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SYSTEMATIC REVIEWS AND META-ANALYSES

Indocyanine green fluorescence angiography prevents anastomotic leakage in rectal cancer surgery: a systematic review and meta-analysis

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Abstract

Background The role of intraoperative use of indocyanine green (ICG) fluorescence angiography (ICGFA) to prevent anastomotic leakage (AL) in rectal cancer surgery remains controversial.

Methods The systematic review for studies evaluating ICGFA in patients undergoing rectal cancer surgery in PubMed, Embase, Web of Science, and the Cochrane Library was performed up to April 30, 2020. The primary outcome was the incidence of AL. The analysis was performed using RevMan v5.3 and Stata v12.0 software.

Results Eighteen studies comprising 4038 patients were included. In the present meta-analysis, intraoperative use of ICGFA markedly reduced AL rate (OR = 0.33; 95% CI: 0.24–0.45; $P < 0.0001$; $I^2 = 0\%$) in rectal cancer surgery, which was still significant in surgeries limited to symptomatic AL (OR = 0.44; 95% CI: 0.31–0.64; $P < 0.0001$; $I^2 = 22\%$). This intervention was also associated with shorter postoperative stays (MD = − 1.27; 95% CI: − 2.42 to − 0.13; $P = 0.04$; $I^2 = 60\%$). However, reoperation rate (OR = 0.61; 95% CI: 0.34–1.10; $P = 0.10$; $I^2 = 6\%$), ileus rate (OR = 1.30; 95% CI: 0.60–2.82; $P = 0.51$; $I^2 = 56\%$), and surgical site infection rate (OR = 1.40; 95% CI: 0.62–3.20; $P = 0.42$; $I^2 = 0\%$) were not significantly different between the two groups.

Conclusion The use of ICGFA was associated with a lower AL rate after rectal cancer resection. However, more multi-center RCTs with large sample size are required to further verify the value of ICGFA in rectal cancer surgery.

Keywords Rectal cancer · Indocyanine green · Fluorescence angiography · Anastomotic leakage · Meta-analysis

Introduction

Anastomotic leakage (AL) is one of the most devastating complications following rectal cancer surgery, accounting for considerable morbidity and mortality [1–3]. Despite big progress in perioperative management has been made in recent years, the reduction of AL rate in rectal cancer surgery still remains unsatisfactory [4, 5]. Due to the differences in AL's definition and classification in present published literatures, it has been reported that the AL rate after rectal cancer surgery ranged from 6 to 19% [6–8].

So far, multiple conditions have been identified as risk factors of AL, like age, male gender, smoking, diabetes, previous chemoradiotherapy, intraoperative complication, anastomotic tension, and hypoperfusion [4, 9]. Of those, insufficient blood perfusion of anastomotic site plays an important role in the pathogenesis of AL [9].

To prevent AL, several clinical signs such as bowel serosal color, temperature and vascular pulsation, as well as some clinical adjuncts including Doppler ultrasound and tissue pulse oximetry have been used to assess bowel perfusion [10]. Nevertheless, none of them is satisfactory in clinical application, due to their subjective nature and the limitation

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of feasibility and reproducibility. In recent years, indocyanine green (ICG) fluorescence angiography (ICGFA) is emerging as a relatively new technique to assess bowel perfusion [11]. ICG is a kind of non-toxic tricarbocyanine iodide dye which can be safely injected intravenously and quickly binds to blood lipoproteins [12]. Under near-infrared light (excitation wavelength of 750–800 nm), ICG could emit fluorescent light at 830 nm or more, which allows surgeons to directly visualize the microperfusion of intestine in real time and avoid insufficient perfusion of the anastomosis site [13]. Recently, several meta-analyses [14–16] have demonstrated that ICGFA can help reduce AL rate in rectal cancer surgery, but most of them were not convincing due to the limited number of included studies and small number of patients.

Herein, we updated this meta-analysis to evaluate whether this technique could decrease AL rate in patients undergoing rectal cancer resection based on recently published studies.

Materials and methods

This systematic review and meta-analysis was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17] (Fig. 1). The study protocol was registered in PROSPERO, and the registration number is CRD42020156416.

Search strategy

A comprehensive and systematic search of electronic databases including PubMed, Embase, Web of Science, and the Cochrane Library was undertaken to identify relevant studies published up to April 30, 2020. The following combination of keywords was searched to identify potential articles: ["indocyanine green" OR "ICG" OR "fluorescence angiography"] AND ["colorectal surgery" OR "colorectal cancer" OR "rectal surgery" OR "rectal cancer"]. No language or publication date restrictions were applied in the search strategy. Meanwhile, the bibliography of the studies and previously published reviews were also searched for additional reports. The search was conducted independently by two authors (HY-P and XL-C).

