Impact of intraoperative indocyanine green fluorescence angiography on anastomotic leakage after laparoscopic sphincter-sparing surgery for malignant rectal tumors

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Author contributions

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Abstract

Purpose

Whether indocyanine green fluorescence angiography (ICG-FA) during rectal surgery is effective in reducing anastomotic leakage remains unclear. This study aimed to investigate the effect of intraoperative ICG-FA on anastomotic leakage after sphincter-sparing surgery for malignant rectal tumors.

Methods

This was a retrospective, single-center cohort study conducted on 852 consecutive patients who underwent laparoscopic sphincter-sparing surgery from January 2007 to June 2017 at our institution. The incidence of anastomotic leakage was compared between patients who underwent ICG-FA to determine the proximal resection margin and those in whom this technique was not performed, using logistic regression analysis, including propensity score.

Results

A total of eight patients were excluded (one patient with previous low anterior resection and seven patients who underwent simultaneous resection for other primary cancers), resulting in 844 patients being analyzed. Before propensity score matching, 141 patients (16.7%) who underwent ICG-FA were compared with 703 patients (83.3%) in whom ICG-FA was not performed. The incidence of anastomotic leakage was 2.8% (4/141) in the ICG-FA group and 12.4% (87/703) in the control group ($p = 0.001$). After propensity score matching ($n = 420$), the patient characteristics between the two groups were well balanced, and the incidence of anastomotic leakage was 2.8% (4/141) in the ICG-FA group and 13.6% (38/279) in the control group ($p = 0.001$). Logistic regression analyses using propensity score showed that patients who underwent ICG-FA had significantly lower odds of anastomotic leakage.

Conclusion

Intraoperative ICG-FA is a promising method to reduce anastomotic leakage after laparoscopic rectal surgery.

Keywords

Indocyanine green; Fluorescence angiography; Anastomotic leakage; Sphincter-sparing surgery

Introduction

Advances in medical technology have allowed surgeons to preserve the anus in an increasing number of rectal cancer patients. However, sphincter-sparing surgery exposes patients to the risk of anastomotic leakage (AL).

AL after rectal cancer surgery has been reported to occur in 6% to 14% of patients [1-4]. Some reports suggest that AL increases postoperative morbidity and mortality, leading to prolonged hospitalization and increased healthcare costs [3, 4]. Furthermore, AL affects functional outcomes and quality of life [5] and negatively impacts local recurrence and cancer-specific survival [6].

Although the risk of AL is multifactorial [1-3, 7-9], tissue perfusion is one of the most important factors [7-9]. Sufficient blood supply is essential to avoid anastomotic leakage and stenosis.

Intraoperative indocyanine green fluorescence angiography (ICG-FA) is useful to assess tissue perfusion in real-time and is associated with improved outcomes in several surgical procedures [10]. Recent studies showed that ICG-FA is a safe and feasible tool for assessing bowel perfusion [11-18]. Moreover, ICG-FA has the potential to reduce AL by changing the surgeon's intraoperative decisions [11, 13-17].

However, very few articles have focused on the use of ICG-FA during rectal surgery, which has a higher incidence of AL than colon surgery. It remains unclear whether ICG-FA is effective in reducing AL in rectal cancer surgery to date. Thus, this study aimed to investigate the effect of intraoperative ICG-FA on AL after laparoscopic rectal surgery.

Methods

Patients

This retrospective cohort study was conducted at the National Cancer Center Hospital East in Kashiwa, Japan. Data were obtained from the prospectively collected database and electronic medical records. This study was conducted in accordance with ethical standards, as laid down in the 1964 Declaration of Helsinki and its later amendments, and the study protocol was approved by the National Cancer Center Institutional Review Board (2017-410). The requirement for acquisition of informed consent from patients was waived owing to the retrospective nature of this study.

A total of 143 patients who underwent elective laparoscopic low anterior resection (LAR) or intersphincteric resection (ISR) with lymphadenectomy for malignant rectal tumors using ICG-FA between June 2016 and June 2017 were included. Furthermore, 709 patients who underwent elective laparoscopic LAR or ISR with lymphadenectomy for malignant rectal tumors without ICG-FA between January 2007 and May 2016 served as the control group, resulting in a total of 852 consecutive patients. To reduce bias related to the surgical technique, a history of left-sided colorectal surgery or simultaneous resection of other primary cancers was considered an exclusion criterion. This led to the exclusion of one patient with a history of LAR and seven patients who underwent simultaneous resection for other primary cancers, resulting in 844 patients who were entered into the study. The flow of patients through the study is shown in Fig. 1.

Surgical technique

The laparoscopic surgical technique has been standardized at our institution, and all procedures were performed by experienced colorectal surgeons. Medial to lateral mobilization and lymph node dissection with ligation of the inferior mesenteric artery (IMA) and vein were performed in all patients. The mobilization of the splenic flexure was determined by the bowel length and tension at the anastomosis. After mobilization of the left-sided colon, total or tumor-specific mesorectal excision was performed, depending on the height of the tumor. The rectum was transected, and the specimen was extracted. The anastomosis was performed with a stapler in LAR and hand-sewn in ISR, and most reconstructions were performed in an end-to-end fashion. A diverting stoma was created at the discretion of each surgeon based on the well-established risk factors for AL (e.g., male, large tumor, preoperative therapy, and a low level of the anastomosis) [1-3, 7-9].

