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REVIEW ARTICLE

Impact of change in the surgical plan based on indocyanine green fluorescence angiography on the rates of colorectal anastomotic leak: a systematic review and meta-analysis

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Abstract

Background In the present study, patients with colorectal anastomoses that were assessed with indocyanine green (ICG) fluorescence angiography (FA) were compared to patients who had only white light visual inspection of their anastomosis. The impact of change in surgical plan guided by ICG-FA on anastomotic leak (AL) rates was assessed.

Methods PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were queried for eligible studies. Studies included were comparative cohort studies and randomized trials that compared perfusion assessment of colorectal anastomosis with ICG-FA and inspection under white light. Main outcome measures were change in surgical plan guided by ICG-FA and rates of AL. Risk of bias was assessed using RoB-2 and ROBINS-1 tools. Differences between the two groups in categorical and continuous variables were expressed as odds ratio (OR) with 95% confidence interval (CI) and weighted mean difference.

Results This systematic review included 27 studies comprising 8786 patients (48.5% males). Using ICG-FA was associated with significantly lower odds of AL (OR 0.452; 95% CI 0.366–0.558) and complications (OR 0.747; 95% CI 0.592–0.943) than the control group. The weighted mean rate of change in surgical plan based on ICG-FA was 9.6% (95% CI 7.3–11.8) and varied from 0.64% to 28.75%. A change in surgical plan was associated with significantly higher odds of AL (OR 2.73; 95% CI 1.54–4.82).

Limitations Technical heterogeneity due to using different dosage of ICG and statistical heterogeneity in operative time and complication rates.

Conclusion Assessment of colorectal anastomoses with ICG-FA is likely to be associated with lower odds of anastomotic leak than is traditional white light assessment. Change in plan based on ICG-FA may be associated with higher odds of AL. PROSPERO registration number: CRD42021235644.

Keywords Fluorescence angiography · Indocyanine green · Colorectal anastomosis · Leak · Change in plan · Meta-analysis

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Colorectal anastomoses can be followed by complications such as anastomotic leak (AL) and stenosis [1]. AL occurs in 6–30% of colorectal anastomoses and represents a challenging problem associated with serious morbidities including perianastomotic abscess, peritonitis, septic shock, and mortality [2]. Furthermore, AL may have an adverse effect on the oncologic outcomes of colorectal cancer (CRC) in terms of increased local recurrence and reduced survival [3]. Thus, prevention of colorectal AL is of paramount importance.

Different methods have been devised to assess colorectal anastomoses intraoperatively. The most commonly used methods include the air leak test and endoscopic examination of the anastomosis [4, 5]. Combined assessment using more than one method has been also described.

The quadruple assessment technique entails checking the mechanical integrity and completeness of the anastomosis by air leak test, endoscopy, and doughnut inspection in addition to assessment of the perfusion by fluorescence angiography (FA) [6].

It has been suggested that impaired blood supply of the anastomosis is a major contributing factor to anastomotic failure [7]. Therefore, assessment of the perfusion of the colonic ends prior to and after the anastomosis may have a useful role in the reduction of the rates of AL. To this end, FA using different fluorophores has been proposed as a real-time method for assessment of the perfusion of colorectal anastomoses [8]. During FA, the well perfused colonic segments appear clearly fluorescent in contrast to the poorly perfused segments that exhibit delayed or no fluorescence. Using this real-time assessment, surgeons are able to change the transection line to a more fluorescent and better perfused segment, this change in surgical plan is assumed to be associated with reduced AL rates.

Although previous meta-analyses [9, 10] have assessed the role of FA in the reduction of colorectal AL; the role of FA was not examined respective to the rate of change in surgical plan based on FA results. Therefore, the present meta-analysis compared the rates of AL and complications in patients with colorectal anastomoses that were assessed with ICG-FA and patients who had only white light visual inspection of their anastomosis. The impact of change in surgical plan guided by ICG-FA on the rates of AL was assessed.

Methods

Registration

This systematic review has been registered a priori in the International prospective register of systematic reviews "PROSPERO" under special identifier CRD42021235644.

Strategy of literature search

This systematic review is reported in adherence to the screening guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) [11]. A systematic search of the current literature has been conducted looking for studies that reported the role of ICG-FA in the assessment of perfusion of colorectal anastomoses. Two authors (S.E. & S.K.) completed the literature search in an independent manner.

Electronic databases including PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were queried for published and ahead-of-publication studies dating from the inception of each database to January 2021. To maximize the sensitivity of the search process we activated the PubMed function "related articles" and hand searched the bibliography section of each retrieved article to screen for other relevant studies.

As per the PRISMA flow chart (Fig. 1), we excluded duplicate reports and conference abstracts without full text. The remaining articles were then screened in a step-wise manner starting with title/abstract screening then finally the full-text versions of the selected articles were reviewed by one of two authors (S.E., S.K.) to check for eligibility. The senior author (S.D.W) reviewed the outcome of the article screening on a regular basis.

Search keywords

The keywords used in the search process included "*colorectal*," "colon*," "*anastomosis*," "*anastomoses*," "*leak**," "*fluorescence*," "*angiography*," "*indocyanine green*," "*ICG*," "*ICG-FA*," "*perfusion*," "*assessment*," *outcome*". In addition, we used the following medical subject headings (MeSH) terms: (Fluorescence), (anastomosis), (anastomotic leak), and (indocyanine green).

The following syntax combination was used for literature search: (Fluorescence OR FA OR ICG-FA) AND (Perfusion) AND (Assessment OR Evaluation) AND (Colon* OR colorectal) AND (Anastomosis OR Anastomoses) AND (Leak* OR outcome).

Study selection

In order to be considered eligible for inclusion, the studies were required to have a control group (bowel assessment under white light) and full-text available in English.

We used the PICO criteria to select the studies eligible for inclusion to this review.

