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ORIGINAL ARTICLE

The effects of intraoperative ICG fluorescence angiography in laparoscopic low anterior resection: a propensity score-matched study

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Abstract

Background It remains unclear whether indocyanine green (ICG) angiography could reduce the rate of postoperative anastomotic leakage (AL) following rectal surgery. The aim was to determine whether intraoperative ICG angiography could decrease symptomatic AL following laparoscopic low anterior resection (LAR).

Methods This is a retrospective study of 149 patients with rectal cancer who underwent laparoscopic LAR at a single institution. Propensity score matching (PSM) was employed to compare groups with and without ICG angiography.

Results Before PSM, the symptomatic AL rate was 10.4% (5/48) in patients with ICG angiography, compared with 6.9% (7/101) in cases without ICG angiography ($P=0.52$). In patients with ICG angiography, poor perfusion of the proximal colon judged by ICG angiography led to additional colon resection in 27.1% (13/48). Symptomatic AL occurred in 30.8% (4/13) of the patients who had revision of the transection site, whereas it occurred in only 2.9% (1/35) of the patients who did not need revision of the transection site ($P=0.015$). After PSM, the symptomatic AL rate was 8.8% (3/34) in patients with ICG angiography, compared with 14.7% (5/34) in cases without ICG angiography ($P=0.71$). In univariate analysis, high BMI, preoperative chemotherapy, and lateral lymph node dissection were significantly associated with symptomatic AL. Multivariate analysis indicated that only lateral lymph node dissection remained significantly associated with AL (odds ratio, 10.05; 95% confidence interval, 1.75–58.61; $P=0.011$).

Conclusions Intraoperative ICG angiography is useful for prediction of AL following laparoscopic LAR.

Keywords Rectal cancer · ICG angiography · Anastomotic leakage · Low anterior resection · A propensity score-matched study

Introduction

Postoperative anastomotic leakage (AL) is the most serious complication associated with colorectal surgery; it can cause morbidity, mortality, and result in a poor prognosis [1, 2]. Despite continuous improvements in surgical procedure and perioperative management, AL still occurs in 3–19% of cases of low anterior resection (LAR); the most commonly reported rates are between 10–13% from large population databases [3–7]. Although the factors associated with AL are multifactorial, insufficient blood perfusion is generally considered as one of the main causes of AL [8–10]. Traditional techniques used to evaluate intestinal perfusion include gross examination, Doppler ultrasound, and oxygen spectroscopy. Near-infrared (NIR) system with indocyanine green (ICG) fluorescence

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angiography has been recently developed for intraoperative, real-time evaluation of intestinal perfusion. This technology is reasonably priced, takes little time, and is easily reproducible. Intraoperative ICG fluorescence imaging is beneficial in several surgical fields (e.g., hepatobiliary, foregut, transplant, and plastic surgeries) [11–14]; however, its possibility to improve postoperative outcomes in colorectal surgery has not been fully elucidated yet. Although some recent studies have reported that ICG angiography is a potentially promising method to assess intestinal perfusion, most of these studies had limitations such as a small population, or the absence of a control group and none was a randomized controlled trial. Therefore, it remains unclear whether ICG angiography can decrease the rate of AL following LAR.

The aim of the present study was to determine whether the use of intraoperative ICG angiography could decrease symptomatic AL at a single institution where a standardized laparoscopic LAR with double stapling technique (DST) anastomosis was done. Propensity score-matched analysis was employed to compare groups of patients with and without intraoperative use of ICG angiography. Furthermore, we also investigated the risk factors of symptomatic AL in 149 rectal cancer patients operated between 2009 and 2016 by univariate and multivariate analyses. As far as we know, the present study is the first to investigate the effect of ICG angiography in laparoscopic LAR with DST anastomosis using a propensity score-matched analysis.

Materials and methods

Study population

Consecutive 155 rectal cancer patients underwent elective laparoscopic LAR with DST anastomosis in our institution between January 2009 and May 2016. Regarding the tumor location, "upper rectum" was defined between the inferior border of the second sacral vertebra and the peritoneal reflection, whereas "lower rectum" was defined between the peritoneal reflection and upper border of the anal canal [15]. To investigate the pure risk factors of AL, cases with a protective stoma were excluded. In detail, six cases treated by preoperative chemoradiotherapy were not included, because a protective stoma was inevitably constructed. Finally, a total of 149 rectal cancer patients were included in this study. Intraoperative ICG angiography had been performed in consecutive 48 patients from August 2013. The institutional review board of Kyoto University approved this study. This study is registered in UMIN Clinical Trials Registry, number UMIN000009731. Patients with allergic sensitivity to iodine were excluded.

