43)	ICG: 24.4 (3)	N/A	ICG 15 (20.0)	N/A	N/A	N/A
	Control: 65.7 (7)	Control: 44 (41)	Control: (3)		Control: 25 (23.4)			
Chivé et al[37]	ICG: 62 (16)	ICG: 63 (39.9)	ICG: 26.5 (6.5)	ICG: 14 (9)/83 (53)/ 61 (39)	N/A	N/A	ICG: 29 (27)/45 (41)/17 (16)/15 (14)	N/A
	Control: 64 (15)	Control: 303 (44.8)	Control: 26.1 (4.5)	Control: 70 (10)/361 (53)/207 (31)			Control: 98 (25)/ 157 (40)/73 (19)/151 (38)	
De Nardi et al[28]	ICG: 66.1 (N/A)	ICG: 58 (49)	ICG: 25.2 (N/A)	ICG: 10 (8)/82 (69)/ 26 (22)	N/A	ICG: 17 (14)	N/A	ICG: 21 (18)
	Control: 65.1 (N/A)	Control: 56 (46)	Control: 25.6 (N/A)	Control: 7 (6)/92 (75)/23 (19)		Control: 19 (16)		Control: 28 (23)
Dinallo et al[33]	ICG: 61.5 (9.0)	ICG: 126 (54)	ICG: 28.3 (4.2)	N/A	ICG: 37 (15.8)	ICG: 38 (16)	N/A	ICG: 16 (7)
	Control: 62.5 (9.1)	Control: 182 (57)	Control: 28.3 (6.1)		Control: 51 (15.9)	Control: 58 (18)		Control: 24 (8)
Foo et al[38]	ICG: 66.6 (10.6)	ICG: 87 (34)	N/A	ICG: 30 (12)/147 (58)/76 (30)	ICG: 39 (15.4)	N/A	N/A	ICG: 49 (19)
	Control: 67.2 (11.0)	Control: 90 (36)		Control: 19 (8)/151 (60)/83 (33)	Control: 18 (7.1)			Control: 60 (24)
Hasegawa et al[39]	ICG: 61 (13.3)	ICG: 111 (79)	ICG: 22.7 (3.5)	ICG: 48 (34)/NA/NA	ICG: 95 (67.4)	N/A	N/A	ICG: 26 (18)
	Control: 61.7 (9.6)	Control: 76 (27)	Control: 23.2 (3.0)	Control: 100 (36)/ NA/NA	Control: 193 (69.2)			Control: 50 (18)
Impellizzeri et al[40]	ICG: 66.3 (N/A)	ICG: 45 (45.9)	N/A	ICG: 11 (11)/66 (67)/ 21 (21)	N/A	ICG: 9 (9)	ICG: 16 (26)/20 (32)/14 (23)/6 (10)	ICG: 13 (13)
	Control: 69.3 (N/A)	Control: 41 (41.8)		Control: 19 (19)/53 (54)/26 (27)		Control: 7 (7)	Control: 14 (20)/ 26 (37)/19 (27)	Control: 11 (11)
Ishii et al[41]	ICG: 60.3 (10.0)	ICG: 38 (44)	ICG: 23.6 (2.9)	ICG: 12 (14)/ 67 (77)/ 8 (9)	N/A	N/A	ICG: 2 (2)/22 (25)/36 (41)/18 (21)/9 (10)	ICG: 24 (28)
	Control: 61.3 (11.0)	Control: 37 (43)	Control: 23.8 (2.9)	Control: 11 (13)/70 (80)/6 (7)			Control: 0 (0)/24 (38)/34 (39)/23 (26)/6 (7)	Control: 21 (24)
Jafari et al[29]	ICG: 57.2 (11.4)	ICG: 69 (38.8)	ICG: 27.8 (5.6)	N/A	ICG: 49 (27.5)	ICG: 22 (12)	N/A	ICG: 113 (63)
	Control: 57 (11.4)	Control: 70 (41.4)	Control: 28.2 (5.9)		Control: 31 (18.3)	Control: 23 (14)		Control: 111 (66)
Jafari et al[42]	ICG: 58 (N/A)	ICG: 4 (25)	ICG: 27 (N/A)	N/A	ICG: 2 (12.5)	ICG: 0 (0)	*ICG: -/6 (38)/4 (25)/6 (38)/0 (0)	ICG: 10 (63)
	Control: 63 (N/A)	Control: 1 (5)	Control: 22 (N/A)		Control: 6 (27.3)	Control: 4 (18)	*Control: -/12 (55)/2 (9)/6 (27)/2 (9)	Control: 16 (73)