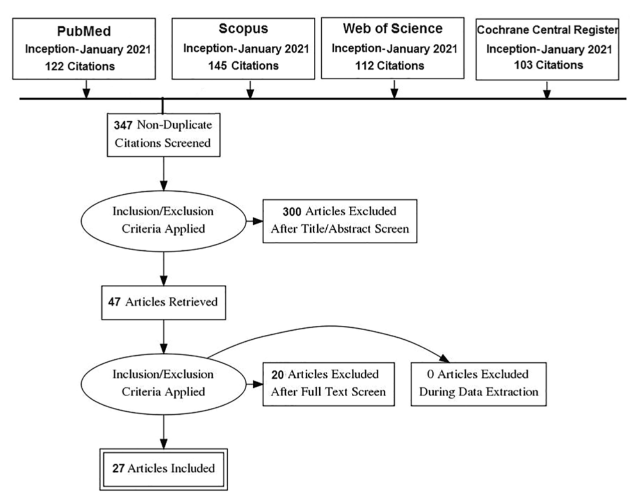

Fig. 1 PRISMA flow chart for study selection and inclusion

- P (*Patients)*: patients with any colorectal condition undergoing resection and any type of colorectal anastomosis or pouch formation
- I (*Intervention)*: ICG-FA for perfusion assessment of the anastomosis
- C (*Comparator)*: visual inspection of the anastomosis under white light.
- O (*Outcome*): change in surgical plan (transection line) based on ICG-FA findings and the rates of AL in patients who had or did not have perfusion assessment by FA

We excluded observational cohort studies without a control group, studies that did not report the rate of change in surgical plan based on ICG-FA findings, studies entailing less than 10 patients in each arm, animal studies, editorials, case reports, reviews, and other meta-analyses.

Discrepancies in study selection were resolved by mutual discussion and consensus between the two authors (S.E. & S.K.) who conducted the literature search and study selection, under the supervision and guidance of the senior author S.D.W.

Assessment of methodological quality, risk of bias, and certainty of evidence

Two authors (S.E., S.K) independently assessed the risk of bias in the studies reviewed. The revised tool to assess risk of bias in randomized trials (RoB 2) [12] was used for appraisal of the risk of bias in the randomized controlled trials, whereas the Risk Of Bias In Non-Randomized Studies-of Interventions (ROBINS-I) [13] was used to assess the quality of non-randomized studies. Any conflicts of interpretation of the results were resolved by mutual agreement. The certainty of evidence for each outcome of this systematic review was graded using the GRADE approach [14] that entails five parameters to judges the evidence certainty: risk of bias, imprecision, inconsistency, indirectness, and publication bias.

Assessment of publication bias

The publication bias among the studies was assessed by the funnel plot of the standard error of the rate of each outcome of each group against the rate of the outcome. Absence of publication bias was confirmed by the symmetry of the funnel plot.

Data extraction

A preformed Excel sheet template was established for extraction of relevant data from each study. Two investigators extracted the following data from the studies included the following:

- Authors, duration, country, and design of the study.
- Number of patients in each group, mean age, sex distribution, and body mass index (BMI).
- Indications for and type of colorectal anastomosis and the surgical approach (open, laparoscopic, robotic-assisted).
- Dose of ICG used and time to fluorescence.
- Operation time and overall complications in each group
- Definition and rate of AL in each group. The definitions of AL in the studies reviewed are shown in Appendix Table S1.
- Number of patients in whom the transection level was changed according to FA results and AL rates in these patients.

Study outcomes

The primary outcome of this systematic review was the change in surgical plan by revision of the transection line based on the findings of ICG-FA and its impact on AL rates. Within the ICG-FA group, the AL rates in patients who had their transection level changed according to ICG-FA findings were compared to AL rates in patients who did not have a change in the surgical plan.

Secondary outcomes included the comparison between ICG-FA group and control group in terms of AL rates, overall complication rates including leak and ileus, and operation time.

Statistical analysis

A meta-analysis was conducted using open-source, cross-platform software for advanced meta-analysis "openMeta [Analyst] ™" version 12.11.14 and Cochrane Review Manger 5.4®. Differences between the two groups with regards to AL and complication rates were expressed as odds ratio (OR) with the 95% confidence interval (CI). Differences between the two groups with regards to operation time were expressed as weighted mean difference (WMD). Statistical heterogeneity was determined by the p value of the Cochrane Q test and the Inconsistency (I^2) statistics (low if $I^2 < 25\%$, moderate if $I^2 = 25–75\%$, and high if $I^2 > 75\%$). Fixed-effect model was used to pool data when no significant statistical heterogeneity was detected, and the binary random-effect model was used for pooling of data when significant ($p < 0.1$) statistical heterogeneity was observed. Sensitivity analyses of RCTs only, studies including rectal cancer patients only, and studies with BMI > 25 kg/m^2 were performed to explore the reasons for heterogeneity when detected.

Results

Characteristics of studies and patients

This systematic review included 27 studies (15–41) published between 2010 and 2021. The studies were based in USA ($n=5$), Italy ($n=6$), Japan ($n=5$), China ($n=2$), Germany ($n=2$), Czech Republic ($n=2$), Russia ($n=1$), France ($n=1$), Spain ($n=1$), South Korea ($n=1$), and one study was based in more than one country. Eighteen studies were retrospective cohort studies, 7 were prospective cohort studies, and 2 were randomized controlled trials. Four studies were multicentric and 23 were single-center studies (Table 1).

Assessment of quality of studies and certainty of evidence

Quality assessment of 25 non-randomized studies revealed that 16 studies had a moderate risk of bias, and 9 had serious risk. (Appendix Table S2). To judge the risk of confounding bias we checked the table comparing the ICG and control groups in regards to baseline characteristics of patients. When all variables had no significant difference ($p>0.05$), the study was judged to have low risk of confounding bias, otherwise the risk was judged to be moderate or high depending on the number and importance of variables that showed significant difference between the two groups. Overall, only 3 studies had low risk of confounding bias as shown in the supplementary table.

Quality assessment of two randomized controlled trials revealed low risk relative to the randomization process and missing outcome data and unclear to high risk of deviation from the intended intervention, measurement of outcome, and selection of reported result (Fig. 2).

As shown in Table 2, the level of evidence certainty was:

– Moderate for the difference in AL rates between the ICG and control groups.