Study selection

Eligible studies met the following criteria: (1) patients undergoing rectal cancer surgery; (2) with reported outcomes comparing AL incidence between the ICGFA and the control group; (3) any sample size; and (4) in the case of duplicate publications, only the most complete study was included. The exclusion criteria are (1) studies published as reviews, case reports, comments, and letters; (2) data was inadequate for meta-analysis or could not be acquired form the author; and (3) articles without technical description of ICGFA assessing

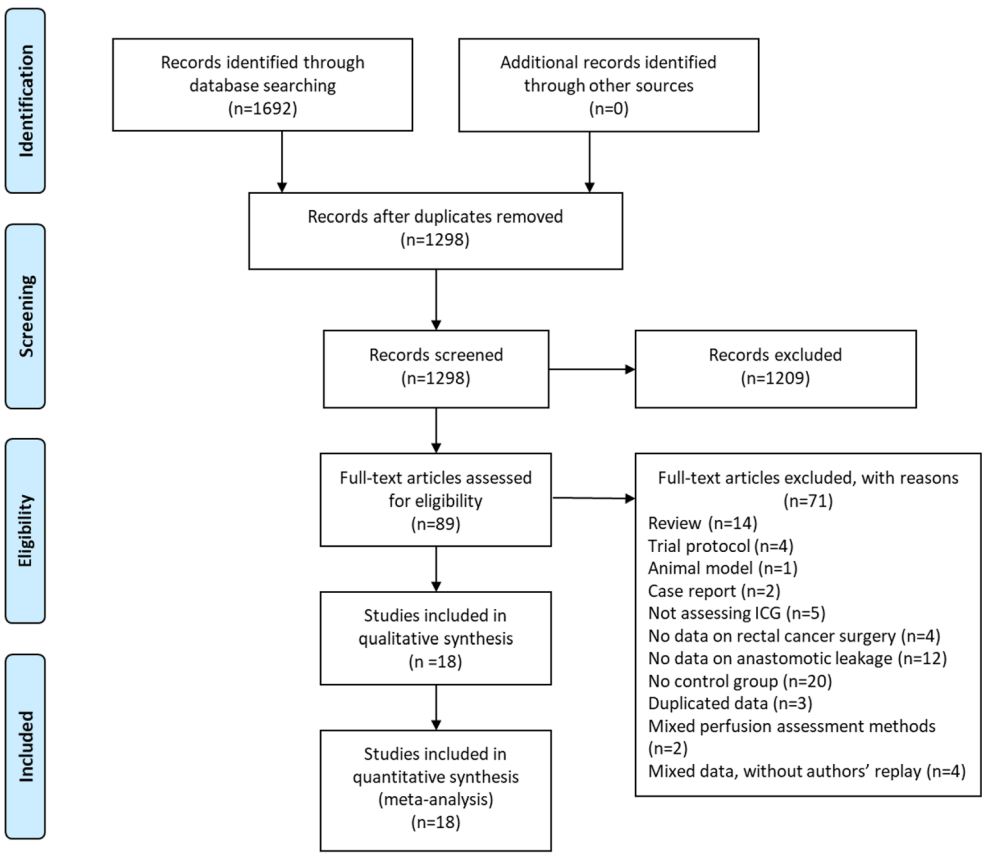

Fig. 1 PRISMA flow diagram of study selection

anastomosis perfusion. All discordant articles were adjudicated by a third reviewer (JK-H).

Data extraction and quality assessment

According to the inclusion and exclusion criteria, two authors (HY-P and XL-C) independently selected the studies and extracted the data. The following information from each article was collected: the first author, year of publication, country of the study, study design, enrollment period, sample size, patient characteristics like age and gender, type of surgery, ICG dosage, the time of ICGFA use, imaging system used, change of surgical plan in the ICGFA group, and the definition and follow-up time of AL.

The primary outcome was AL, identified clinically, radiologically, and endoscopically. The secondary outcomes were surgical site infection (which included wound infection and abdominal infection), ileus (which was defined as prolonged gastrointestinal recovery after surgery leading to abdominal distension, vomiting, oral intolerance, and delayed elimination [18]), reoperation (which caused by any severe postoperative complications), and postoperative stays.

We assessed the quality of studies independently after reading the full text of each study. The Cochrane Collaboration Risk of Bias Tool was used to evaluate the quality of involved RCTs [19], and the Newcastle-Ottawa Scale (NOS) was employed to evaluate the quality of observational studies [20].