Table 2 continues on next page

Table 2. Continued

Study	Age, mean (SD), y	Female Patients (*n*, %)	BMI (mean ± SD), kg/m^2	ASA Status, I/II/ >II (*n*, %)	Active Smokers (*n*, %)	Diabetes (*n*, %)	Cancer Stage (AJCC 0/1/2/3/ 4)	Neoadjuvant Therapy (%)
Kim et al[43]	ICG: 58 (11)	ICG: 128 (41)	ICG: 23.9 (3.7)	ICG: 76 (25)/220 (71)/5 (2)	N/A	N/A	ICG: 35 (11)/88 (28)/83 (27)/98 (32)/6 (2)	ICG: 96 (310
	Control: 57 (11)	Control: 131 (38)	Control: 23.9 (2.9)	Control: 86 (25)/254 (73)/2 (1)			Control: 21 (6)/ 114 (33)/90 (26)/110 (32)/ 12 (4)	Control: 104 (30)
Kin et al[44]	ICG: 58.2 (13.2)	ICG: 80 (46)	ICG: 27 (4.9)	ICG: 3 (2)/74 (43)/95 (55)	ICG: 17 (9.8)	ICG: 23 (13)	N/A	ICG: 35 (20)
	Control: 58.1 (13.2)	Control: 80 (46)	Control: 26.5 (5.3)	Control: 5 (3)/81 (47)/87 (50)	Control: 19 (11.0)	Control: 17 (10)		Control: 35 (20)
Kojima et al[45]	ICG: 70.9 (8.9)	ICG: 12 (44)	ICG: 20.9 (3.9)	ICG 5 (19)/18 (67)/4 (15)	N/A	N/A	ICG: 2 (7)/5 (19)/ 7 (26)/5 (19)/8 (30)	N/A
	Control: 72 (8.9)	Control: 13 (48)	Control: 21.5 (4.1)	Control: 2 (7)/21 (78)/4 (15)			Control: 0 (0)/6 (22)/5 (19)/14 (52)/2 (7)	
Kudszus et al[46]	ICG: 67.8 (25.2) Control: 69	ICG: 116 (58) Control: 116 (58)	ICG: 25.3 (8.4) Control: 25.7 (7.8)	N/A	N/A	N/A	N/A	N/A
Mizrahi et al[31]	ICG: 58 (12) Control: 58 (13)	ICG: 14 (47) Control: 12 (40)	ICG: 25.9 (5.7) Control: 27.2 (6.2)	N/A	ICG: 2 (6.7) Control: 0 (0)	ICG: 2 (7) Control: 3 (10)	N/A	ICG: 17 (57) Control: 14 (47)
Otero-Pineiro et al[3]	ICG: 68 (11.4)	ICG: 29 (36)	ICG: 26.1 (4.1)	ICG: 2 (3)/65 (81)/13 (16)	ICG: 20 (25.0)	ICG: 17 (21)	N/A	ICG: 37 (46)
	Control: 66.6 (12.3)	Control: 81 (40)	Control: 25.4 (3.9)	Control: 8 (4)/169 (83)/27 (13)	Control: 63 (30.9)	Control: 28 (14)		Control: 113 (55)
Shapera and Hsiung[47]	ICG: 58 (N/A) Control: 60 (N/A)	ICG: 32 (43) Control: 13 (43)	ICG: 27 (N/A) Control: 28 (N/A)	N/A	N/A	ICG: 8 (11) Control: 4 (13)	N/A	ICG: 8 (11) Control: 9 (30)
Skrovina et al[48]	ICG: 62.4 (9)	ICG: 16 (32)	ICG: 27 (4)	ICG: 0 (0)/36 (72)/14 (28)	ICG: 14 (28.0)	ICG: 8 (16)	ICG: 9 (18)/21 (42)/9 (18)/8 (16)/3 (6)	ICG: 34 (68)
	Control: 65 (9.4)	Control: 21 (42)	Control: 27 (5)	Control: 0 (0)/31 (62)/19 (38)	Control: 5 (10.0)	Control: 10 (20)	Control: 10 (20)/ 13 (26)/11 (22)/ 15 (30)/1 (2)	Control: 37 (74)
Spinelli et al[30]	ICG: 39.4 (14.1)	ICG: 11 (34)	ICG: 22.2 (0.7)	ICG: 8 (25)/23 (72)/1 (3)	N/A	N/A	N/A	N/A
	Control: 45.8 (15.9)	Control: 15 (47)	Control: 22.8 (0.5)	Control: 10 (31)/21 (66)/1 (3)				
Starker and Chinn[49]	ICG: 62.4 (N/A)	ICG: 112 (47)	ICG: 28.4 (N/A)	ICG: 12 (5)/152 (64)/ 74 (31)	ICG: 40 (16.8)	ICG: 6 (3)	N/A	N/A
	Control: 60.8 (N/A)	Control: 59 (54)	Control: 27.4 (N/A)	Control: 7 (6)/66 (61)/36 (33)	Control: 16 (14.7)	Control: 6 (6)		
Su et al[50]	ICG: 59.1 (11.1)	ICG: 36 (43)	ICG: 24.6 (3.4)	ICG: 28 (33)/50 (60)/ 6 (7)	N/A	N/A	ICG: -/9 (11)/32 (38)/43 (51)/-	ICG: 14 (17)
	Control: 60.2 (9.8)	Control: 50 (48)	Control: 23.8 (2.7)	Control: 45 (43)/50 (48)/10 (10)			Control: -/15 (14)/44 (42)/6 (6)/-	Control: 30 (29)
Tsang et al[51]	ICG: 69.8 (9.9)	ICG: 23 (37)	ICG: 23.5 (3.8)	ICG: 2 (3)/41 (65)/19 (30)	ICG: 9 (14.3)	ICG: 24 (38)	ICG -/8 (10)/28 (44)/19 (30)/3 (5)	ICG: 4 (6)
	Control: 67.7 (11.7)	Control: 22 (32)	Control: 22.4 (3.6)	Control: 3 (4)/42 (62)/24 (35)	Control: 7 (10.3)	Control: 17 (25)	Control: -/10 (15)/23 (34)/31 (46)/1 (2)	Control: 4 (6)
Wada et al[54]	ICG: 67.5 (N/A) Control: 66.5 (N/A)	ICG: 14 (41) Control: 10 (29)	ICG: 22.2 (N/A) Control: 22.5 (N/A)	N/A	ICG: 9 (26.5) Control: 14 (41.2)	ICG: 4 (12) Control: 4 (12)	N/A	ICG: 4 (12) Control: 5 (15)