Procedure

Surgical procedures were done by board-certified laparoscopic surgeons [16]. The laparoscopic surgical technique was standardized and essentially unchanged between 2009 and 2016, as described previously [17–19]. After clamping distally to the tumor, the rectum was divided by a linear stapler with enough precompression time before stapler firing [19]. In cases of intraoperative ICG angiography, we intravenously injected ICG (5 mg) after dividing the colonic mesentery at the planned transection site, and then the blood perfusion of the proximal colon was evaluated using a NIR camera system (PDE-neo System; Hamamatsu Photonics K.K., Hamamatsu, Japan), as described previously [20, 21]. When the fluorescence intensity of the intestine at the initially planned transection site was judged to be poor, the transection site was moved to a more proximal side judged to be well-perfused under ICG fluorescence. Intracorporeally, end-to-end DST anastomosis was performed.

Anastomotic leakage (AL)

AL was defined as disruption of the anastomosis which was diagnosed by radiographic examination, digital examination, and sigmoidoscopy, as previously described [19]. Based on the grading system [22], AL was classified into three grades: grade A did not require any intervention; grade B required active intervention; and grade C required reoperation. Only symptomatic AL (grade B and C) was analyzed, because routine contrast enemas to detect asymptomatic AL (grade A) were not done.

Statistical analysis

Categorical and continuous variables were analyzed with Fisher's exact test and Mann–Whitney *U* test, respectively. To minimize the effect of potential confounders on selection bias, a propensity score matching analysis was used. Pairs were formed, such that matched subjects had similar values of the propensity scores. Therefore, for a subject in a certain group, all the subjects from the other group whose propensity score lay within a specified distance (caliper distance) were identified. Nearest neighbor matching was performed at a 1:1 fixed ratio. We chose a caliper distance of 0.20 of the standard deviation of the logit of the propensity score. Patients were matched between the two groups concerning patient-, tumor-, and surgery-related characteristics listed in Table 1.

To identify the independent risk factor for AL, multivariate logistic regression analysis was performed using the factors with a P value of < 0.10. All analyses were two-sided,