Statistical analysis

Dichotomous and continuous variables were evaluated using odds ratio (OR) and mean difference (MD) with their 95% confidence intervals (CIs), respectively. For studies that only reported median with range or interquartile range, data were converted into mean with standard deviation (SD) following the method reported by McGrath et al [21] Heterogeneity among studies was assessed using χ^2 and I^2 statistics. P value < 0.05 and $I^2 > 50\%$ indicate significant heterogeneity. In this case, a random-effect model was used; otherwise, a fixed-effect model was performed. Publication bias was evaluated using funnel plot and Begg's test. A P value < 0.05 was considered significant. All statistical analyses were performed using Review Manager Software, version 5.3 (Cochrane, London, UK) and Stata, version 12.0 (Stata Corp, College Station, TX).

Level of evidence

The quality of evidence of each outcome was assessed using GRADE approach [22]. Briefly, each endpoint was given a score, which ranges from very low to high, on the basis of following domains: risk of bias, inconsistency, indirection, and imprecision (Table 3).

Results

The literature search identified a total of 1692 papers. After reading the titles or abstracts, 1209 studies were excluded because they did not meet the inclusion criteria. Through screening the full text of the 89 remaining articles, 22 comparative studies [23–44] which contained rectal cancer surgery were possible to extract data. For studies with mixed data [23, 27, 28, 34, 41, 44, 45], the authors were contacted for separate data related to rectal cancer surgery, and 3 of the authors [23, 27, 44] provided data. Finally, 18 studies [23–27, 29–33, 36–40, 42–44] were included in the present study.

Characteristics of studies and quality assessment

The summarized information of these studies was presented in Tables 1 and 2. A total of 4038 patients from 8 countries were included into this study. The sample size ranged from 36 to 844. Among these studies, there were 2 RCTs [23, 27], 3 prospective studies [38, 40, 44], and 13 retrospective studies [24–26, 29–33, 36, 37, 39, 42–44], which were published from 2013 to 2020. With respect to the ICGFA assessing anastomosis perfusion, the doses of ICG and imaging systems used were variant, and the change of surgical plan ranged from 1.1 to 28.7% in these studies. In addition, the definition and follow-up time of AL were different in these studies. The details of quality assessment of included studies were shown in supplementary file (Table S1 and S2). Both RCTs had high risk of bias in at least one assessed category, and the observational studies were ranged from 6 to 8 assessed by NOS, Table 3.

Outcome assessment

Primary outcome: anastomotic leakage

The meta-analysis of 18 studies [23–27, 29–33, 36–44] included 4038 patients undergoing rectal cancer surgery, comprising 1495 in the ICGFA group and 2543 in the control group. The overall AL rate was 8.4% (3.9% in the ICGFA group and 11.0% in the control group). The pooled analysis demonstrated that the use of ICGFA could significantly decrease the incidence of AL after rectal cancer surgery (OR: 0.33; 95% CI: 0.24–0.45; $P < 0.0001$; $I^2 = 0\%$) (Fig. 2a). Additionally, when surgeries limited to symptomatic AL (Clavien-Dindo [46] grade $\geq$ II) [23–27, 29, 31, 32, 40, 42–44], the use of ICGFA showed a positive effect on reducing AL rate (OR = 0.44; 95% CI: 0.31–0.64; $P < 0.0001$; $I^2 =$ 22%) (Fig. 2b). Then, we also conducted subgroup analyses based on study design (RCT vs. non-RCT), country (western vs. eastern), sample size (≥ 100 vs. < 100), the time of ICGFA use (before anastomosis vs. both before and after anastomosis), and the follow-up duration of AL (within 30 days, beyond