Intraoperative ICG-FA

First, the surgeon chose the proximal resection line after extracorporeal macroscopic inspection under white light. Prior to the resection, a bolus of 5.0 mg ICG was injected intravenously. The visualization of the ICG fluorescence of the initially planned resection line was assessed as *sufficient* or *insufficient* by the surgical team in a completely dark operating theater using the IMAGE1 S™ system (Karl Storz SE & Co. KG, Tuttlingen, Germany), 1588 Advanced Imaging Modalities (AIM) Platform and SPY Fluorescence technology (Stryker, Kalamazoo, MI, USA), or HyperEye Medical System Handy (Mizuho Medical Co. Ltd., Tokyo, Japan). If the ICG fluorescence of the planned resection line was well visualized, bowel perfusion was assessed as *sufficient*, and the resection line was not changed (Fig. 2). If the planned resection line was only partially visualized (Fig. 2) or not visualized at all, bowel perfusion was assessed as *insufficient*, and the resection line was moved further proximally until it was clearly visible under ICG-FA.

Definition of anastomotic leakage

AL was implied by the presence of clinical symptoms such as the discharge of gas or feces from the pelvic drain or wound, or fistula formation, as previously described [19]. All cases with clinical suspicion of AL were ascertained by one or more of the following examinations: contrast enema radiography, contrast radiography through the drain, computed tomography (CT), or rectoscopy. In cases with diverting stoma, the anastomotic site was checked daily after surgery by digital examination during hospitalization. If anastomotic dehiscence was detected with the presence of clinical symptoms or clinical suspicion of AL, AL was confirmed using the same method employed for cases without diverting stoma. The severity of AL was classified according to the Clavien-Dindo (C-D) classification system [20]. In this study, an AL of C-D grade ≥ II within 30 days of surgery was defined as symptomatic AL.

Clinical variables and outcome parameters

Patient demographics and perioperative data were collected from the prospectively collected database and electronic medical records. Preoperative tumor staging was performed by digital examination, barium enema, CT, pelvic magnetic resonance imaging, and colonoscopy according to the TNM Classification of Malignant Tumors (7th edition). Bowel obstruction was defined as a mechanical block preventing the passage of the colonoscope. The distance between the lower edge of the tumor and the anal verge (AV) was measured by digital examination and colonoscopy. The distance between the anastomotic site and the AV was measured by digital examination in the operating theater. Ligation of the IMA proximal to the origin of the left colic artery was defined as a *high ligation* and ligation distal from it was defined as a *low ligation*.

The primary endpoint of this study was the incidence of symptomatic AL after laparoscopic sphincter-sparing resection.

Statistical analysis

The primary objective was to evaluate whether ICG-FA reduces the incidence of symptomatic AL after laparoscopic rectal surgery. Considering that the incidence of AL was low overall and that the assignment of patients to the group with or without ICG-FA was not random, a propensity score approach was used to adjust for potential confounding factors and ensure comparability.

The propensity score was estimated using a logistic regression model. The outcome variable was the conduct of ICG-FA, and plausible baseline confounding variables, shown in Table 1, were included as covariates. Age and the distance between the anastomotic site and the AV were regarded as continuous variables. Logarithmic-transformed tumor size was used. The other covariates were dichotomized according to their clinically appropriate cutoff values.

A greedy matching was performed using a standardized deviation width of 0.20 for the logit transformation of the estimated propensity score (EPS) [21]. Patients who underwent ICG-FA were matched to those who did not undergo ICG-FA at a ratio of 1:2. Imbalance of patient characteristics before and after matching was examined using histograms and box plots of the EPS and standardized differences. For the matched patient set, odds ratios and their 95% confidence intervals (CIs) were estimated using univariable (conditional) logistic regression analyses. Risk ratios and their 95% CIs were estimated using (unconditional) log-linear models in the same manner.

We performed multivariable logistic regression analysis using stepwise selection with a significance level of 5%, adjusted for the same variables as in the estimation of propensity score analyses. Moreover, a simple logistic model adjusted for EPS was applied. Continuous EPS was modeled using restricted cubic smoothing splines. Next, the inverse probability treatment weighting (IPTW) method was used to estimate the average causal treatment effect. Two types of weights (standard and exposed weights) were calculated using EPS [22]. The Taylor series method was used to estimate robust variance. We finally applied stratified logistic regression models. Five strata were constructed in a post-hoc manner: five equal-sized groups categorized according to the quintiles of the EPS.

SAS software, Release 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses. All *p* values are reported as two-sided.

Results

Patient characteristics

Patient and tumor characteristics are presented in Table 1. Before EPS matching, there were no missing values for the variables shown in Table 1. Intraoperative ICG-FA was performed in 141 patients (16.7%) (ICG-FA group) but was not performed in 703 patients (83.3%) (control group). Preoperative and operative variables related to AL were selected, and propensity scores were estimated using a multivariable logistic regression model that included the following 13 covariates: sex, age, body mass index, history of smoking, American Society of Anesthesiologists physical status classification, maximal tumor size, clinical stage, preoperative therapy, operative procedure, lateral lymph node dissection, distance between the anastomotic site and the AV, diverting stoma, and transanal tube. The distance between the tumor and the AV was not included in the model to avoid problems with multicollinearity because of the correlation with the distance between the anastomotic site and the AV. The distribution of the EPS was nearly equal between the two groups. Patients in the ICG-FA group were matched to those in the control group at a ratio of 1:2. The EPS-matched cohort consisted of 141 patients in the ICG-FA group and 279 in the control group.

The characteristics before and after EPS matching are summarized in Tables 1 and 2, respectively. Before EPS matching (n = 844), the ICG-FA group had a higher frequency of smoking history (p = 0.03), advanced clinical stage (p = 0.009), preoperative therapy (p = 0.01), intersphincteric resection (p = 0.004), lateral lymph node dissection (p = 0.001), and diverting stoma (p < 0.0001) than the control group (Table 1). After EPS matching (n = 420), all adjustment covariates were well balanced, resulting in a decrease in standardized differences to less than 0.10 (Table 2, Online Resource 1).