Table 1 Comparison of characteristics before and after propensity score matching

Characteristic	Before matching			After matching		
	Non-ICG (*n* = 101)	ICG (*n* = 48)	*P* value	Non-ICG (*n* = 34)	ICG (*n* = 34)	*P* value
1. Patient-related						
Age (years, median)	67	66	0.53	66.5	67.5	0.7
Sex, *n* (%)						
Male	70 (69.3)	31 (64.6)	0.58	24 (70.6)	20 (58.8)	0.44
Female	31 (30.7)	17 (35.4)		10 (29.4)	14 (41.2)	
BMI (kg/m^2, median)	21.4	22.5	0.13	22.5	22.2	0.8
Albumin (g/dL, median)	4.1	4.1	0.21	4.1	4.1	0.64
Hemoglobin (g/dL, median)	13.2	13.3	0.53	12.9	13.3	0.51
Diabetes mellitus, *n* (%)						
No	89 (88.1)	41 (85.4)	0.61	30 (88.2)	30 (88.2)	1
Yes	12 (11.9)	7 (14.6)		4 (11.8)	4 (11.8)	
Anticoagulation therapy, *n* (%)						
No	85 (84.1)	40 (83.3)	1	26 (76.5)	29 (85.3)	0.54
Yes	16 (15.8)	8 (16.7)		8 (23.5)	5 (14.7)	
Steroid therapy, *n* (%)						
No	99 (98)	44 (91.7)	0.085	32 (94.1)	33 (97.1)	1
Yes	2 (2)	4 (8.3)		2 (6)	1 (3)	
Smoking (Brinkman index), *n* (%)						
< 400	72 (71.3)	33 (68.8)	0.85	20 (58.8)	25 (73.5)	0.31
≥ 400	29 (28.7)	15 (31.2)		14 (41.2)	9 (26.5)	
2. Tumor-related						
Preoperative chemotherapy, *n* (%)						
No	79 (78.2)	43 (89.6)	0.11	29 (85.3)	30 (88.2)	1
Yes	22 (22.8)	5 (10.4)		5 (14.7)	4 (11.8)	
Location, *n* (%)						
Ra	65 (64.4)	38 (79.2)	0.88	25 (73.5)	26 (76.5)	1
Rb	36 (35.6)	10 (20.8)		9 (26.5)	8 (23.5)	
UICC-TNM stage, *n* (%)						
0, I, II	75 (74.3)	33 (68.8)	0.56	25 (73.5)	23 (67.6)	0.61
III, IV	26 (25.7)	15 (31.3)		9 (26.5)	11 (32.4)	
Tumor size (mm, median), *n* (%)						
< 50	77 (76.2)	33 (68.8)	0.42	21 (61.8)	24 (70.6)	0.61
≥ 50	24 (23.8)	15 (31.3)		13 (38.2)	10 (29.4)	
3. Surgery-related						
Operation time (min, median)	294	317.5	0.049	313	313	0.72
Intraoperative bleeding (mL, median)	30	0	0.001	22.5	7.5	0.24
Ligation of IMA, *n* (%)						
High	95 (94.1)	45 (93.8)	1	32 (94.1)	32 (94.1)	1
Low	6 (5.9)	3 (6.3)		2 (5.9)	2 (5.9)	
Number of cartridge for rectal transection, *n* (%)						
1,2	96 (95)	44 (91.7)	0.47	32 (94.1)	32 (94.1)	1
≥ 3	5 (5)	4 (8.3)		2 (5.9)	2 (5.9)	
Precompression before stapler firing, *n* (%)						
No	0 (0)	0 (0)	1	0 (0)	0 (0)	1
Yes	101 (100)	48 (100)		34 (100)	34 (100)	
Placement of a transanal tube, *n* (%)						
No	3 (3)	2 (4.2)	0.65	1 (2.9)	1 (2.9)	1
Yes	98 (97)	46 (95.8)		33 (97.1)	33 (97.1)	

Table 1 (continued)

Characteristic	Before matching			After matching		
	Non-ICG ($n = 101$)	ICG ($n = 48$)	P value	Non-ICG ($n = 34$)	ICG ($n = 34$)	P value
Placement of a pelvic drain, n (%)						
No	1 (1)	1 (2.1)	0.54	0 (0)	0 (0)	1
Yes	100 (99)	47 (97.9)		34 (100)	34 (100)	
Anastomosis level from anal verge (cm, median)	4	5	0.03	5	5	0.79
Lateral lymph node dissection, n (%)						
No	96 (95)	45 (93.8)	0.71	32 (94.1)	33 (97.1)	1
Yes	5 (5)	3 (6.3)		2 (5.9)	1 (2.9)	

and values of $P < 0.05$ were considered statistically significant. All statistical analyses were conducted using the JMP Pro software (SAS Institute Inc, NC).

Results

Patients' population

From January 2009 to May 2016, 149 consecutive rectal cancer patients (101 male and 48 female) who underwent laparoscopic LAR with DST anastomosis were investigated in this study. In all cases, the tumor location was within 10 cm from the anal verge. The upper rectum was 103 cases, while the lower rectum was 46 cases. Intraoperative ICG fluorescence angiography was introduced to evaluate intestinal perfusion from August 2013. Intraoperative ICG angiography was performed in 48 patients (32.2%; ICG group) and not performed in the remaining 101 patients (67.8%; non-ICG group) (Table 1). No adverse events related to ICG angiography were observed.

The overall rate of symptomatic AL (grades B and C) across both groups was 8.1% (12 of 149) (Table 2). The rate was 10.4% (5 of 48) in the ICG group, compared with 6.9% (7 of 101) in the non-ICG group ($P = 0.52$). Symptomatic AL needing reoperation (grade C) occurred in 4.7% of all patients (7 of 149), 8.3% of the ICG group (4 of 48), and 3.0% of the non-ICG group (3 of 101).

In 13 patients (13/48: 27.1%) of the ICG group, the surgical team changed the initially planned transection site of the proximal colon due to the "hypoperfused" appearance on ICG fluorescence. The median length of additionally resected bowel was 2 cm (range, 1–6.5 cm). Symptomatic AL occurred in four (4/13: 30.8%) of the patients who had a revision of the transection site based on ICG angiography, while it occurred in one case (1/35: 2.9%) of the patients who did not need a revision: the difference in the AL rate between these two groups was statistically significant (30.8% vs. 2.9%; $P = 0.015$). Table 3 shows the postoperative complications. The frequency of all other complications did not differ between the two groups. No fatal event was observed in either group.