Table 1 Basic information of included studies

Reference	Country	Study interval	Study design	Sample size	Number of patients (I:C)	Age (I:C), (mean or median), year	Sex (I:C), (male, %)	BMI (I:C), (mean or median), Kg/m^2	Neoadjuvant chemoradiotherapy (I:C), (%)	Surgery procedure
Alekseev, 2020 [23]	Russia	2017–2019	S; RCT	325	166:159	NA	NA	NA	NA	AR
Bonadio, 2020 [24]	Italy	I: 2015–2017; C: 2014–2015	S; R	66	33:33	71.9/69.0	63.6/45.5	25.6/25.7	48.5/42.4	AR
Boni, 2016 [25]	Italy	I:2014–2015; C:2012–2013	S; R	80	42:38	69.0/67.0	66.7/57.9	27.0/29.0	78.0/60.0	LAR
Brescia, 2018 [26]	Italy	2014–2017	S; R	52	21:31	NA	NA	NA	NA	AR
De Nardi, 2019 [27]	Italy	2016–2017	S; RCT	108	56:53	NA	NA	NA	NA	LAR
Hasegawa, 2020 [29]	Japan	I:2016–2017; C: 2007–2016	S; R	844	141:703	63.0/62.0	70.2/64.0	22.3/22.9	18.4/11.0	LAR; ISR
Impellizzeri, 2020 [30]	Italy	I:2017–2019 C:2014–2016	S; R	73	37:36	NA	NA	NA	NA	LAR
Ishii, 2019 [31]	Japan	I:2017–2018; C:2014–2018	S; R	220	116:104	64.0/65.0	59.5/58.7	22.3/22.8	33.6/22.1	HAR; LAR; ISR
Jafari, 2013 [32]	USA	2011–2012	S; R	38	16:22	58.0/63.0	75.0/72.7	27.0/27.0	63.0/68.0	LAR
Kim, 2017 [33]	Korea	I:2013–2016; C:2010–2016	S; R	657	310:347	58.0/57.0	58.7/62.2	23.9/23.9	31.0/30.0	LAR; ISR
Mizrahi, 2018 [36]	USA	I:2015–2016; C:2013–2015	S; R	60	30:30	58.0/58.0	53.3/60.0	25.9/27.2	56.7/46.7	L-LAR
Otero-Piñeiro, 2020 [37]	Spain	I:2016–2018; C:2011–2016	S; R	284	80:204	68.0/66.6	63.8/60.3	26.1/25.4	46.2/55.7	HAR; LAR
Ris, 2018 [38]	Switzerland	2013–2016	M; P	455	90:365	NA	NA	NA	NA	LAR
Shapera, 2019 [39]	USA	2012–2018	S; R	36	22:14	NA	NA	NA	NA	LAR
Skrovina, 2019 [40]	Czech	I:2015–2017; C: before 2015	S; P	100	50:50	62.4/65.0	68.0/58.0	27.0/27.0	68.0/74.0	LAR
Wada, 2018 [42]	Japan	I:2013–2016; C:2009–2016	S; R	149	48:101	66.0/67.0	64.6/69.3	22.5/21.4	10.4/22.8	LAR
Watanabe, 2019 [43]	Japan	2014–2017	M; R	422	211:211	66.0/66.0	60.7/62.1	22.3/22.4	19.9/23.2	LAR
Wojcik, 2020 [44]	France	2017–2018	S; P	68	26:42	NA	NA	NA	NA	AR

I ICG group, *C* control group, *S* single center, *M* multiple center, *R* retrospective study, *P* prospective study, *RCT* randomized controlled trial, *NA* not available, *AR* anterior resection, *LAR* low anterior rectal resection, *ISR* Intersphincteric resection, *HAR* high anterior resection

Table 2 The detailed information of included studies

Reference	ICG dose	Time of ICG use (before or after anastomosis)	Imaging system	Change of surgical plan in ICG group (%)	Definition of AL	Clavien-Dindo grade of AL	Follow-up of AL occurrence (days)
Alekseev, 2020 [23]	0.2 mg/kg	Before	SPIES system	NA	Clinical, endoscopic, radiological	≥ I	30
Bonadio, 2020 [24]	0.2 mg/kg	Before and after	SPIES system	18.2	Clinical; radiological	≥ I	30
Boni, 2016 [25]	0.2 mg/kg	Before and after	SPIES system	4.7	Clinical; radiological	≥ I	NA
Brescia, 2018 [26]	0.25 mg/kg	Before and after	SPIES system	4.8	Radiological	≥ II	NA
De Nardi, 2019 [27]	0.3 mg/kg	Before and after	SPIES system	11.0	Clinical, laboratory, radiological, endoscopy, or surgery	≥ I	30
Hasegawa, 2020 [29]	5.0 mg	Before	SPIES system	17.0	Clinical; physical examination; endoscopic; radiological	≥ II	30
Impellizzeri, 2020 [30]	25 mg	Before and after	SPIES system	4.0	NA	≥ I	60
Ishii, 2019 [31]	5.0 mg	Before	1588/1688 AIM laparoscope system	5.2	Clinical; endoscopic; radiological	≥ I	30
Jafari, 2013 [32]	6–8 mg	Before	Firefly system	19.0	Endoscopic; radiological	≥ II	60
Kim, 2017 [33]	10 mg	Before ± after	Firefly system	NA	Endoscopic; radiological	≥ I	90
Mizrahi, 2018 [36]	0.1–0.3 mg/kg	Before and after	PINPOINT System	13.3	Physical examination; clinical; endoscopic; radiological	≥ I	60
Otero-Piñeiro, 2020 [37]	2.5 mg/ml	Before and after	PINPOINT System	28.7	Clinical; physical examination; radiological	≥ I	30
Ris, 2018 [38]	7.5 mg	Before and after	PINPOINT System	1.1	NA	≥ I	NA
Shapera, 2019 [39]	25 mg	Before and after	Firefly system	NA	NA	≥ I	30
Skrovina, 2019 [40]	0.2 mg/kg	Before	SPIES and Firefly system	12.0	radiological	≥ I	30
Wada, 2018 [42]	5 mg	Before	PDE-neo system	27.1	Radiological; physical examination; endoscopic	≥ II	NA
Watanabe, 2019 [43]	0.25 mg/kg	Before	SPIES system	5.7	NA	≥ II	30
Wojcik, 2020 [44]	0.1 mg/kg	Before	FLUOBEAM and PINPOINT system	10.9	Clinical, radiological	≥ I	30