Table 1 Characteristics of patients and studies

Study	Duration	Country	Design	Number	Male	Age	BMI	Condition
[15]	March 2015–Oct 2018	Japan	Prospective cohort	384	231	69	22.1	Left colon/rectal cancer
[16]	Jan 2014–Dec 2018	Germany	Retrospective	351	178	70	26	Colorectal cancer
[17]	Jun 2015–Nov 2019	Italy	Retrospective	272	146	69.2	25.7	Left colon/rectal cancer
[18]	Aug 2015–Jan 2019	Czech Republic	Prospective cohort	200	110	62.6	27	Rectal cancer
[19]	Oct 2017–June 2019	China	Retrospective	189	103	59.1	24.2	Colon cancer
[20]	2018–2019	Russia	RCT	377	184	63	NA	Colorectal adenoma/carcinoma
[21]	Jan 2014–April 2015	Italy	Retrospective	66	36	71.8	25.6	Rectal cancer
[22]	Jan 2016–Nov 2017	Italy	RCT, multicenter	240	126	66.1	25.4	Left colon/rectal cancer
[23]	June 2016–June 2017	Japan	Retrospective	844	549	63	22.6	Rectal cancer
[24]	Nov 2014–Feb 2019	Italy	Retrospective	196	110	69	NA	Colorectal adenoma/carcinoma
[25]	March 2014–Dec 2018	Japan	Retrospective	488	262	68	22.8	Colorectal cancer
[26]	Sept 2014–Sept 2017	Japan	Retrospective, multicenter	422	259	66	22.3	Rectal cancer
[27]	Aug 2018–Sept 2019	China	Prospective cohort	131	86	68.7	22.9	Colorectal adenoma/carcinoma
[28]	Jun 2017–Dec 2018	France	Prospective cohort	111	70	67.1	26	Sigmoid/rectal cancer
[29]	Aug 2015–Feb 2017	Czech Republic	Prospective cohort	100	63	63.7	27	Rectal cancer
[30]	Nov 2011–June 2018	Spain	Retrospective	284	174	67.3	25.7	Rectal cancer
[31]	2011–2015	Italy	Retrospective, multicenter	64	38	42.5	22.4	Ulcerative colitis and FAP
[32]	June 2013–June 2016	USA	Retrospective	554	308	62	28.3	Colorectal cancer
[33]	Jan 2012–April 2018	USA	Retrospective	104	59	59	27.5	Lt colon and rectal lesions
[34]	Jan 2009–May 2016	Japan	Retrospective	149	101	66.5	22	Rectal cancer
[35]	Jan 2013–Dec 2016	Multicenter	Prospective multicenter	1677	279	64	25	Colorectal lesions
[36]	2013–2016	USA	Retrospective	60	34	58	26.5	Rectal cancer
[37]	Oct 2014–Nov 2015	Italy	Prospective cohort	80	50	68	28	Rectal cancer
[38]	July 2010–March 2016	South Korea	Retrospective	657	398	57.5	23.9	Rectal cancer
[39]	Nov 2005–Dec 2012	USA	Retrospective	346	108	58.1	26.7	Lt colon and rectal lesions
[40]	2011–2012	USA	Retrospective	38	26	60.5	27	Rectal cancer
[41]	1998–2008	Germany	Retrospective	402	170	68.4	25.5	Colorectal cancer

BMI body mass index, *RCT* randomized controlled trial, *FAP* familial adenomatous polyposis

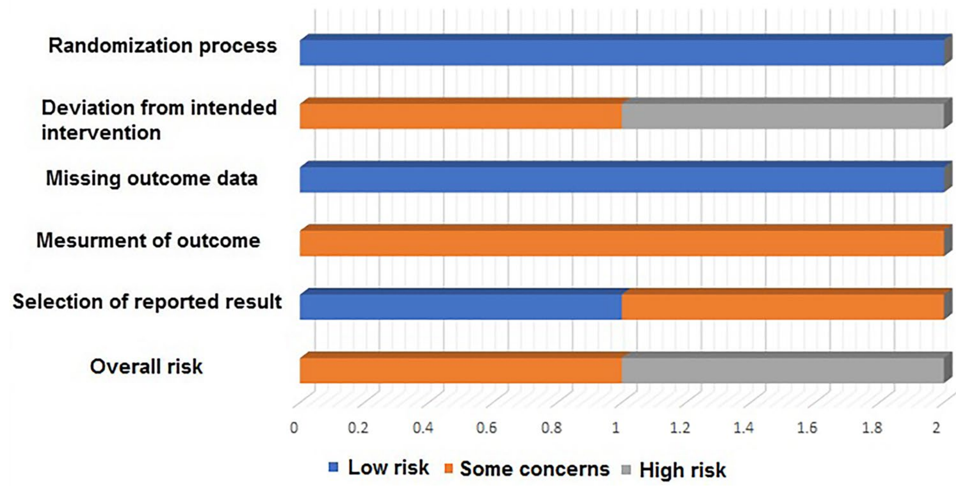

Fig. 2 Quality assessment of randomized controlled trials

– Low for the impact of change in surgical plan on AL and the difference in ileus between the ICG and control groups.
– Very low for the difference in operation time and overall complications between the ICG and control groups

Characteristics of patients

Overall, the studies included 8786 patients of a median age of 65 (range, 42.5–71.8) years and a median BMI of 25.6 (range, 22–28.3) kg/m^2. 48.5% of patients were males and 51.5% were females. Eleven studies used ICG-FA in rectal cancer patients, six used it in left-sided colonic and rectal lesions, whereas ten studies included patients with different benign and malignant lesions in the colon and/or rectum (Table 1). Colorectal resections were performed in 4486 (51%) patients by laparoscopy, in 2966 (33.7%) by open approach, in 1068 (12.1%) by robotic-assisted approach, and in 284 (3.2%) by TaTME.

Technique of ICG-FA

The dose of ICG varied and the majority of studies (10 studies) used a dose of 0.1–0.25 mg/kg of ICG, whereas some studies used a fixed dose of 5–25 mg, not based on body weight. The time elapsed until fluorescence was 60 s in 13 studies, 30 s in one study, 90 s in one study, and two to three minutes in one study. In 13 studies both proximal and distal bowel segments were assessed with ICG-FA, whereas in six studies only the proximal bowel was assessed. Eight studies did not specify the bowel segment assessed and only reported assessment of the transection line (Table 3).