Perfusion assessment

Intraoperative ICG-FA succeeded in all patients, and there were no adverse events related to the injection of ICG. The perfusion of the resection line was assessed as *sufficient* in 117 patients (83.0%). It was initially regarded as *insufficient* in 24 patients (17.0%), and the resection line was consecutively moved further proximally.

Anastomotic leakage

The overall incidence of AL was 10.8% (91/844) and 10.0% (42/420) in the entire and EPS-matched cohorts, respectively. The incidence of AL was significantly lower in the ICG-FA group than in the control group in both the entire cohort (4/141, 2.8% vs. 87/703, 12.4%; p = 0.001) and EPS-matched cohort (4/141, 2.8% vs. 38/279, 13.6%; p = 0.001) (Table 3). In the ICG-FA group, two patients (2/117, 1.7%) in whom the perfusion of the resection line had been assessed as *sufficient* and two patients (2/24, 8.3%) in whom it had initially been judged as *insufficient* developed AL. In patients in whom perfusion had been assessed as *sufficient* using ICG-FA, the median time to ICG fluorescence visualization was 36 seconds (range: 14–107 seconds), and there was no relation between the visualization time and the incidence of AL.

In the univariable logistic regression analysis, ICG-FA significantly reduced the risk of AL (OR, 0.21; 95% CI: 0.075–0.57, p = 0.002) (Table 4). In the multivariable logistic regression analysis without backward elimination adjusted for the same variables as in the estimation of EPS analysis, ICG-FA significantly reduced the risk of AL (OR, 0.17; 95% CI: 0.061–0.50, p = 0.001). In the multivariable logistic regression analysis with stepwise selection, ICG-FA significantly reduced the risk of AL (OR, 0.16; 95% CI: 0.057–0.45, p = 0.001). In the unconditional univariable logistic regression analysis for the EPS-matched cohort, ICG-FA significantly reduced the risk of AL (OR, 0.19; 95% CI: 0.065–0.53, p = 0.002). In the multivariable logistic regression analysis adjusted for EPS using restricted cubic smoothing splines, ICG-FA significantly reduced the risk of AL (OR, 0.20; 95% CI: 0.070–0.55, p = 0.002). IPTW analysis for standard and exposed weights based on EPS showed similar results for the multivariable analyses (for standard and exposed weights, OR, 0.23; 95% CI: 0.071–0.73, $p = 0.01$). Finally, in the univariable logistic regression analysis stratified into five groups constructed by EPS, ICG-FA significantly reduced the risk of AL (OR, 0.19; 95% CI: 0.067–0.53, $p = 0.002$). ICG-FA strongly and consistently reduced the risk of AL with lower odd ratios (ORs, 0.16–0.23) across all regression analyses using EPS.

Discussion

To the best of our knowledge, this is the largest study focusing on the use of ICG-FA in lower rectal surgery. We showed its efficacy in reducing the risk of symptomatic AL in patients undergoing laparoscopic sphincter-sparing surgery by using specifically selected statistical methods to reduce the effect of selection bias and confounding factors.

AL is one of the most devastating complications in sphincter-sparing surgery. Ensuring optimal tissue perfusion is considered one of the most important factors in preventing AL. Usually, bowel perfusion is only roughly approximated by surgeons, using indicators such as tissue color or palpable pulsations in the mesentery. However, these assessments have shown a low accuracy in predicting AL in colorectal surgery [23]. Several methods to assess bowel perfusion intraoperatively, such as Doppler technology, have been reported [24], but they are not widely used, mainly because of the lack of reproducibility.

ICG-FA has been associated with improved outcomes in a number of surgical procedures [10], including gastrointestinal surgery [11, 13-18], and is considered a feasible and reproducible technique for real-time assessment of bowel perfusion without much difficulties and with a minimal learning curve [12].

Kudszus et al. [11], who were the first to show the usefulness of ICG-FA in colorectal surgery, reported that ICG-FA led to a change in the location of the initially planned proximal resection line in 13.9% (28/201) of patients. ICG-FA significantly reduced AL by 4.0% compared with the control group (3.5% vs. 7.5%). Jafari et al. [12] assessed the feasibility and utility of ICG-FA in left-sided colectomy and anterior resection. The incidence of AL in their study was 1.4% (2/139). ICG-FA led to a change in the surgical strategy in 8.0% (11/139). Most changes occurred in the resection of the proximal margin. No AL was observed in these patients. However, the anastomotic site was, on average, 10.4 cm proximal from the AV and at least 8 cm proximal in 74.1% (103/139) of patients. Therefore, these results do not apply to lower rectal surgery.

Boni et al. [13] reported that ICG-FA could be safely and effectively performed in rectal surgery. The use of ICG-FA changed the surgical plan in 4.7% (2/42) of their patients. AL did not occur in the ICG-FA group, as compared to an incidence of 5.2% (2/38) in the control group. However, the differences were not statistically significant. Kim et al. [14] reported that AL in robot-assisted sphincter-sparing surgery was significantly less frequent in the ICG-FA group than in the control group (0.6% vs. 5.2%). Wada et al. [15] investigated the effect of ICG-FA in laparoscopic LAR with double-stapling anastomosis using a propensity score-matched analysis. They reported a statistically non-significant reduction in AL to 8.8% (3/34) and 14.7% (5/34) in the ICG-FA and control groups, respectively. All these studies had several limitations such as small sample size and an inherent bias as most of them were retrospective.