I=ICG group; C=Control group; AL = Anastomotic leakage; NA = Not available

Table 3 Summary of findings

Outcomes assessment	Included studies	ICGGA (*n*)	Control (*n*)	Test of heterogeneity		Meta-analysis			Quality of evidence (GRADE)
				I^2 (%)	*P* value	OR or MD	95% CI	*P* value	
Anastomotic leakage	18	1495	2543	0	0.71	0.33	0.24–0.45	< 0.0001	Low[a, f]
Ileus	6	526	742	56	0.04	1.30	0.60–2.82	0.51	Very low[a, b, d]
Surgical site infection	6	427	606	0	0.72	1.40	0.62–3.20	0.42	Very low[a, d]
Reoperation	5	515	634	6	0.37	0.61	0.34–1.10	0.10	Very low[a, d]
Postoperative stays	5	549	672	60	0.04	− 3.00	− 5.46 to − 0.13	0.03	Very low[a, b, d]

Downgrade quality of evidence: [a] risk of bias, [b] inconsistency; [c] indirectness; [d] imprecision. Upgrade quality of evidence: [f] large effect; [g] plausible confounding would change the effect; [h] dose-response gradient. *OR* odds ratio, *MD* mean difference

30 days, and unknown). All of these results were not significantly different by these stratifications with $P = 0.27$, 0.95, 0.33, 0.27, and 0.26, respectively (Table 4 and Fig. S1–5).

Secondary outcomes

Other postoperative complications The incidence of ileus was reported in 6 studies [25, 32, 33, 36, 37, 42] (Fig. 3a). The ileus rates were 7.2% in the ICGFA group and 7.3% in the control group. The pooled OR was 1.30 (95% CI: 0.60–2.82; $P = 0.51$; $I^2 = 56\%$).

Six studies [25, 32, 36, 37, 42, 43] reported that the surgical site infection rates were 2.8% in the ICGFA group and 1.8% in the control group. The pooled OR was 1.40 (95% CI: 0.62–3.20; $P = 0.42$; $I^2 = 0\%$) (Fig. 3b).

Reoperation A total of 5 studies [23, 25, 32, 37, 42, 43] reported on reoperation (Fig. 4), of which, the reoperation rate was 3.3% in the ICGFA group and 6.5% in the control group. The pooled OR was 0.61 (95% CI: 0.34–1.10; $P = 0.10$; $I^2 = 6\%$).

Postoperative stays Five studies [23, 25, 37, 40, 43] provided data on postoperative stays (Fig. 5). The pooled analysis suggested that the use of ICGFA was significantly associated with shorter postoperative stays (MD = − 1.27 (95% CI: − 2.42 to − 0.13; $P = 0.04$; $I^2 = 60\%$)).

Table 4 Subgroup analyses of the efficacy ICGFA versus no ICGFA in preventing AL in rectal cancer patients

Subgroup	Included studies	ICGGA (n)	Control (*n*)	Test of heterogeneity		Meta-analysis		
				I^2 (%)	*P* value	OR	95% CI	*P* value
Total AL	18	1495	2543	0	0.71	0.33	0.24–0.45	< 0.0001
Symptomatic AL	12	926	1547	22	0.23	0.44	0.31–0.64	< 0.0001
Study design								
RCT	2	222	212	0	0.82	0.44	0.25–0.80	0.007
Non-RCT	16	1273	2331	0	0.63	0.30	0.24–0.43	< 0.0001
Country								
Eastern	5	826	1466	58	0.05	0.36	0.17–0.77	0.008
Western	13	669	1077	0	0.99	0.35	0.23–0.53	< 0.0001
Sample size								
≥ 100	10	1268	2297	19	0.27	0.35	0.25–0.48	< 0.0001
< 100	8	227	246	0	0.71	0.22	0.09–0.54	0.001
The time of ICG performance								
Before anastomosis	8	774	1392	4	0.40	0.39	0.27–0.56	< 0.0001
Before and after anastomosis	9	411	804	0	0.98	0.26	0.14–0.49	< 0.0001
Follow-up duration								
Within 30 days	10	901	1573	0	0.91	0.34	0.24–0.48	< 0.0001
Beyond 30 days	4	393	435	0	0.93	0.15	0.05–0.45	0.0006
Unknown	4	201	535	46	0.14	0.46	0.22–0.96	0.04