Table 2 continues on next page

Table 2. Continued

Study	Age, mean (SD), y	Female Patients (*n*, %)	BMI (mean ± SD), kg/m^2	ASA Status, I/II/>II (*n*, %)	Active Smokers (*n*, %)	Diabetes (*n*, %)	Cancer Stage (AJCC 0/1/2/3/4)	Neoadjuvant Therapy (%)
Watanabe et al[55]	ICG: 64.5 (9.7)	ICG: 83 (39)	ICG: 22.3 (3.5)	ICG: 40 (19)/162 (77)/9 (4)	N/A	ICG: 47 (22)	*ICG: -/76 (36)/51 (24)/61 (29)/23 (11)	ICG: 42 (20)
	Control: 64.3 (8.8)	Control: 80 (38)	Control: 22.4 (2.9)	Control: 31 (15)/167 (79)/13 (6)		Control: 49 (23)	Control: -/70 (33)/63 (30)/61 (29)/17 (8)	Control: 49 (23)
Wojcik et al[2]	ICG: 66.7 (11.1)	ICG: 13 (31)	ICG: 25.7 (3.4)	ICG: 10 (24)/24 (57)/8 (19)	ICG: 4 (9.5)	ICG: 3 (7)	N/A	ICG: 18 (43)
	Control: 68.8 (12)	Control: 13 (31)	Control: 26.3 (4.6)	Control: 7 (17)/27 (64)/8 (19)	Control: 9 (21.4)	Control: 3 (7)		Control: 18 (43)
Total or average	ICG: 62.6†	ICG: 1473 (45)	ICG: 25.2	ICG: 329 (13)/1474 (66)/478 (22)	ICG: 370 (22.4)	ICG: 239 (13.4)	ICG: 55 (9)/304 (26)/370 (30)/369 (27)/93 (9)	ICG: 650 (29)
	Control: 63.1†	Control: 1748 (43)	Control: 25.2	Control: 437 (14)/1821 (67)/608 (20)	Control: 480 (25.3)	Control: 271 (14.2)	Control: 42 (7)/416 (27)/503 (27)/454 (31)/219 (9)	Control: 795 (27)

The control group are patients who were not evaluated with fluorescence angiography.
*AJCC stage 0 and 1 combined as AJCC stage 1.
†Weighted mean.
AJCC: American Joint Committee on Cancer Staging System; ASA: American Society of Anesthesiologists; BMI: body mass index; ICG: indocyanine green; NA: Not available.

varied from 0.1–0.5 mg/kg and other times were reported as absolute doses of 2.5–25 mg (Table 1). Seven studies regularly evaluated anastomoses after their formation with a second dose of ICG, and two evaluated anastomoses a second time only if they appeared subjectively hypoperfused. Mizrahi et al[31] and Impellizzeri et al[40] completed ICG angiography three times for each patient: before bowel transection, laparoscopically after anastomosis formation, and transrectally after anastomosis formation. Some authors ($n = 13$) also used an air-leak test to assess anastomoses; in these studies ICG and control groups were treated similarly.

Outcome and Meta-Analysis Results

Subgroup analysis of RCTs showed that ICG use was associated with reduced odds of AL (odds ratio [OR] 0.64; 95% CI, 0.42–0.99; $I^2 = 0\%$; $p = 0.04$; Fig. 2C), although the effect size was smaller than when all studies were included, with a reduction of AL from 12.1% to 8.1%. Meta-analysis of all studies revealed that ICG use was associated with reduced odds of AL after colorectal surgery (OR 0.42; 95% CI, 0.33–0.55; $p < 0.001$; $I^2 = 10\%$; Fig. 2A) with a reduction from 11.8% to 4.6%. Subgroup analysis revealed that benefits were more pronounced in rectal cancer operations (OR 0.36; 95% CI, 0.21–0.44; $I^2 = 19\%$; $p < 0.001$; Fig. 2B), with AL reduced from 10.8% to 4.2%.