Comparing ICG-FA and control groups

Demographics

ICG-FA was used for perfusion assessment in 3614 (41.1%) patients, whereas 5172 (58.9%) had regular assessment under white light. 55.2% of patients in the ICG-FA group were males versus 43% in the control group. The median age and BMI of patients in the two groups were comparable (65.7 vs 65.5 years) and (25.6 vs 25.7 kg/m^2).

Outcomes

The mean operation time of the ICG-FA and control groups was comparable (219 vs 214 min) with a weighted mean difference of 1.32 (95% CI − 14.75–17.4, $I^2 = 93.7$) (Fig. 3).

AL developed in 139/3614 (3.8%) patients in the ICG-FA group versus 429/5172 (7.5%) patients in the control group. The use of ICG-FA was associated with significantly lower odds of AL than the control group (OR 0.452; 95% CI 0.366–0.558, $I^2 = 0$) (Fig. 4).

Ileus developed in 58/1553 (3.7%) patients in the ICG-FA group as compared to 71/1795 (3.9%) patients in the control group. The use of ICG-FA was associated with similar odds of ileus to the control group (OR 1.16; 95% CI 0.72–1.88, $I^2 = 23.7$).

The overall complication rates were 322/1733 (18.5%) in the ICG-FA group and 486/1988 (24.4%) in the control group (Appendix Table S3). The use of ICG-FA was associated with significantly lower odds of complications than the control group (OR 0.747; 95% CI 0.592–0.943, $I^2 = 44$) (Fig. 5).

Table 2 Assessment of the certainty of evidence for the study outcomes

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Change in surgical plan	No change in plan	Relative (95% CI)	Absolute (95% CI)		
Impact of change in plan on anastomotic leak												
24	Observational studies*	Serious[a]	Not serious[b]	Serious[c]	Not serious[d]	None	13/331 (3.9%)	106/3283 (3.2%)	OR 2.73 (1.54–4.82)	51 more per 1000 (from 17 to 106 more)	⨁⨁◯◯ Low	Critical
Anastomotic leak												
27	Observational studies*	Serious[a]	Not serious[b]	Not serious[c]	Not serious[d]	None	139/3614 (3.8%)	429/5172 (8.3%)	OR 0.452 (0.366–0.558)	44 fewer per 1000 (from 51 to 35 fewer)	⨁⨁⨁◯ Moderate	Important
Ileus												
14	Observational studies*	Serious[a]	Not serious[b]	Serious[e]	Not serious[d]	None	58/1553 (3.7%)	71/1795 (4.0%)	OR 1.16 (0.72–1.88)	6 more per 1000 (from 11 fewer to 32 more)	⨁⨁◯◯ Low	Important
Overall complications												
17	Observational studies*	Serious[a]	Serious[f]	Serious[g]	Not serious[d]	None	567/1733 (32.7%)	510/1988 (25.7%)	OR 0.747 (0.592–0.943)	52 fewer per 1000 (from 87 to 11 fewer)	⨁◯◯◯ Very low	Important
Operation time												
21	Observational studies*	Serious[a]	Very serious[h]	Serious[i]	Serious[j]	None	2296	3122	–	MD 1.32 (− 4.75–17.4)	⨁◯◯◯ Very low	Important

CI confidence interval; *OR* odds ratio; *MD* mean difference

*ROBINS-I tool was used

[a]All studies had a moderate or serious risk of bias according to ROBINS-I tool

[b]The I^2 index was < 25%, indicating minimal heterogeneity across the studies

[c]Other factors can contribute to the occurrence of anastomotic leak, thus the impact of using ICG-FA is indirect

[d]The 95% confidence interval was narrow indicating good precision

[e]Other factors can contribute to the occurrence of ileus, thus the impact of using ICG-FA is indirect

[f]The I^2 index was > 25% and < 75%, indicating moderate heterogeneity across the studies

[g]Other factors can contribute to the occurrence of complications, thus the impact of using ICG-FA indirect

[h]The I^2 index was > 75% denoting severe heterogeneity across the studies

[i]Other factors can contribute to an increased operation time, thus the impact of using ICG-FA is indirect

[j]The 95% Confidence interval was wide

Table 3 Variation in the dose of ICG and time to fluorescence across the studies

Study	Dose of ICG	Time to fluorescence	Bowel assessed
[15]	0.1 mg/kg	1 min	Proximal only
[16]	0.1–0.2 mg/kg	NR	NR
[17]	0.2 mg/kg	1 min	Proximal and distal
[18]	0.2 mg/kg	1 min	Proximal only
[19]	25 mg	NR	Proximal and distal
[20]	0.2 mg/kg	2–3 min	Proximal and distal
[21]	0.2 mg/kg	1.5 min	Proximal and distal
[22]	0.3 mg/kg	1 min	Proximal and distal
[23]	5 mg	1 min	Proximal only
[24]	25 mg	1 min	Proximal and distal
[25]	5 mg	1 min	Proximal only
[26]	0.25 mg/kg	1 min	NR
[27]	10 mg	1 min	NR
[28]	0.1 mg/kg	NR	NR
[29]	0.2 mg/kg	NR	NR
[30]	2.5 mg/ml	NR	Proximal and distal
[31]	0.1–0.2 mg/kg	0.5 min	Proximal and distal
[32]	2 ml	1 min	Proximal and distal
[33]	25 mg	1 min	NR
[34]	5 mg	NR	Proximal only
[35]	2.5 mg/ml	1 min	Proximal and distal
[36]	3.5 ml	NR	Proximal and distal
[37]	0.2 mg/kg	0.5–1 min	NR
[38]	10 mg	1 min	Proximal and distal
[39]	3 ml	NR	Proximal only
[40]	6–8 mg	NR	Proximal and distal
[41]	0.2–0.5 mg/kg	NR	NR

ICG indocyanine green, *NR* not reported

Impact of change in surgical plan on leak rates

Overall, change in surgical plan related to the level of transection and anastomosis based on the findings of ICG-FA was made in 331 (9.1%) of 3614 patients. The weighted mean rate of change in surgical plan was 9.6% (95% CI 7.3–11.8; $I^2=88.6\%$) (Fig. 6). The rates of change in surgical plan ranged from 0.6% to 28.7% across the studies; all changes were related to proximal transection.