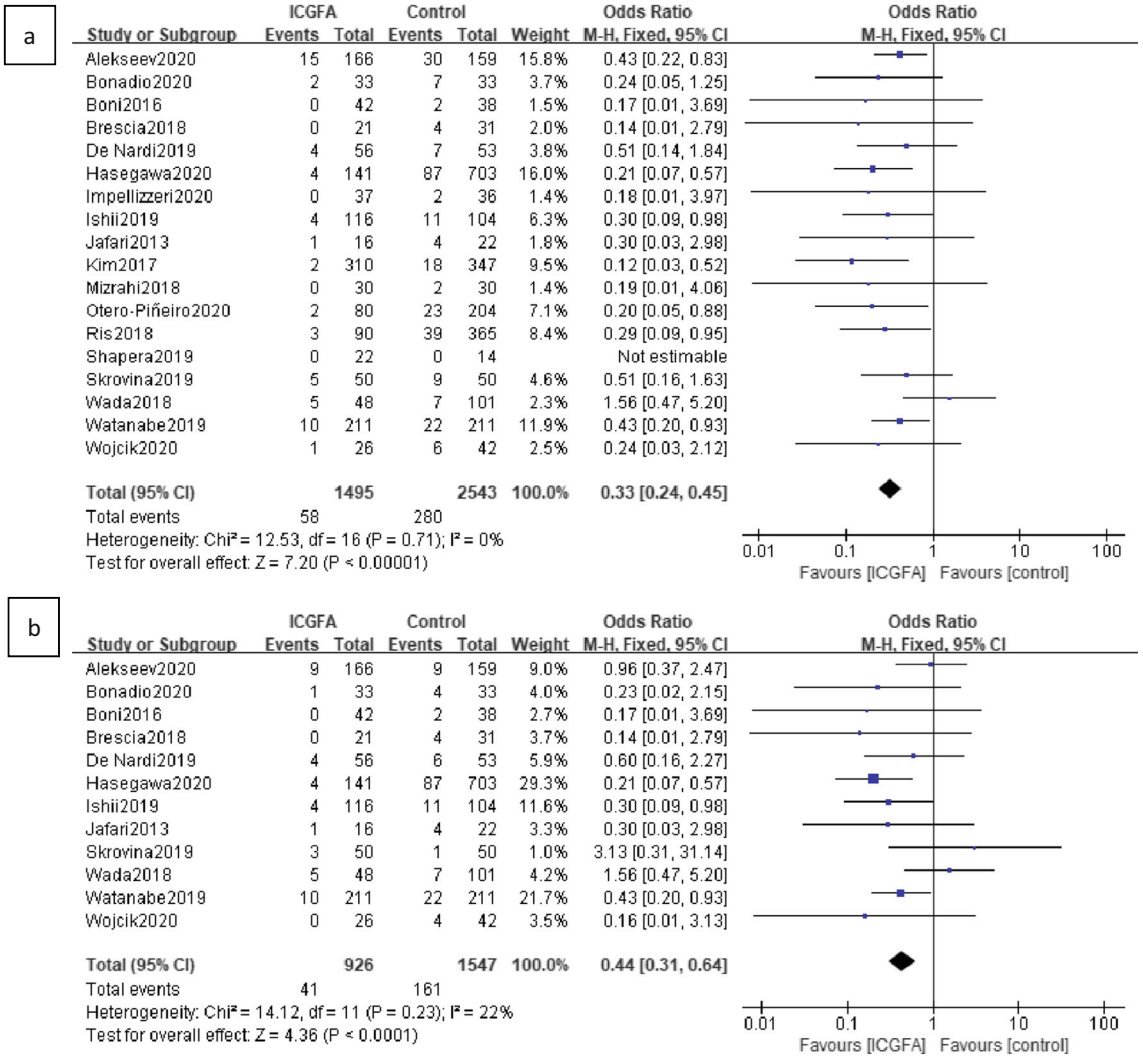

Fig. 2 Forest plot evaluating (**a**) overall anastomotic leakage and (**b**) symptomatic leakage between the ICGFA and the control group in rectal cancer patients

Publication bias

The funnel plot and Begg's test were used to assess the potential publication bias in the meta-analysis of the primary outcome. As shown in supplementary file (Fig. S6), the funnel plot was almost symmetric, and the *P* value of Begg's test was 0.202, which indicated that there was a low risk of publication bias in this study.

Discussion

This is the largest meta-analysis ever published to study the influence of ICGFA on AL in patients with rectal cancer surgery. Our pooled analysis of 4038 patients demonstrated that the intraoperative use of ICGFA was associated with a lower AL rate after rectal cancer resection. In addition, this intervention was associated with shorter postoperative stays, which might be related to the reduction in AL.