RCTs suggested that ICG use was not associated with a change in the need for reoperation due to AL (OR 0.72; 95% CI, 0.29–1.80; $I^2 = 0\%$; $p = 0.48$), with 3.7% of ICG patients needing reoperation and 3.5% of controls. Additionally, there was no difference in LOS (mean difference [MD] 3.22; 95% CI, –3.15 to 9.59; $p = 0.32$; $I^2 = 98\%$), operative duration (MD 2.72; 95% CI, –21.0 to 26.42; $p = 0.82$; $I^2 = 88\%$), or mortality (0.0% ICG vs 0.3% control). There was no difference in the rate of diversion with ICG use (OR 0.14; 95% CI, 0.01–2.56; $I^2 = 97\%$; $p = 0.18$), despite 32.7% of patients receiving ostomies when ICG was used compared to 61.3% for the control group.

When all studies were evaluated, ICG use was also associated with reduced odds of reoperation for AL (OR 0.66; 95% CI, 0.44–0.98; $p = 0.04$; $I^2 = 3\%$; Fig. 2D), decreasing from 3.3% to 2.2%. Many studies suggested a decreased LOS with ICG use; however, overall LOS was not statistically significant between groups (MD –0.61; 95% CI, –1.38 to 0.17; $I^2 = 90\%$; $p = 0.12$). When the study by De Nardi et al[28] was excluded from LOS analysis owing to their ICG group having significantly skewed data (median LOS 6 days vs mean 17 days), ICG use became associated with a statistically significant 1-day-shorter LOS (MD –0.96; 95% CI, –1.48 to –0.43; $p < 0.001$; $I^2 = 73\%$). Operative duration (MD –2.45; 95% CI, –12.79 to 7.90; $I^2 = 92\%$; $p = 0.64$), mortality (0.2% ICG vs 0.3% non-ICG), and rates of anastomotic diversion (OR 0.86; 95% CI, 0.60–1.24; $I^2 = 83\%$; $p = 0.42$) were similar between groups. Patients receiving ICG had 251 (10.5%) transection lines altered intraoperatively owing