AL developed in 13 (3.9%) of the 331 patients who had their surgical plans changed based on ICG-FA versus 106 (3.2%) of 3283 of patients without plan changes (Appendix Table S4). A change in surgical plan was associated with significantly higher odds of AL (OR 2.73; 95% CI 1.54–4.82, $I^2=4.4\%$) (Fig. 7).

There were eight studies with change in plan rate > 15%. These studies had a majority of male patients and patients with increased BMI. In six studies, ICG-FA was used in the setting of LAR for rectal cancer.

Sensitivity analysis of anastomotic leak

Sensitivity analysis of the randomized controlled trials only ($n=2$) concluded that the use of ICG-FA was associated with significantly lower odds of AL than the control group (OR 0.52, 95% CI 0.304–0.98, $I^2=0$).

Subgroup analyses of anastomotic leak

- o Subgroup analysis of studies that included patients with rectal cancer only ($n=11$) concluded that the use of ICG-FA was associated with significantly lower odds of AL than the control group (OR 0.362, 95% CI 0.242–0.541, $I^2=8.5$).

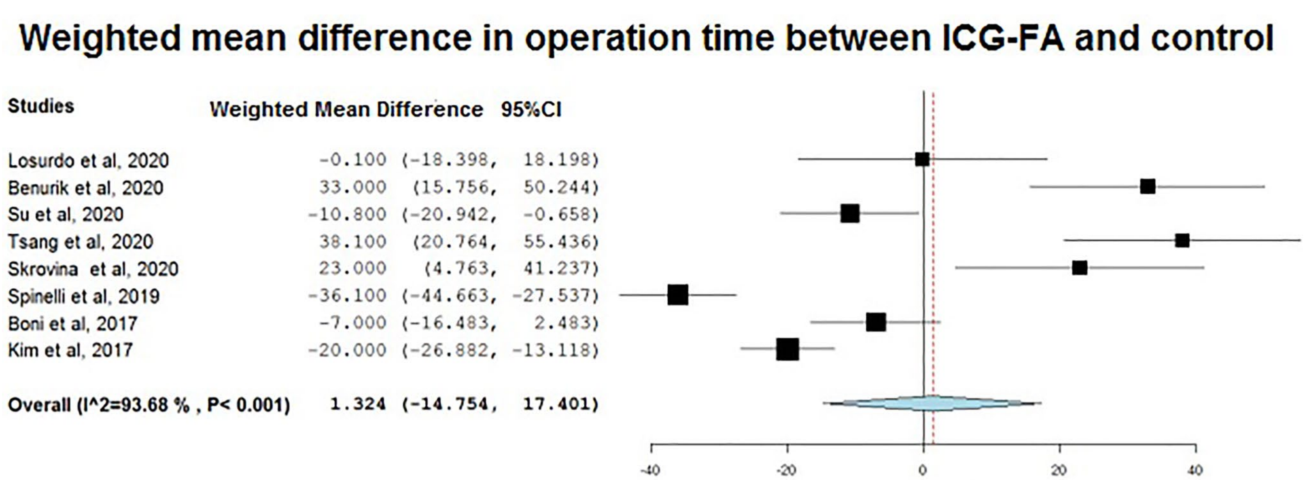

Fig. 3 Forest plot for the weighted mean difference in operation time between the two groups