The negative effects of AL in rectal cancer surgery are undeniable. In medical cost, Ashraf et al. [47] reported the average cost was £17,220 in rectal cancer surgery patients who suffered from AL, which was significantly higher than those without (£ 6319). Besides, many studies have identified that AL was an independent risk factor for poor long-term survival in rectal cancer [48, 49]. Thus, it is crucial to prevent AL after rectal cancer resection. As mentioned above, a lot of patient-related (male gender, age, and diabetes), tumor-related (neoadjuvant chemoradiotherapy and low anastomosis), and surgery-related parameters (anastomotic tension and hypoperfusion) have been identified as risk factors for the incidence of AL [4]. However, among these risk factors, anastomotic perfusion represents one of the few modifiable variables.

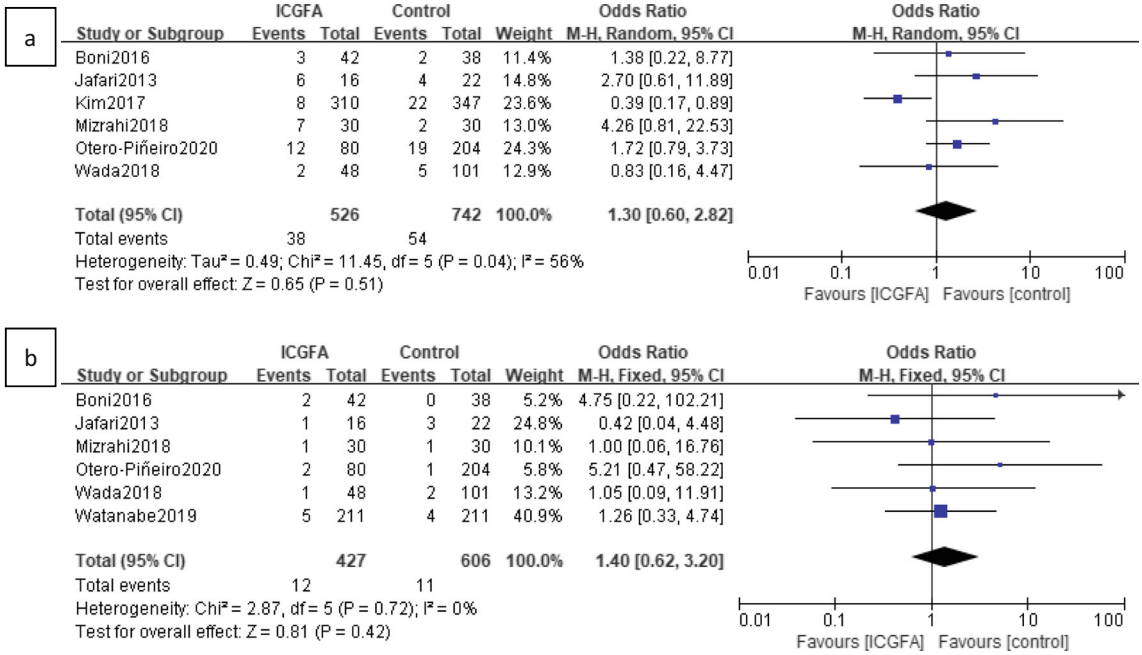

Fig. 3 Forest plot evaluating (**a**) ileus and (**b**) surgical site infection between the ICGFA and the control group in rectal cancer patients

In recent years, there has been ongoing interest on the use of ICGFA to assess anastomotic perfusion due to its relative ease of use, low cost, and satisfactory safety [33, 38]. Several recently published meta-analyses [14–16, 18] have demonstrated that the risk of developing AL after colorectal surgery was decreased significantly in patients with ICGFA, which was in line with our result. However, most of them were not convincing due to the limited number of included observational studies. Compared to these studies, the strength of our meta-analysis is the thorough inclusion of all applicable RCTs, prospective, and retrospective studies, which allowed us to analyze a larger sample size than previous meta-analyses. Besides, our study is more specific in the interventions in that we included rectal cancer patients only, which is a population that is likely to benefit the most from the interventions because of the high incidence of AL in rectal cancer resection compared to colon cancer surgery.

By performing subgroup analyses, we are able to explain the study heterogeneity. First, by limiting our analysis to patients who had a symptomatic AL, we found that the use of ICGFA still showed a superior effect on the reduction of clinically important AL, which further demonstrated the clinical value of this new technique. Second, with including two recently published RCTs, we could find that there was no subgroup difference based on study design (RCT vs. non-RCT), which provided us a more definitive proof of the benefit of ICGFA on AL reduction. Third, we also explored whether the time of ICGFA performance (before anastomosis vs. both before and after anastomosis) could affect the primary outcome. We found that assessing bowel perfusion both before and after anastomosis (OR = 0.26) seemed more effective than merely doing this before anastomosis (OR = 0.39) on the reduction of AL, even there was no significant subgroup difference existed. Therefore, applying ICGFA both before and after anastomosis to evaluate bowel perfusion may be a better choice to prevent AL in future clinical practice. In addition, we further performed subgroup analyses based on country (Western vs. Eastern), sample size (≥ 100 vs. < 100), and the follow-up duration (within 30 days vs. beyond 30 days vs. unknown) and found that there were no significant differences