Thus far, ours is the largest study that focuses on ICG-FA in sphincter-sparing surgery, and propensity score adjustment was adopted to ensure the comparability between the groups by balancing the distribution of selection bias and potential confounders. The standardized difference decreased to less than 0.10 in all adjustment covariates after matching. Several statistical analyses showed similar results, and the odds ratios were nearly consistent (ORs, 0.16–0.23), suggesting a successful adjustment for confounding variables.

Only one study in the literature by Kin et al. [25] found that there was no reduction in the incidence of AL when using ICG-FA in colorectal surgery. However, the authors acknowledged selection bias and small sample size as limitations.

Our study has several limitations worth mentioning. First, it was a retrospective, single-center cohort study. It is not possible to control all biases with this study design. Although the propensity score adjustment seemed to be effective in minimizing the inherent bias, there might still be residual or confounding variables. Nonetheless, as ICG-FA has been increasingly used in clinical practice in recent years, our results remain meaningful. Second, there were differences in the period of operation between the two groups (i.e., the surgeons in the ICG-FA group had more experience than those in the control group), and these may have influenced the incidence of complications. Hence, we should consider the impact of the learning curve. However, we deem this limitation to be minimal because all procedures were performed by experienced colorectal surgeons, and the incidence of AL in the control group did not differ from year to year (data not shown). With respect to the retrospective nature and sequential time interval, a well-designed, multicenter randomized controlled trial is required to confirm our result. Third, there were minor changes in the surgical technique over time, such as the level of the ligation of the IMA, splenic flexure mobilization, and reconstruction technique, which might have a potential influence on the incidence of AL. Patients operated later during the study period mainly underwent high ligation of the IMA and splenic flexure mobilization. Reconstruction was performed in an end-to-end or side-to-end fashion at the discretion of each surgeon, and most patients (803/844, 95.1%) underwent end-to-end anastomosis. However, recent studies show that these techniques do not impact on the incidence of AL [26-30]. As for the ligation of the IMA, a recent multicenter randomized controlled trial reported an AL incidence of 8.1% for the high-ligation group and 6.7% for the low-ligation group, with no significant difference between the two groups [27]. As regards splenic flexure mobilization, a recent meta-analysis reported a lower incidence of AL in the group without splenic flexure mobilization [29]. The authors mentioned that this result should be interpreted with caution. This study had several limitations such as its small sample size and an inherent bias. However, it can be interpreted that omitting the splenic flexure mobilization may not increase the incidence of AL. With respect to the reconstruction technique, a recent meta-analysis compared the surgical outcomes of different reconstruction techniques (end-to-end, side-to-end, colonic J pouch, and transverse coloplasty) and showed that although the reconstruction technique influenced the functional outcomes, no superiority was identified for any of the techniques with respect to the incidence of AL [30]. Therefore, we believe that these differences in the surgical technique may not affect our results. Fourth, the quality of bowel perfusion was assessed using three different types of ICG-imaging systems. However, ICG-FA succeeded in all cases. Therefore, the use of these devices did not result in differences that would affect the assessment. Fifth, bowel perfusion on the distal side of the anastomosis was not assessed in this study. Nevertheless, the evaluation method for ICG-FA in colorectal surgery varies in the literature (Table 5) and the standard criteria have not yet been established.

Conclusion

ICG-FA offers a more accurate intraoperative assessment of tissue perfusion that impacts surgeons' decision-making and reduces the risk of symptomatic AL in patients undergoing rectal surgery. A well-designed, multicenter randomized controlled trial will help substantiate the results of our study [31].

COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of potential conflicts of interest

Funding: This study has not received any direct or indirect funding from extramural sources.

Conflicts of interest: The authors declare that they have no conflict of interest.

Research involving human participants and/or animals

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (National Cancer Center Institutional Review Board; reference number: 2017-410) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent: The requirement for acquisition of informed consent from patients was waived owing to the retrospective nature of this study.

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Figure legends

Fig. 1

Patient flow diagram and exclusion criteria. ICG-FA, indocyanine green fluorescence angiography; ISR, intersphincteric resection; LAR, low anterior resection

Fig. 2

The forceps were placed at the proximal resection line under white light (**a** and **c**). If the ICG fluorescence of the planned resection line (arrow) was well visualized, the resection line was not changed (**b**). If the planned resection line (arrow) was only partially visualized (**d**) or not visualized at all, the resection line was moved further proximally until it was clearly visible under indocyanine green fluorescence angiography

Online Resource 1

In the estimated propensity score matched cohort, all adjustment covariates were well balanced, which resulted in a decrease in standardized differences. ASA-PS, American Society of Anesthesiologists physical status classification; BMI, body mass index; LLND, lateral lymph node dissection

Table 1

Comparison of characteristics of the entire cohort (*n* = 844)

Variables	**ICG-FA group (*n* = 141)**	**Control group (*n* = 703)**	***p* value[b]**	**Standardized difference**
Sex[a], n (%)				
Male	99 (70.2)	450 (64.0)	0.16	0.13
Female	42 (29.8)	253 (36.0)		
Age[a], years, median (IQR)	63 (51–69)	62 (55–68)	0.75	0.007
BMI[a], kg/m^2, median (IQR)	22.3 (20.5–25.2)	22.9 (20.8–24.9)	0.35	0.10
>25	104 (73.8)	528 (75.1)	0.74	0.031
≤25	37 (26.2)	175 (24.9)		
History of smoking[a], n (%)				
No	46 (32.6)	299 (42.5)	0.029	0.21
Yes	95 (67.4)	404 (57.5)		
ASA physical status classification[a], n (%)				
I	48 (34.0)	293 (41.7)	0.092	0.16
II, III	93 (66.0)	410 (58.3)		
Histological type, n (%)				
Adenocarcinoma	135 (95.7)	668 (95.0)	0.72	0.034
Neuroendocrine tumor	6 (4.3)	35 (5.0)		
Maximal tumor size, cm, median (IQR)	3.5 (2.1–5.0)	3.0 (2.0–4.6)	0.075	0.15
log(Maximal tumor size)[a], median (IQR)	1.3 (0.7–1.6)	1.1 (0.7–1.5)	0.075	0.16
Distance between tumor and AV, cm, median (IQR)	6.0 (5.0–8.0)	7.0 (5.0–9.0)	0.21	0.12