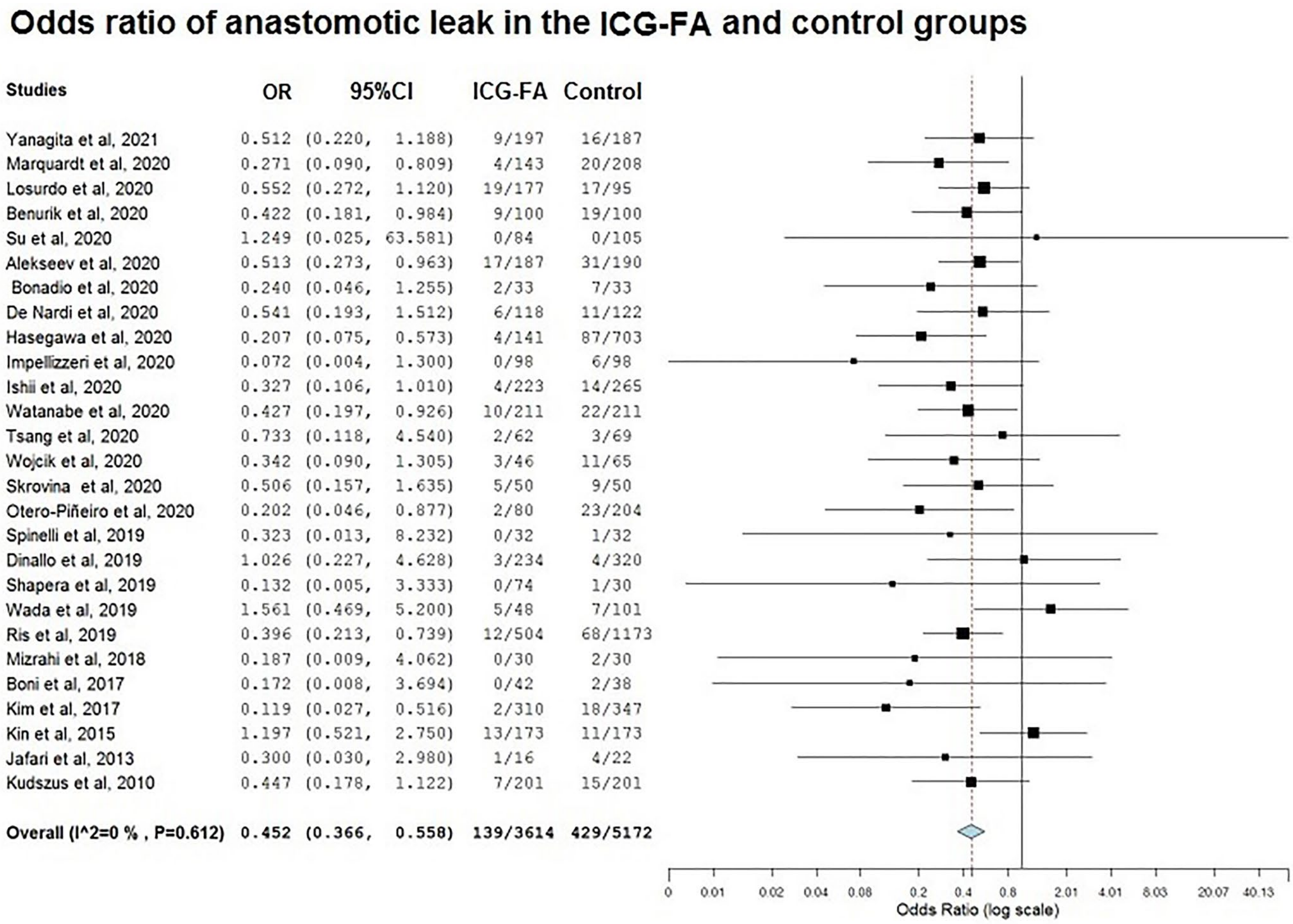

Fig. 4 Forest plots for the odds ratio of anastomotic leak in the two groups

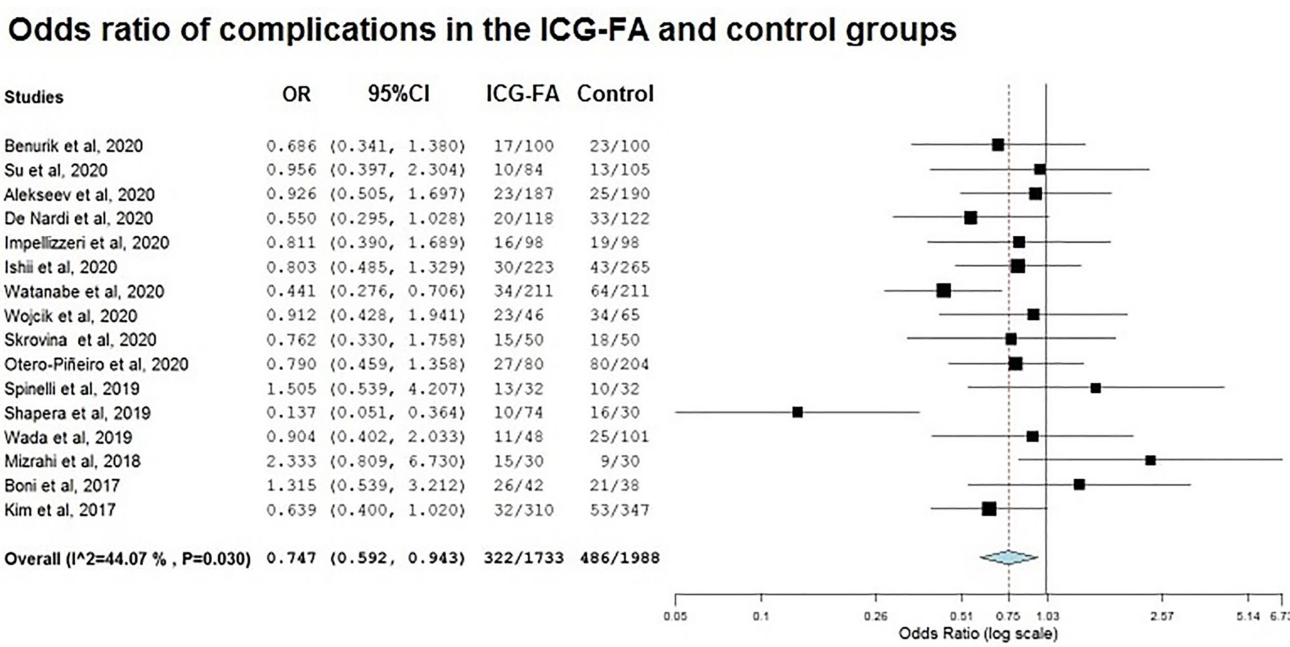

Fig. 5 Forest plots for the odds ratio of overall complications in the two groups