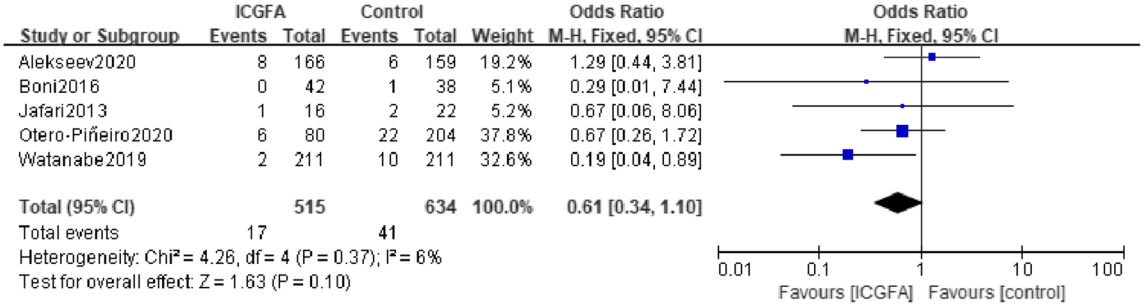

Fig. 4 Forest plot evaluating reoperation between the ICGFA and the control group in rectal cancer patients

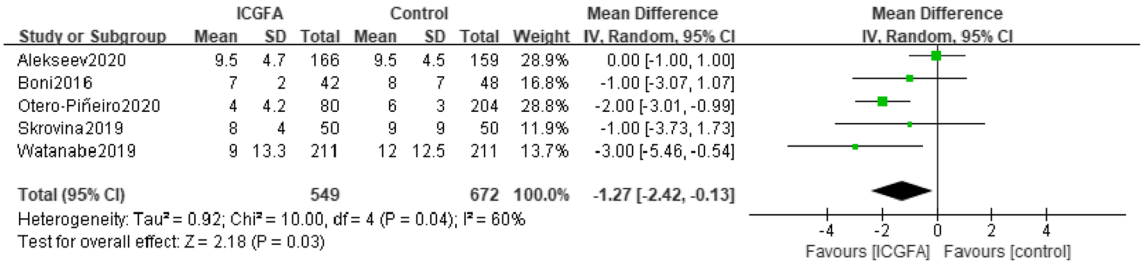

Fig. 5 Forest plot evaluating postoperative stays between the ICGFA and the control group in rectal cancer patients

based on these stratifications. Therefore, considering the low heterogeneity and low risk of publication bias, the intraoperative use of ICGFA may be a promising tool to prevent AL in rectal cancer surgery.

Currently, accumulating studies [50–52] focusing on quantitative fluorescence angiography has provided us a more thorough understanding of how ICGFA can facilitate the reduction of AL rate. A systematic review [53] of 13 studies by Lütken et al. found that the leakage of anastomotic site was closely associated with the inflow parameters such as time-to-peak, slope, and $t_{1/2}$ max, which scientifically demonstrated that the effect observed in our meta-analysis is realized at the anastomotic site. Quantifying the ICGFA generates objective and precise perfusion values, which may help surgeons decide whether the change of surgical plan is needed and eliminate the subjective limitations of qualitative (visual) method [54].

There were several limitations in the present study. First, the predominately included studies were observational studies. The insufficiency of RCTs may lead to increase the risk of bias, and more high-quality RCTs are required to provide more credible evidence on this issue. Second, the administrated dosage of ICG and imaging systems among these studies were different, which might also cause bias due to the difference in signal detectability. Additionally, the definition of AL was inconsistent in these studies (Table 2). Skrovina et al. [40] diagnosed AL just by radiological finding, while Kim et al. [33] identified AL based on not only radiological examination but also physical and endoscopic examinations. These variations might bring heterogeneity to the outcome analysis.

In conclusion, this systematic review and meta-analysis offered encouraging evidence that the intraoperative use of ICGFA was associated with an appreciable reduction in AL. However, taking in account the abovementioned limitations and low level of evidence of the comparisons, more multicenter RCTs with large sample size are required to verify the result of our study.

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Data availability All data generated or analyzed during this study are included in the published article.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

Ethical approval Considering the nature of this study, ethical approval was not required.

Human and animal rights This study is a systematic review with meta-analysis of outcomes which does not include research directly involving human or animal participation.

Informed consent Considering the nature of this study, informed consent was not required.

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