Clinical stage[a], n (%)				
I, II	107 (75.9)	597 (84.9)	0.009	0.23
III, IV	34 (24.1)	106 (15.1)		
Bowel obstruction, n (%)				
No	131 (92.9)	675 (96.0)	0.10	0.14
Yes	10 (7.1)	28 (4.0)		
Preoperative therapy[a], n (%)				
No	115 (81.6)	626 (89.0)	0.013	0.21
Yes	26 (18.4)	77 (11.0)		
Operative procedure[a], n (%)				
Low anterior resection	76 (53.9)	468 (66.6)	0.004	0.26
Intersphincteric resection	65 (46.1)	235 (33.4)		
Level of vessel ligation, n (%)				
High ligation of IMA	139 (98.6)	360 (51.2)	<0.0001	1.3
Low ligation of IMA	2 (1.4)	343 (48.8)		
Splenic flexure mobilization, n (%)				
No	72 (51.1)	568 (80.8)	<0.0001	0.66
Yes	69 (48.9)	135 (19.2)		
Lateral lymph node dissection[a], n (%)				
No	89 (63.1)	536 (76.2)	0.001	0.29
Yes	52 (36.9)	167 (23.8)		
Distance between anastomosis and AV[a], cm, median (IQR)	4.0 (3.0–6.0)	4.5 (3.0–6.0)	0.25	0.12
Diverting stoma[a], n (%)				

No	33 (23.4)	338 (48.1)	<0.0001	0.53
Yes	108 (76.6)	365 (51.9)		
Transanal tube[a], n (%)				
No	88 (62.4)	494 (70.3)	0.066	0.17
Yes	53 (37.6)	209 (29.7)		

ASA, American Society of Anesthesiologists; AV, anal verge; BMI, body mass index; ICG-FA, indocyanine green fluorescence angiography; IMA, inferior mesenteric artery; IQR, interquartile range.

[a]Variables used for propensity score analyses.

[b]Statistical analyses were performed using chi-squared test or Mann-Whitney U test.

Table 2

Comparison of characteristics of the EPS-matched cohort (n = 420)

Variables	**ICG-FA group (n = 141)**	**Control group (n = 279)**	***p* value[b]**	**Standardized difference**
Sex[a], n (%)				
Male	99 (70.2)	203 (72.8)	0.58	0.056
Female	42 (29.8)	76 (27.2)		
Age[a], years, median (IQR)	63 (51–69)	63 (54–68)	0.69	0.031
BMI[a], kg/m^2, median (IQR)	22.3 (20.5–25.2)	23.2 (21.2–25.2)	0.075	0.19
>25	104 (73.8)	202 (72.4)	0.77	0.031
≤25	37 (26.2)	77 (27.6)		
History of smoking[a], n (%)				
No	46 (32.6)	86 (30.8)	0.71	0.039
Yes	95 (67.4)	193 (69.2)		
ASA physical status classification[a], n (%)				
I	48 (34.0)	100 (35.8)	0.72	0.038
II, III	93 (66.0)	179 (64.2)		
Histological type, n (%)				
Adenocarcinoma	135 (95.7)	268 (96.1)	0.88	0.016
Neuroendocrine tumor	6 (4.3)	11 (3.9)		
Maximal tumor size, cm, median (IQR)	3.5 (2.1–5.0)	3.5 (2.1–5.0)	0.95	0.018
log(Maximal tumor size)[a], median (IQR)	1.3 (0.7–1.6)	1.3 (0.7–1.6)	0.95	0.004
Distance between tumor and AV, cm, median (IQR)	6.0 (5.0–8.0)	6.0 (5.0–8.0)	0.54	0.023

Clinical stage[a], n (%)				
I, II	107 (75.9)	218 (78.1)	0.60	0.053
III, IV	34 (24.1)	61 (21.9)		
Bowel obstruction, n (%)				
No	131 (92.9)	261 (93.6)	0.80	0.025
Yes	10 (7.1)	18 (6.5)		
Preoperative therapy[a], n (%)				
No	115 (81.6)	229 (82.1)	0.89	0.013
Yes	26 (18.4)	50 (17.9)		
Operative procedure[a], n (%)				
Low anterior resection	76 (53.9)	145 (52.0)	0.71	0.039
Intersphincteric resection	65 (46.1)	134 (48.0)		
Level of vessel ligation, n (%)				
High ligation of IMA	139 (98.6)	191 (68.5)	<0.0001	0.89
Low ligation of IMA	2 (1.4)	88 (31.5)		
Splenic flexure mobilization, n (%)				
No	72 (51.1)	200 (71.7)	<0.0001	0.43
Yes	69 (48.9)	79 (28.3)		
Lateral lymph node dissection[a], n (%)				
No	89 (63.1)	170 (60.9)	0.66	0.045
Yes	52 (36.9)	109 (39.1)		
Distance between anastomosis and AV[a], cm, median (IQR)	4.0 (3.0–6.0)	4.0 (3.0–5.5)	0.54	0.039
Diverting stoma[a], n (%)				

No	33 (23.4)	57 (20.4)	0.48	0.072
Yes	108 (76.6)	222 (79.6)		
Transanal tube[a], n (%)				
No	88 (62.4)	185 (66.3)	0.43	0.081
Yes	53 (37.6)	94 (33.7)		

ASA, American Society of Anesthesiologists; AV, anal verge; BMI, body mass index; EPS, estimated propensity score; ICG-FA, indocyanine green fluorescence angiography; IMA, inferior mesenteric artery; IQR, interquartile range.