Propensity score matching analysis

There was a certain amount of bias between the ICG group and non-ICG group. In fact, clinical factors associated with intraoperative ICG angiography included operation time, intraoperative bleeding and level of anastomosis (Table 1). Therefore, a propensity score was calculated based on identified characteristics that were not distributed equally between the two groups. The matching criteria included patient-related parameters (i.e., sex, age, body mass index (BMI), serum levels of albumin and hemoglobin, anticoagulation therapy, steroid therapy, diabetes mellitus, and smoking), tumor-related parameters (i.e., tumor location, tumor size, TNM stage and preoperative chemotherapy)

Table 2 Comparison of anastomotic leakage before and after propensity score matching

Characteristic	Before matching			After matching		
	Non-ICG ($n = 101$)	ICG ($n = 48$)	P value	Non-ICG ($n = 34$)	ICG ($n = 34$)	P value
Anastomotic leakage, n (%)						
Grade B + C	7 (6.9%)	5 (10.4%)	0.52	5 (14.7%)	3 (8.8%)	0.71
Grade C	3 (3.0%)	4 (8.3%)	0.21	2 (5.9%)	2 (5.9%)	1
Emergent surgery	1 (1.0%)	1 (2.0%)	0.54	1 (2.9%)	0 (0%)	1

Table 3 Comparison of postoperative complications before and after propensity score matching

Characteristic	Before matching			After matching		
	Non-ICG ($n=101$)	ICG ($n=48$)	*P* value	Non-ICG ($n=34$)	ICG ($n=34$)	*P* value
No complication, n (%)	76 (75.2%)	37 (77.1%)	0.84	23 (67.68%)	27 (79.4%)	0.41
Grade II *n* (%)						
Urinary infection	3 (3.0%)	1 (2.1%)	1	1 (2.9%)	1 (2.9%)	1
Pneumonia	4 (4.0%)	2 (4.2%)	1	3 (8.8%)	1 (2.9%)	0.61
Ileus	4 (4.0%)	0 (0%)	0.31	1 (2.9%)	0 (0%)	1
Wound infection	2 (2.0%)	1 (2.1%)	1	1 (2.9%)	1 (2.9%)	1
Intraabdominal abscess	0 (0%)	1 (2.1%)	0.32	0 (0%)	0 (0%)	1
Colitis	2 (2.0%)	0 (0%)	1	0 (0%)	0 (0%)	1
Anastomotic leakage	4 (4.0%)	1 (2.1%)	1	3 (8.8%)	1 (2.9%)	0.61
Grade III, *n* (%)						
Bleeding at anastomotic site	1 (1.0%)	1 (2.1%)	0.54	0 (0%)	1 (2.9%)	1
Ileus	1 (1.0%)	0 (0%)	1	0 (0%)	0 (0%)	1
Urethral stricture	1 (1.0%)	0 (0%)	1	0 (0%)	0 (0%)	1
Anastomotic leakage	3 (3.0%)	4 (8.3%)	0.21	2 (5.9%)	2 (5.9%)	1

and surgery-related parameters (i.e., intraoperative bleeding, operation time, level of inferior mesenteric artery (IMA) ligation, number of cartridge used for rectal transection, precompression before stapler firing, transanal tube, pelvic drain, lateral lymph node dissection, and the anastomotic level from anal verge). By propensity score matching (PSM), 34 cases were selected in each group (Table 1). After PSM, the rate of symptomatic AL (grades B and C) in the ICG group and non-ICG group was 8.8% (3 of 34) and 14.7% (5 of 34), respectively ($P=0.71$) (Table 2). ICG angiography reduced the rate of AL by 5.9% compared with the control (non-ICG) group, although not statistically significant.

The incidence rates of symptomatic AL needing reoperation (grade C) were comparable in the ICG group and non-ICG group (5.9% vs. 5.9%; $P=1$). There were no significant differences in other complications of grade II or higher between the two groups (Table 3).