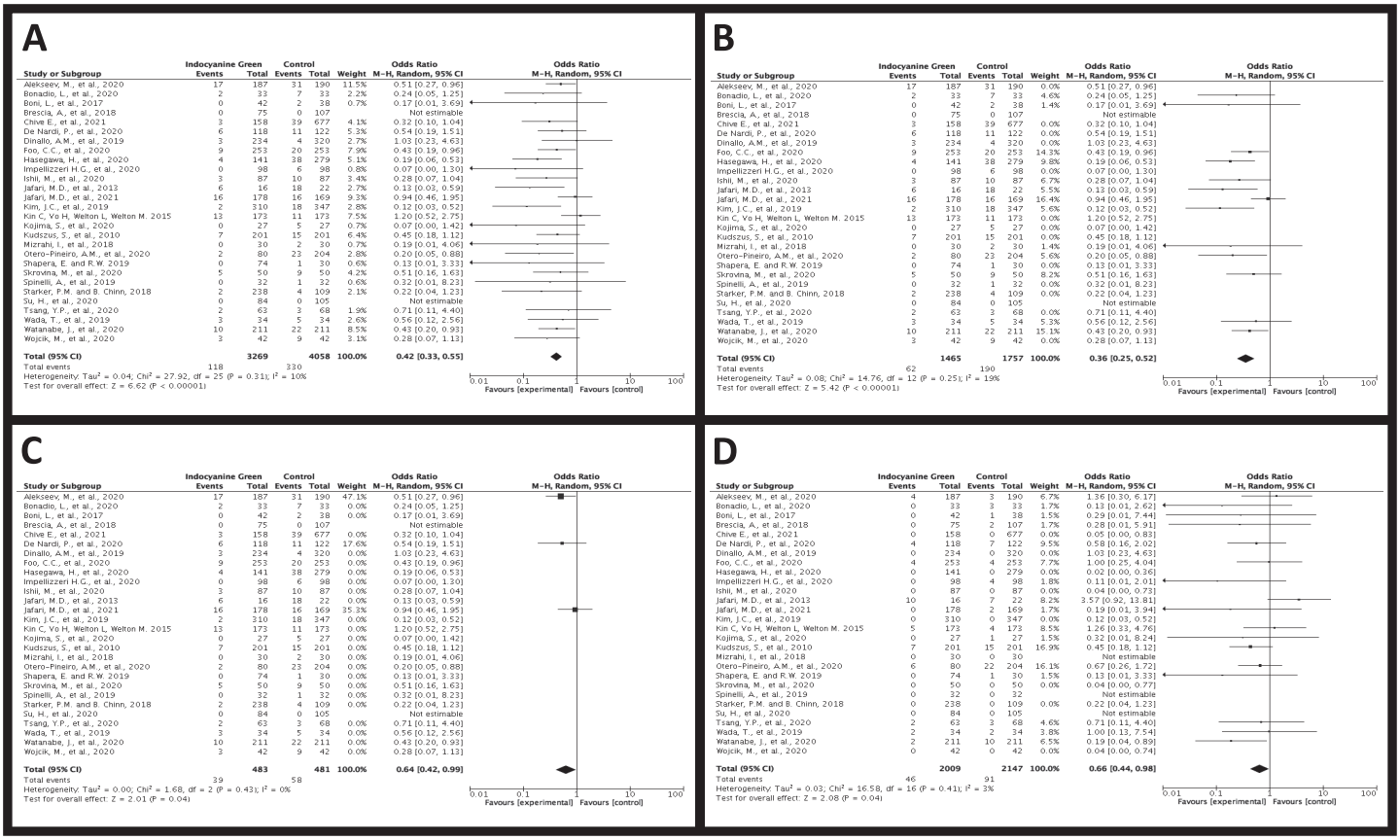

Figure 2. Forest plot demonstrating: (A) the overall odds of anastomotic leak for experimental (indocyanine green [ICG]) and non-ICG cohorts; (B) odds of anastomotic leak for subgroup analysis of patients undergoing resection for rectal cancer; (C) odds of anastomotic leak for subgroup analysis of randomized controlled trials; (D) odds of requiring reoperation for anastomotic leak for all patients. *: Experimental group represents those exposed to indocyanine green compared to the control group (who were not evaluated with indocyanine green angiography).

to concerns about perfusion, which was reported in 24 studies, whereas the non-ICG group had only 5 (2.0%) but were only reported in five studies (OR 2.38; 95% CI, 0.48–11.71; $I^2 = 76\%$; $p = 0.29$). Only 3.0% (8/265) of patients who experienced AL after transection line change due to ICG. Secondary outcomes such as ureteric injury and long-term outcomes could not be evaluated owing to lack of reporting.

Finally, when studies with all patients undergoing diversion (100% diversion for both ICG and control) were evaluated, ICG use showed a nonstatistically significant decrease in the odds of AL (OR 0.39; 95% CI, 0.15–1.05; $p = 0.06$), decreasing from 8.3% to 2.5%. Similarly, when evaluating studies with variable diversion rates (41% of ICG patients diverted and 49% of control patients diverted), odds of AL decreased with ICG use (OR 0.39; 95% CI, 0.27–0.55; $I^2 = 36\%$; $p < 0.001$), with AL rates decreasing from 12.3% to 4.9%.

Study Risk of Bias Assessment

Two RCTs had a low risk of bias, and one had some concerns of bias due to nonblinding and undisclosed randomization processes per ROB2 assessment (Supplemental Table S3). Nonrandomized studies ($n = 25$) were of moderate quality with an average MINORS rating of 16.8 ± 2.9 (Table 1). Nearly all nonrandomized studies failed to report any loss to follow-up, and none reported any prospective calculation of study size, leading to most lost points (Supplemental Table S2).

DISCUSSION

ICG use was associated with nearly 2.5-fold decreased odds of AL, decreased reoperation for AL, and an even greater 3-fold AL reduction for those undergoing rectal resection. However, evaluation of RCT evidence alone indeed suggests a much smaller AL effect size, with no difference in rate of reoperation or LOS. These differences should be taken into consideration when evaluating the true effect of ICG and suggest that additional high-quality randomized trials are required to validate promising findings from cohort studies before routine ICG adoption.

Results from this study should be contrasted to findings from systematic reviews published in the last year.[16–18,52,53] Although these are thorough reviews with reproducible methods, they all focus their conclusions primarily on collation of retrospective cohort