[a]Variables used for propensity score analyses.

[b]Statistical analyses were performed using chi-squared test or Mann-Whitney U test.

Table 3

Comparison of perioperative outcomes in the entire cohort and the EPS-matched cohort

Variables	**Entire cohort (*n* = 844)**			**EPS-matched cohort (*n* = 420)**		
	ICG-FA group (*n* = 141)	**Control group (*n* = 703)**	***p* value[a]**	**ICG-FA group (*n* = 141)**	**Control group (*n* = 279)**	***p* value[a]**
Operative time, minutes, median (IQR)	231 (166–324)	267 (212–353)	<0.0001	231 (166–324)	311 (231–412)	<0.0001
Intraoperative bleeding, mL, median (IQR)	42 (20–78)	54 (18–148)	0.045	42 (20–78)	70 (23–196)	0.001
Anastomotic leakage, n (%)	4 (2.8)	87 (12.4)	0.001	4 (2.8)	38 (13.6)	0.001
Postoperative mortality, n (%)	0 (0)	1 (0.1)	0.65	0 (0)	0 (0)	NA

EPS, estimated propensity score; ICG-FA, indocyanine green fluorescence angiography; IQR, interquartile range.

[a]Statistical analyses were performed using chi-squared test or Mann-Whitney U test.

Table 4

Comparison of several logistic regression analyses setting anastomotic leakage as the outcome variable

Model	***n***	**Odds ratio (95% CI)**	***p* value**
Univariable logistic	844	0.21 (0.075–0.57)	0.002
Multivariable logistic (without backward elimination)	844	0.17 (0.061–0.50)	0.001
Multivariable logistic (with stepwise selection)	844	0.16 (0.057–0.45)	0.001
Univariable logistic in EPS-matched cohort	420	0.19 (0.065–0.53)	0.002
Multivariable logistic (adjusted for EPS)	844	0.20 (0.070–0.55)	0.002
IPTW logistic (standard and exposed weights)	844	0.23 (0.071–0.73)	0.013
Univariable logistic stratified by five groups constructed by EPS	844	0.19 (0.067–0.53)	0.002

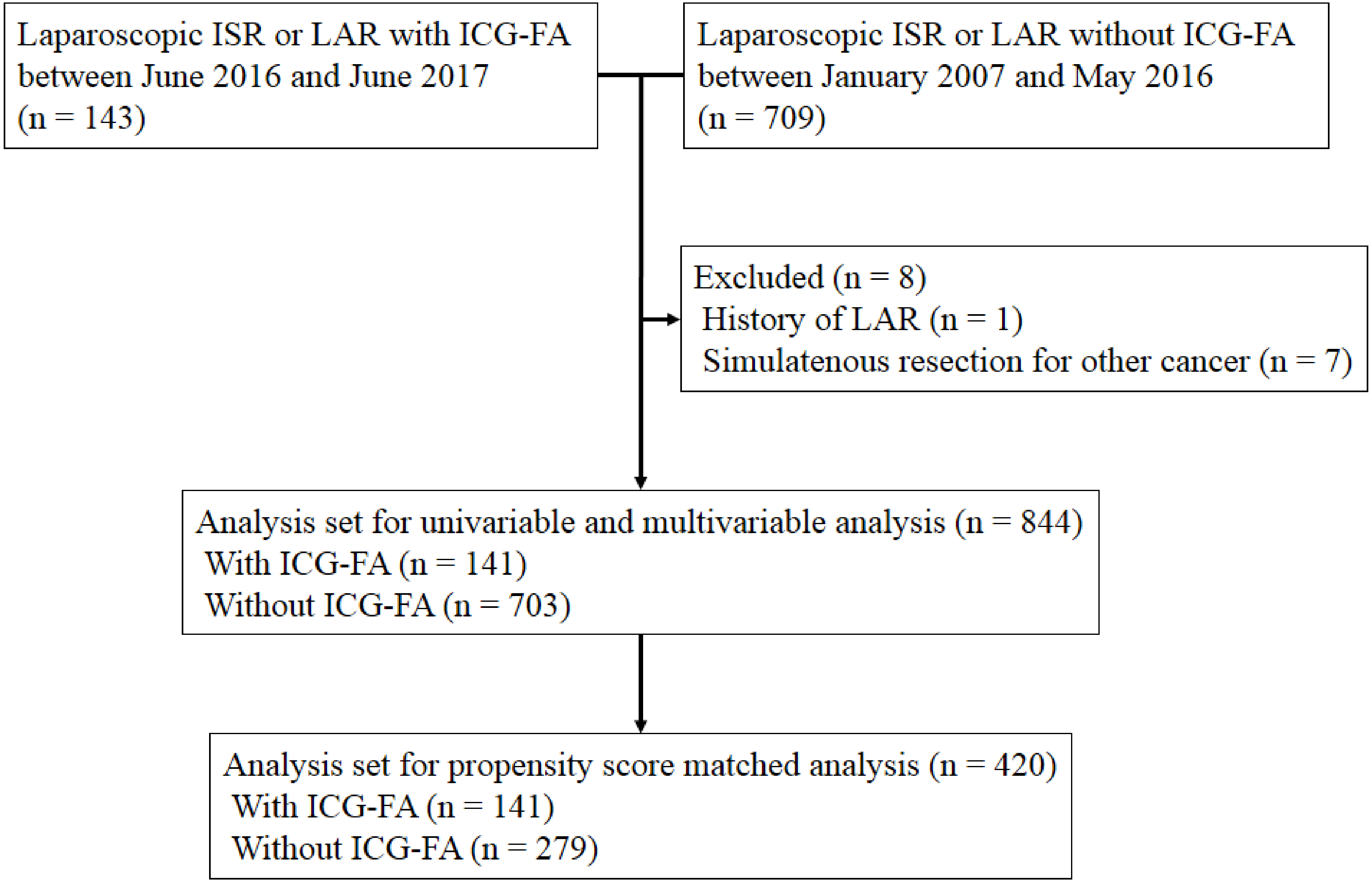
EPS, estimated propensity score; IPTW, inverse probability treatment weighting; CI, confidence interval.