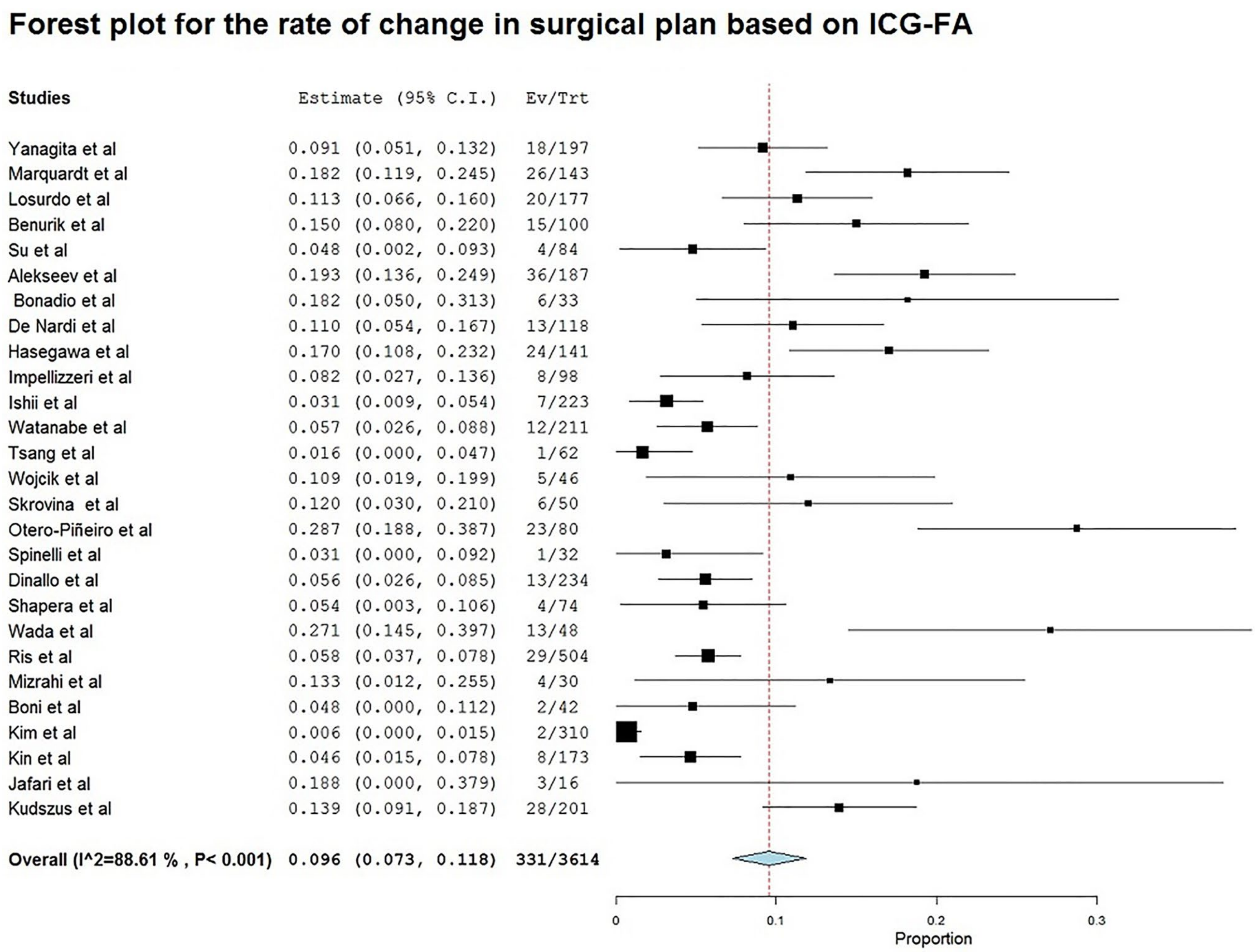

Fig. 6 Forest plot for the weighted mean rate of change in surgical plan based on ICG-FA findings

p Subgroup analysis of studies including patients with mean BMI > 25 kg/m^2 ($n = 16$) concluded that the use of ICG-FA was associated with significantly lower odds of AL than the control group (OR 0.52, 95% CI 0.393–0.69, $I^2 = 0$).

Assessment of publication bias

As displayed in Supplementary Figs. 1–5, the funnel plots were symmetrical denoting absence of publication bias in all study outcomes.

Discussion

The present meta-analysis found that AL rates were lower when ICG-FA was used and that an alteration in the surgical plan and anastomosis level based on the findings of ICG-FA may render the patients at a higher risk to develop AL as compared to other patients with well perfused transection level who had normal ICG-FA assessment.

AL following colorectal anastomoses can be attributed to a number of factors, the most important of which is possibly the insufficient blood supply [42]. Assessment of bowel perfusion is an essential step to minimize the incidence of AL. Perfusion assessment is usually done by visual inspection under white light, examining the bowel color and peristalsis, pulsation of the marginal artery, and bleeding of the resected bowel margin. Although these are useful clinical indicators of good perfusion, this method is subjective [43].

Therefore, perfusion assessment using different fluorophores under the near infrared light has gained increasing popularity in recent years as it can properly assess microperfusion. Indeed, this feature was demonstrated by several studies and meta-analyses that documented decreased rates of AL in patients assessed with ICG-FA intraoperatively as compared to patients who had the regular assessment [9, 10].