Table 3. Surgical outcomes from included studies

Study	Anastomotic Distance from Anal Verge, cm (SD)	Stapled Anastomosis (*n*, %)	Laparoscopic Operations *n*, %)	Other Anastomotic Integrity Tests Applied	Mortality (*n*, %)	Diversion (*n*, %)	Number of Changed Transection Lines (*n*, %)	Surgical Duration, min (SD)
Alekseev et al[27]	ICG: 8.3 (1.8) Control: 8.8 (1.8)	ICG: 187 (100) Control: 190 (100)	ICG: 87 (47) Control: 77 (41)	Air leak	ICG: 0 (0) Control: 0 (0)	ICG: 133 (71) Control: 134 (71)	ICG: 36 (19) Control: N/A	ICG: 176 (53.3) Control: 185 (47.5)
Bonadio et al[1]	ICG: > 5 cm for 19, < 5 cm for 14* Control: > 5 cm for 19, < 5 cm for 14	ICG: 25 (76) Control: 27 (82)	ICG: 33 (100) Control: 33 (100)	Air leak	N/A	ICG: 19 (58) Control: 14 (42)	ICG: 6 (18) Control: 0 (0)	ICG: 217 (40.7) Control: 201 (92.6)
Boni et al[35]	ICG: 6.3 (2) Control: 7.2 (3)	ICG: 30 (71) Control: 31 (82)	ICG: 42 (100) Control: 38 (100)	Air leak	ICG: 0 (0) Control: 0 (0)	ICG: 42 (100) Control: 38 (100)	ICG: 2 (5) Control: N/A	ICG: 165 (25) Control: 172 (18)
Brescia et al[36]	N/A	N/A	N/A	None reported	ICG: 0 (0) Control: 1 (0.9)	N/A	ICG: 5 (7) Control: N/A	ICG: 180 (35) Control: 175 (30)
Chivé et al[37]	N/A	N/A	ICG: 112 (71) Control: 313 (46)	Air leak	N/A	N/A	ICG: 6 (4) Control: N/A	N/A
De Nardi et al[28]	All > 5 cm and < 15 cm*	N/A	N/A	Air leak	N/A	ICG: 26 (22) Control: 25 (20)	ICG: 13 (11) Control: N/A	ICG: 224.5 (54.5) Control: 209.3 (49.7)
Dinallo et al[33]	N/A	N/A	ICG: 217 (93) Control: 293 (92)	Air leak	ICG: 1 (0.4) Control: 2 (0.6)	ICG: 14 (6) Control: 20 (6)	ICG: 13 (6) Control: N/A	ICG: 234.9 (39.5) Control: 214.5 (32.7)
Foo et al[38]	ICG: 12.6 (4.5) Control: 17.8 (4.2)	ICG: 243 (96) Control: 238 (94)	ICG: 227 (90) Control: 216 (85)	Air leak	N/A	ICG: 127 (50) Control: 131 (52)	ICG: 53 (21) Control: N/A	ICG: 218.2 (90.6) Control: 227 (80.6)
Hasegawa et al[39]	ICG: 4.3 (2.2) Control: 4.2 (2.2)	ICG: 76 (54) Control: 145 (52)	N/A	None reported	ICG: 0 (0) Control: 0 (0)	ICG: 108 (77) Control: 222 (80)	ICG: 24 (17) Control: N/A	ICG: 240.3 (117.0) Control: 318 (134.1)
Impellizzeri et al[40]	N/A	ICG: 98 (100) Control: 98 (100)	ICG: 98 (100) Control: 98 (100)	Air leak	ICG: 0 (0) Control: 0 (0)	ICG: 30 (31) Control: 32 (33)	ICG: 8 (8) Control: 0 (0)	ICG: 165.3 (55.5) Control: 163.3 (51.8)
Ishii et al[41]	ICG: 6 (1.7) Control: 6.2 (1.7)	ICG: 69 (79) Control: 72 (83)	ICG: 87 (100) Control: 87 (100)	None reported	N/A	ICG: 52 (60) Control: 48 (55)	ICG: 6 (7) Control: N/A	N/A
Jafari et al[29]	ICG: 5.2 (3.1) Control: 5.2 (3.3)	N/A	ICG: 150 (84) Control: 146 (86)	Air leak	ICG: 0 (0) Control: 1 (0.6)	ICG: 131 (74) Control: 136 (80)	N/A	N/A
Jafari et al[42]	ICG: 3.5 (N/A) Control: 5.5 (N/A)	N/A	N/A	Air leak	N/A	ICG: 12 (75) Control: 17 (77)	ICG: 3 (19) Control: 1 (5)	ICG: 285 (N/A) Control: 264 (N/A)
Kim et al[43]	ICG: 3 (2) Control 3.5 (1.7)	N/A	ICG: 310 (100) Control: 347 (100)	Air leak	N/A	ICG: 170 (55) Control: 120 (35)	N/A	ICG: 177 (43) Control: 197 (47)
Kin et al[44]	ICG: 11.1 (4.2) Control: 11.3 (4.3)	ICG: 167 (97) Control: 167 (97)	ICG: 111 (64) Control: 73 (42)	None reported	N/A	ICG: 29 (17) Control: 29 (17)	ICG: 8 (5) Control: N/A	N/A
Kojima et al[45]	N/A	ICG: 26 (96) Control: 26 (96)	ICG: 27 (100) Control: 26 (96)	None reported	ICG: 0 (0) Control: 0 (0)	ICG: 6 (22) Control: 4 (15)	N/A	N/A
Kudszus et al[46]	N/A	ICG: 119 (59) Control: 119 (59)	N/A	None reported	N/A	N/A	N/A	N/A
Mizrahi et al[31]	ICG: 2.7 (1.1) Control: 2.9 (1.2)	ICG: 12 (40) Control: 18 (60)	ICG: 30 (100) Control: 29 (97)	Air leak	ICG: 1 (3.3) Control: 0 (0)	ICG: 30 (100) Control: 30 (100)	ICG: 4 (13) Control: 3 (1)	ICG: 347 (91) Control: 347 (84)
Otero-Pineiro et al[3]	ICG: 5.0 (2) Control: 4.9 (2.5)	ICG: 70 (88) Control: 160 (78)	ICG: 80 (100) Control: 203 (100)	Air leak	ICG: 2 (2.5) Control: 0 (0)	ICG: 58 (73) Control: 147 (72)	ICG: 23 (29) Control: N/A	ICG: 144.4 (44.2) Control: 146.7 (53.2)
Shapera and Hsiung[47]	N/A	ICG: 74 (100) Control: 30 (100)	ICG: 74 (100) Control: 30 (100)	None reported	ICG: 0 (0) Control: 0 (0)	N/A	ICG: 4 (5) Control: N/A	N/A
Skrovina et al[48]	ICG: 4.6 (1.3) Control: 4.6 (1.5)	ICG: 50 (100) Control: 50 (100)	ICG: 50 (100) Control: 50 (100)	None reported	ICG: 0 (0) Control: 0 (0)	ICG: 50 (100) Control: 50 (100)	ICG: 6 (12) Control: N/A	ICG: 242 (48) Control: 219 (45)
Spinelli et al[30]	N/A	N/A	ICG: 28 (88) Control: 30 (94)	None reported	N/A	ICG: 32 (100) Control: 32 (100)	N/A	ICG: 315 (16.5) Control: 351 (18.4)
Starker and Chinn[49]	N/A	N/A	ICG: 207 (87) Control: 54 (50)	None reported	ICG: 0 (0) Control: 0 (0)	ICG: 13 (5) Control: 15 (14)	ICG: 11 (5) Control: N/A	N/A
Su et al[50]	N/A	ICG: 84 (100) Control: 105 (100)	ICG: 84 (100) Control: 105 (100)	None reported	N/A	N/A	ICG: 4 (5) Control: N/A	ICG: 125.8 (34.9) Control: 136.6 (35.9)
Tsang et al[51]	N/A	N/A	ICG: 60 (95) Control: 62 (91)	None reported	N/A	N/A	ICG: 1 (2) Control: 0 (0)	ICG: 178.9 (55.2) Control: 140.8 (44.8)