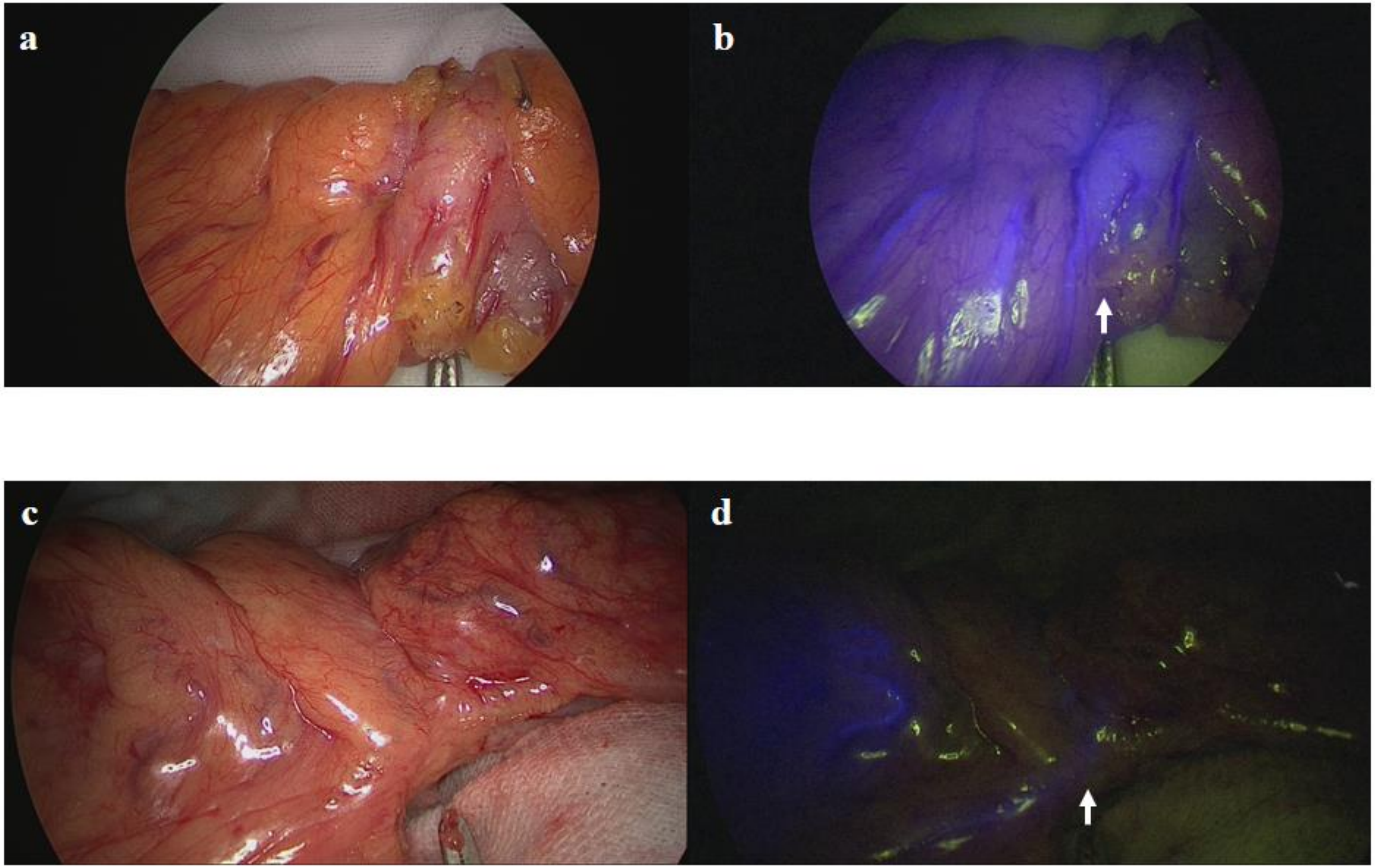
Table 5

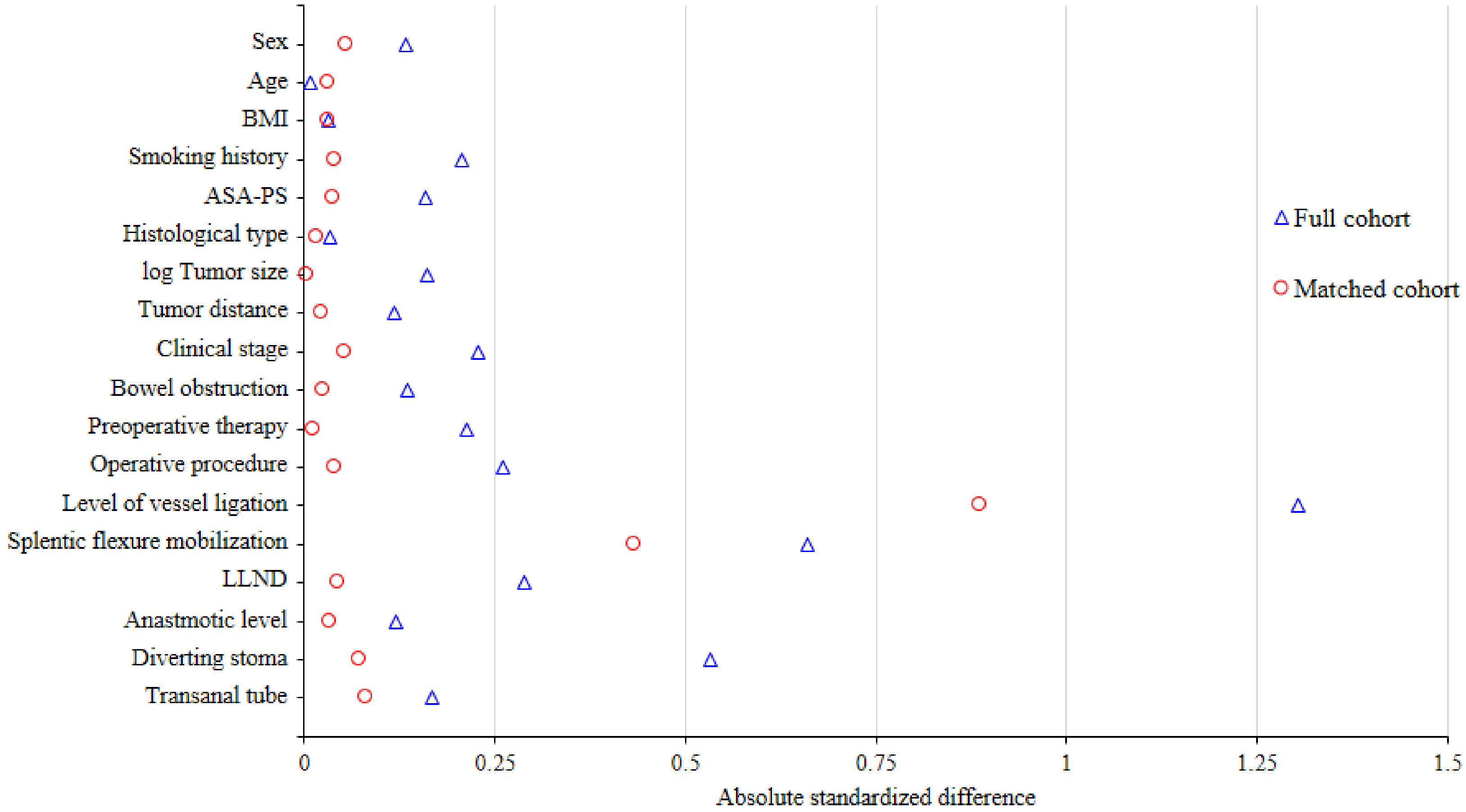
Comparison of the evaluation methods for ICG fluorescence angiography in colorectal surgery

Reference	Operative procedure (Approach)	System	ICG dose	Perfusion Assessment
Kudszus [11]	Colorectal resection (Laparoscopic and open)	IC-View®	0.2–0.5 mg/kg	The visualization of the ICG fluorescence was assessed as *sufficient* before or after anastomosis.
Jafari [12]	Left sided colon and rectal resection (Laparoscopic and robotic)	Pinpoint™ system	3.75–7.5 mg	The visualization of the ICG fluorescence was assessed as *sufficient* before and after anastomosis.
Boni [13]	Rectal resection (Laparoscopic)	IMAGE1 S™ system	0.2 mg/kg	The visualization of the ICG fluorescence was assessed as *sufficient* before anastomosis.
Kim [14]	Rectal resection (Robotic)	Firefly™	10 mg	The visualization of the ICG fluorescence was assessed as *sufficient* before and after anastomosis.
Wada [15]	Rectal resection (Laparoscopic)	PDE-neo system	5 mg	The visualization of the ICG fluorescence was assessed as *sufficient* before anastomosis.
Watanabe [17]	Rectal resection (Laparoscopic)	IMAGE1 S™ system and 1588 AIM Platform	0.25 mg/kg	The visualization of the ICG fluorescence within 60 seconds was assessed as *sufficient* before anastomosis.