Risk factors for symptomatic AL

Next, we investigated the risk factors for symptomatic AL in this series. Univariate analysis indicated that symptomatic AL was significantly associated with high BMI (≥ 25), preoperative chemotherapy, and lateral lymph node dissection (Table 4). Moreover, there was a tendency for the level of anastomosis within 30 mm of the anal verge to increase AL, with *P* value less than 0.10. The use of ICG angiography was neither positively nor negatively associated with symptomatic AL. There were no significant differences in terms of age, sex, serum levels of albumin and hemoglobin, tumor location, tumor size, TNM stage, level of IMA ligation, intraoperative bleeding, number of cartridges used for rectal division, precompression before stapler firing, transanal tube, or pelvic drain.

In the multivariate analysis including factors with a *P* value of ≤ 0.10, only lateral lymph node dissection remained significantly associated with AL [Table 5; odds ratio (OR), 10.05; 95% confidence interval (CI), 1.75–58.61; $P=0.011$].

Discussion

There is a controversy regarding whether intraoperative ICG angiography can reduce the AL rate following colorectal surgery [23]. Kudszus et al. reported that ICG angiography resulted in a proximal change of the initially planned transection site in 13.9%, and that ICG angiography could reduce the AL rate by 4% compared with a control group (7.5% vs. 3.5%) in a case-matched retrospective study [24]. Although this study had a relatively large sample size ($n=402$), heterogeneous operative methods (including right and left colectomy) were included together upon analysis. In a retrospective study of robotic-assisted rectal surgery, Jafari et al. reported that ICG angiography resulted in a proximal change of the initially planned transection site in 19%, and that the AL rate was decreased to 6% by ICG angiography compared with 18% in a control group [25]. This study had a relatively small sample size ($n=38$) and included about 75% cases with a protective diverting stoma. Kim et al. recently reported that ICG angiography significantly reduced the AL rate compared to a control group (0.6% vs. 5.2%) in a retrospective observational study of robotic-assisted rectal surgery [26]. Although this study had a relatively large sample size ($n=657$), there were some significant differences

Table 4 Univariate analysis of patient-, tumor-, surgery-related factors

Variable	Patients with AL		*P* value
	n	%	
Age, years			0.76
< 70	7/94	7.4	
≥ 70	5/55	9.1	
Sex			0.33
Male	10/101	9.9	
Female	2/48	4.2	
BMI, kg/m^2			0.017
< 25	7/127	5.5	
≥ 25	5/22	22.7	
Albumin, g/dL			1
< 3.5	0/9	0	
≥ 3.5	12/140	8.6	
Hemoglobin, g/dL			1
< 11	1/17	5.9	
≥ 11	11/132	8.3	
Location			0.19
Upper	6/103	5.8	
Lower	6/46	13	
Tumor size, cm			0.3
< 5.0	7/110	6.4	
≥ 5.0	5/39	12.8	
UICC-TNM stage			1
0, I, II	9/108	8.3	
III, IV	3/41	7.3	
Preoperative chemotherapy			0.042
No	7/122	5.7	
Yes	5/27	18.5	
Intraoperative bleeding, mL			0.39
< 100	9/127	7.1	
≥ 100	3/22	13.6	
Ligation of IMA			1
High ligation	12/140	8.6	
Low ligation	0/9	0	
Lateral lymph node dissection			0.0015
No	8/141	5.7	
Yes	4/8	50	
Anastomosis level from anal verge, mm			0.09
< 30	4/23	17.4	
≥ 30	8/126	6.3	
Number of cartridges for rectal transection			0.54
1, 2	11/140	7.9	
≥ 3	1/9	11.1	
Precompression before stapler firings			1
No	0/0	0	
Yes	12/149	8.1	
Placement of a pelvic drain			1
No	0/2	0	
Yes	12/147	8.2	
Placement of a transanal tube			1
No	0/5	0	
Yes	12/144	8.3	
ICG angiography			0.52
No	7/101	6.9	
Yes	5/48	10.4	