Table 3 continues on next page

Table 3. Continued

Study	Anastomotic Distance from Anal Verge, cm (SD)	Stapled Anastomosis (*n*, %)	Laparoscopic Operations *n*, %)	Other Anastomotic Integrity Tests Applied	Mortality (*n*, %)	Diversion (*n*, %)	Number of Changed Transection Lines (*n*, %)	Surgical Duration, min (SD)
Wada et al[54]	ICG: 5 (N/A) Control: 5 (N/A)	N/A	ICG: 34 (100) Control: 34 (100)	None reported	N/A	N/A	ICG: 13 (38) Control: N/A	ICG: 313 (N/A) Control: 313 (N/A)
Watanabe et al[55]	ICG: 6.9 (1.9) Control: 6.4 (1.9)	ICG: 211 (100) Control: 211 (100)	ICG: 211 (100) Control: 211 (100)	None reported	ICG: 0 (0) Control: 0 (0)	ICG: 107 (51) Control: 110 (52)	ICG: 12 (6) Control: N/A	ICG: 321.3 (98.5) Control: 319.3 (111.8)
Wojcik et al[2]	N/A	N/A	ICG: 40 (95) Control: 36 (86)	Air leak	ICG: 0 (0) Control: 1 (2.4)	ICG: 21 (50) Control: 25 (60)	ICG: 4 (10) Control: N/A	ICG: 215 (53) Control: 207 (62)
Total or average	ICG: 5.8† Control: 6.3†	ICG: 1541 (85) Control: 1687 (86)	ICG: 2399 (92) Control: 2591 (87)	Air leak = 14 None reported = 15	ICG: 4 (0.2) Control: 5 (0.3)	ICG: 1078 (48) Control: 1379 (55)	ICG: 265 (11) Control: 5 (2)	*ICG: 200.8 *Control: 175.0

The control group are patients who were not evaluated with fluorescence angiography.
In cases where more than2 groups were compared with meta-analysis, data that were nearest to statistical significance are presented.
*Excluded from calculations.
†Weighted mean.
ICG: indocyanine green; N/A: Not applicable.

studies. In fact, of these systematic reviews, retrospective studies accounted for 72.3–100% of included studies. Additionally, the largest studies included in these analyses were those of Kim et al[32] and Dinallo et al,[33] both of which report outcomes in retrospective cohorts. This remained a substantial limitation for these reviews. Despite this limitation, these studies reproducibly demonstrated reduced AL, with decreased reoperation and LOS with ICG use. [16–18,30,31] Here, we have again demonstrated similar effects when all studies are included in meta-analysis.

Although this updated systematic review, to some degree, supports the decreased leak rate finding established by prior ICG reviews,[12–18] our evaluation of RCT evidence alone perhaps suggests that a more tempered approach to ICG adoption in colorectal surgery is required. When only RCTs were evaluated, AL is still reduced, but with a much smaller effect size. It remains uncertain why such a difference exists, as the patient demographics remain similar. However, considering their retrospective nature it remains possible that an unmeasured or unreported confounder accounts for the difference between findings from RCT and retrospective cohorts that we have demonstrated here. Although directing practice decisions based on systematic review of cohort studies has become common,[34] findings should continue to be critiqued and if possible corroborated with RCT evidence.