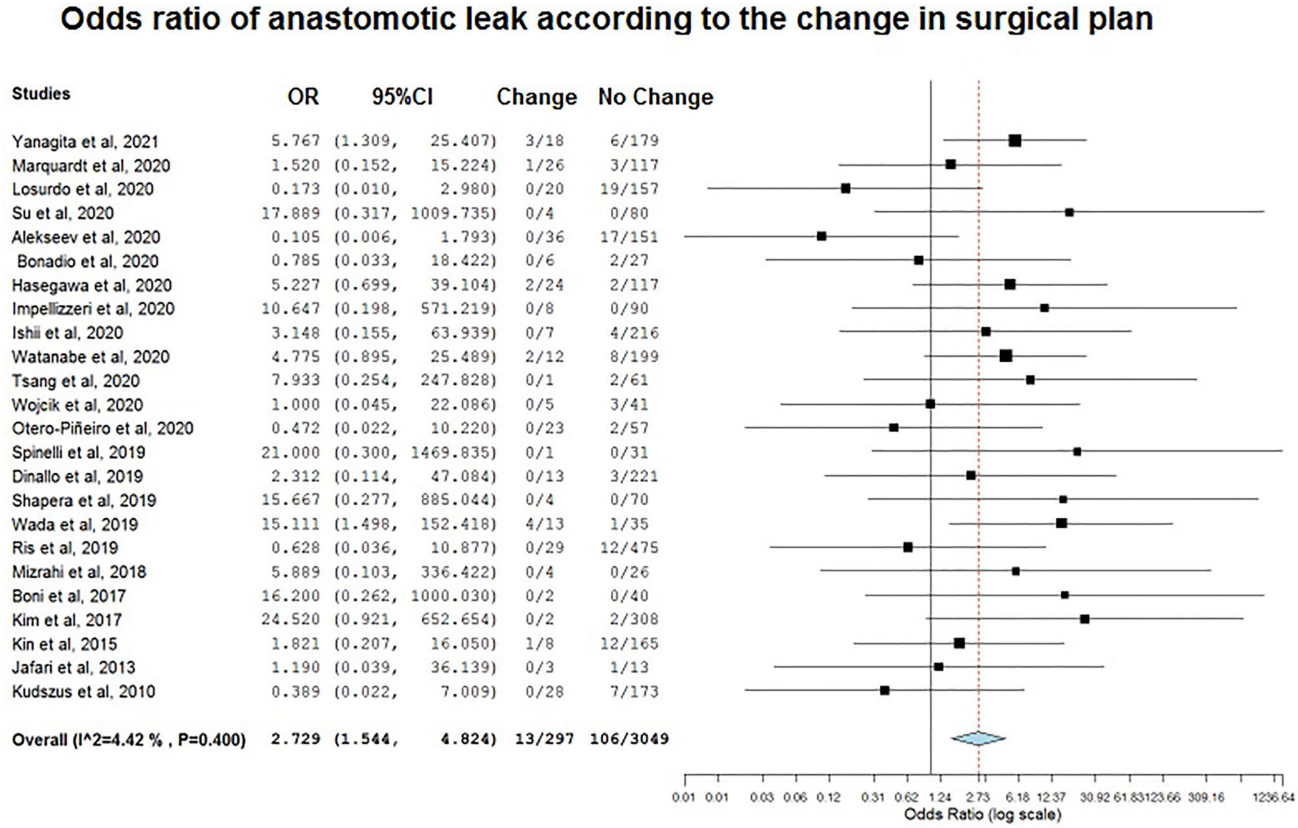

Fig. 7 Forest plot for the odds of anastomotic leak according to change in surgical plan

The beneficial effect of ICG-FA in reducing leak rates is mostly attributed to its ability to detect areas of low or absent perfusion, and thus guide the surgeon to revise the transection/anastomosis level to be done in a better perfused area. The impact of change in surgical plan based on the findings of ICG-FA on the AL rates was not thoroughly examined in previous studies and systematic reviews. Therefore, the present meta-analysis was designed mainly to address this research point.

This meta-analysis included 27 studies entailing more than 8,000 patients; therefore, it is considered the largest and most comprehensive review on the role of ICG-FA in colorectal anastomosis assessment. ICG-FA guided the change in surgical plan in 9% of patients and showed a wide variation as the plan was changed in less than 1% to more than 25% of patients. This variation can be attributed to technical factors such as the dose of ICG infused and also to patient-related factors. The studies that had a high rate of plan change (> 15%) included patients with high-risk anastomoses such as male patients with narrow pelvis and increased BMI undergoing low anterior resection for rectal cancer.

Interestingly, we found that patients who had a change in plan based on ICG-FA had higher AL rates than patients in whom ICG-FA demonstrated adequate perfusion that did not warrant revision of the anastomosis. This result was substantiated by the meta-analysis which showed that patients with a change were 2.7 times more likely to experience AL than were patients without a change. The explanation might be that the anastomoses that require revision due to poor perfusion may still remain high risk and susceptible to delayed, postoperative ischemic changes [44]. In addition, revising the anastomosis involves more proximal transection, which may impose more tension on the revised anastomosis, especially in patients with a short colon or without adequate colonic mobilization [45].

In light of this observation, patients who require a change in plan according to ICG-FA are at higher risk of AL and thus may require additional measures to early predict and prevent the onset of leak. The use of trending C-reactive protein levels may be helpful as shown in the PREDICT study that found CRP trajectory to accurately rule out AL after colorectal resection [46]. Furthermore, the adherence to enhanced recovery after surgery (ERAS) protocols has been associated with a reduction of the rate of complications, including AL [47]. One recently proposed strategy that may help reduce AL rates is the application of microbiome-altering measures; however; this strategy is still under investigation and needs more research to draw better conclusions

[48]. Higher risk anastomosis as assessed by the operating surgeons may also need a proximal diverting ileostomy to protect the anastomosis and minimize the consequence of AL if occurred.

In concordance with the previously published systematic reviews [9, 10], we found the use of ICG-FA to be associated with significantly lower rates of AL as compared to the control group. This observation was also associated with a significantly lower overall complications rate in favor of the ICG-FA group. On subgroup analyses of randomized trials alone (to minimize selection bias), studies on rectal cancer (since they entail low- and high-risk anastomoses), and studies including patients with increased BMI (as obesity is a risk factor for AL), the lower odds of AL in favor of ICG-FA were retained, which confirm the consistent clinical utility of this method. The explanation of lower leak rates with the use of ICG-FA is reasonably attributed to the ability of the surgeons to recognize sub-optimally perfused bowel segment. It has been assumed that the construction of an anastomosis between colonic ends with inadequate perfusion, which may otherwise appear healthy under white light, can strongly contribute to the onset of AL.

The strengths of the present meta-analysis are the inclusion of large number of trials entailing > 8000 patients, the low risk of bias in most of the studies, and having three randomized trials may also ensure a higher level of evidence. The present study emphasized the impact of plan change based on ICG-FA on leak rates which may help guide postoperative care of the patients having colorectal anastomoses.

It is noteworthy that despite the benefit of ICG-FA in reducing the rates of colorectal AL, this technique is not entirely objective and the assessment remains at the discretion of the operating surgeon. To overcome this limitation, a discriminant marker of perfusion called the angiography effect can be used. This effect describes the rapid onset of the fluorescence signal within the first seconds after injection. Diana and colleagues developed a quantitative, software-based analysis of the fluorescence signal to allow real-time visualization of the perfusion values [49, 50]. This quantitative approach of perfusion assessment with fluorescence angiography may further clarify the benefits of this technique and improve the ultimate outcome.

Limitations of this meta-analysis include the statistical heterogeneity that was obvious on analyzing the differences in operation time and complication rates between the two groups. The studies used different dosage of ICG which may create some technical heterogeneity. Also, the review included studies on different types of colorectal conditions and anastomoses; however; this may be useful to examine the utility and versatility of ICG-FA in different settings. Finally, we can argue that even without ICG-FA assessment surgeons may also change the surgical plan based on their visual inspection and perception of perception the anastomosis. Nonetheless; no mention of the rates of plan change and its impact on AL in the control group was made in the studies. An optimal comparison would be between ICG-FA and control groups in regards to plan change and its impact on AL rates in each group. Currently, a multinational randomized controlled trial, The IntAct trial is undergoing and may help draw more definitive conclusions on the role of ICG-FA in assessment of colorectal anastomosis and prevention of AL [51].

Conclusion

Assessment of colorectal anastomoses with ICG-FA is likely to be associated with lower odds of anastomotic leak as compared to traditional white light assessment. Change in surgical plan based on ICG-FA may be associated with higher odds of AL.

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Declarations

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