Sherwinter [18]	Rectal resection (Laparoscopic)	Pinpoint™ system	2.5 mg	The visualization of the ICG fluorescence was assessed as *sufficient* after anastomosis.
Kin [25]	Colorectal resection (Laparoscopic and open)	SPY Imaging System™	n. r.	The visualization of the ICG fluorescence was assessed as *sufficient* before anastomosis.

ICG, indocyanine green; n. r., not reported


Laparoscopic ISR or LAR with ICG-FA between June 2016 and June 2017 (n = 143)
Laparoscopic ISR or LAR without ICG-FA between January 2007 and May 2016 (n = 709)
Excluded (n = 8)
History of LAR (n = 1)
Simulatenous resection for other cancer (n = 7)
Analysis set for univariable and multivariable analysis (n = 844)
With ICG-FA (n = 141)
Without ICG-FA (n = 703)
Analysis set for propensity score matched analysis (n = 420)
With ICG-FA (n = 141)
Without ICG-FA (n = 279)


a
b
c
d


Sex
Age
BMI
Smoking history
ASA-PS
Histological type
log Tumor size
Tumor distance
Clinical stage
Bowel obstruction
Preoperative therapy
Operative procedure
Level of vessel ligation
Splentic flexure mobilization
LLND
Anastmotic level
Diverting stoma
Transanal tube
Full cohort
Matched cohort
0
0.25
0.5
0.75
1
1.25
1.5
Absolute standardized difference