RCT evidence also suggested a similarly reduced benefit of ICG with regard to secondary outcomes, compared to cohort studies. Whereas collation of results from all studies suggests a reduction in need for reoperation for AL, which is in keeping with previous reviews, [12–18] RCT evidence does not support these findings. Considering the sample size of RCT patients, a type II error may contribute to this finding. Regardless, the strength of prior results should be tempered until additional RCT evidence can evaluate this outcome. Decreased reoperation for AL has been suggested owing to a reduction of ALs caused by perfusion deficits across all grades, or downgrading AL severity; previous reviews of retrospective studies have suggested that this contributes to their findings of decreased LOS. Again, collation of RCT evidence does not support any change in LOS, and strong recommendation for ICG use in prior studies should be tempered, as RCTs currently do not appear to affect clinically significant AL.

The final difference between outcomes from RCT and all other studies that should be noted is ostomy use. Meta-analysis of all studies, both in our study and others, has suggested that the number of diverting ostomies was similar between groups.[12–18] On the other hand, RCT evidence suggests a small decrease that is not statistically significant. In theory, decreased ostomies may occur owing to increasing ICG trust by surgeons, leading them to forego diversion in cases of adequate anastomotic ICG assessment. If this is the case, it may explain the smaller effect size between groups for all outcomes in the RCT

evaluation; control groups may receive more diverting ostomies, and this may reduce the recognition of early ALs. This may alternatively be interpreted as ICG identifying the highest-risk anastomoses, leading to fewer but more selective ostomies. This will be an important marker to follow as evidence continues to mount regarding the efficacy of ICG on long-term outcomes.

Despite the reduced estimated effects in RCTs, there does appear to be an AL reduction with ICG use. We suspect that the primary mechanism through which FA reduces AL is through improved assessment of collateral vascular supply at the region of anastomotic reconstruction. Transection lines were changed in 10.5% of cases with ICG use compared to only 2.0% of non-ICG cases, which was not statistically significant, but represents a three-fold increase, suggesting that ICG has greater sensitivity to identify inadequately perfused anastomoses. Chan et al[16] found a similar pooled 9.7% change in transection line, whereas RCTs have found that 11% and 19.2% of transection lines were altered with ICG. [27,28] This perhaps explains why beneficial effects were most pronounced in higher-risk rectal cancer anastomoses, where neoadjuvant chemoradiation, increased tension, and limited microvascular collaterals predispose them to AL from perfusion deficits.[5,7]

This study has several limitations. The first is that only three RCT studies have evaluated this technology and have been compared to a much larger group of 27 cohort studies; therefore, although RCT evidence shows a reduced ICG effect, it is possible that this has occurred owing to a smaller sample. It is imperfect to compare such a small number of studies to a larger population; however, because nearly 1000 patients are evaluated in the well-conducted RCTs, we believe that data are crucial to present and compare to retrospective cohorts. This is especially true considering the differences in results and strong suggestions by previous reviews to adopt ICG. Beyond this, included studies also had heterogeneous intraoperative and postoperative protocols. ICG FA techniques, timing, and dose varied amongst studies and most reported subjective FA assessment. Use of adjunctive testing techniques such as the bubble test and sigmoidoscopy also varied, and postoperative protocols to investigate anastomoses, including endoscopy and imaging, were diverse but remained similar within groups. The heterogeneity of these techniques may explain substantial heterogeneity and I^2 values for some of our secondary outcomes. We advise readers to consider this when evaluating the secondary outcomes of this study. Follow-up period was limited to 30 days in most studies, and delayed anastomotic complications, especially for patients undergoing diversion, may be underreported. Finally, our study attempted to assess ICG use for ureteric identification, but no comparative study has evaluated this outcome after colorectal surgery; this remains a topic of interest for future studies.

This study represents the first collation of RCT evidence evaluating the effect of ICG angiography on colorectal surgery outcomes and AL. Although RCT evidence supports reduced AL, the effect size is much smaller than previously reported by systematic reviews of cohort studies. Important clinical outcomes including reoperation and LOS are also not reduced with ICG in RCT evaluation. These results highlight potential bias from inclusion of primarily retrospective studies and highlight the need for additional high- quality prospective and RCT evidence evaluating this topic. Until additional evidence is available, we suggest that a more tempered approach to ICG adoption in colorectal surgery is required.

CONCLUSION

Although ALs appear to be reduced with ICG, the effect size appears much more modest when evaluating only RCT evidence. Additionally, whereas collation of retrospective studies suggests reduced reoperation for AL and LOS with ICG, these clinical benefits have not been reproduced in RCTs. Further RCT evidence is required before broad uptake of this technology; until then we advocate for conservative assessment of retrospective ICG outcomes.

Acknowledgment

This work was presented at Digestive Diseases Week 2021 (May 14, 2021, virtual) and Edmonton's Tom Williams Surgical Research Day 2021 (May 14, 2021, virtual).

Supplemental Material

Supplemental materials are available online with the article.

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