between the ICG group and non-ICG group in the clinicopathological features, and a protective diverting stoma was constructed in about 45% cases. In a case-matched retrospective study of laparoscopic LAR, Boni et al. reported that ICG angiography resulted in a proximal change of the initially planned transection site in 4.7%, and that the AL rate was decreased to 0% by ICG angiography compared to 5% in a control group, although the differences were not statistically significant [27]. This study also had a relatively small sample size ($n = 80$) with an inherent selection bias, and a protective diverting stoma was constructed in all cases. Kin et al. have recently reported the controversial results on the beneficial effect of ICG angiography in a case-matched retrospective study [28]. In their experience, the proximal resection site was changed in 4.6% by ICG angiography, but ICG angiography could not reduce the AL rate compared to a historical control (7.5% vs. 6.4%; $P = 0.64$). Although this study had a relatively large sample size ($n = 346$), several operative methods including left colectomy and sigmoidectomy were included together upon analysis. Until now, there are a few reports to investigate the effectiveness of ICG angiography during LAR for rectal cancer. The AL rate in LAR is higher than that of other colorectal surgeries and the rate of constructing a protective ileostomy is commonly high. Creation of a protective ileostomy is generally considered to decrease the severe complications that AL can evoke. In the present study, six cases with a protective ileostomy (i.e., three cases with ICG angiography and three cases without ICG angiography) were excluded from the analysis to investigate the pure effect of ICG angiography, because a diverting stoma could be constructed in high-risk patients. In addition, the operative techniques and the surgeons were identical in both groups, which might have decreased the effects of other technical factors related to AL. The present study demonstrates that, after PSM of patient-, tumor-, and surgery-related parameters, the use of ICG angiography did reduce the AL rate by 5.9% compared with a control group (8.8% vs. 14.7%; Table 2). In addition, the use of ICG angiography did altered the proximal transection site in 27.1%

Table 5 Multivariate analysis of risk factors associated with anastomotic leakage

Variables	OR	95% CI	*P* value
BMI (≥ 25)	4.13	0.95–16.91	0.058
Preoperative chemotherapy (Yes)	2.64	0.60–10.67	0.189
Lateral lymph node dissection (Yes)	10.05	1.75–58.61	0.011
Anastomosis level from anal verge (< 30 mm)	1.91	0.33–8.85	0.439

(13/48) due to the appearance on the ICG angiography. Importantly, the AL rate of the patients with good perfusion who did not need a revision of the transection site was very low (1/35: 2.9%), whereas that of the patients with poor perfusion who needed a revision was high (4/13: 30.8%) ($P = 0.015$). These results might indicate that creation of a protective stoma should be taken into consideration in the patients who are judged to need a revision of the transection site. An important observation in the present study is that the hypoperfused intestine visualized with ICG angiography may appear to be normal in white light mode, which indicates that this technology could enable us to detect the poor-perfused areas more precisely. We previously reported that the quantitative evaluation of ICG fluorescence was useful in determining the transection site of the proximal colon during laparoscopic colorectal surgery, and that Fmax (fluorescence difference between maximum and baseline) was the most indicative for AL among several parameters [21]. Therefore, we have investigated the utility of quantitative evaluation in this series, and found that Fmax at the transection site was significantly lower in the patients who had a revision of the transection site than in those who did not need a revision (median, 51.7 arbitrary units (AU) vs. 82.0 AU, respectively; $P = 0.0002$, Mann–Whitney *U* test) (Supplementary Fig. 1). Considering the difference of the AL rates between these 2 groups (i.e., 30.8% vs. 2.9%), quantitative evaluation could be superior to surgeon's visual interpretation. Although 4 of the 13 patients who had revision of the transection site still developed AL, AL might have been avoided by additional bowel resections of the proximal colon. Furthermore, we have evaluated the relationship between AL and Fmax, and found that, with a Fmax cutoff value of 52.0 AU, the sensitivity and specificity for the prediction of AL were 100% (5/5) and 83.7% (36/43), respectively (Supplementary Table 1). Re-evaluation of the more proximal portion by ICG angiography may have revealed inadequate perfusion, which was not done in this series. Evaluation of the blood supply of the rectal stump is also important.

Although several factors, including sex, BMI, preoperative chemoradiotherapy, level of anastomosis, tumor size, multiple stapler firings, operation time, protective diverting stoma, transanal tube and intestinal microbes, have been identified as possible causes of AL [3, 29–32], the complete pathogenesis is still unknown. Regarding technical factors, we previously reported that precompression before stapler firings is essential to obtain adequate staple formation in animal models [33–35] as well as in a clinical setting [19]. With the exception of surgery-related anastomotic failure, one of the main factors related to AL is poor intestinal perfusion. Especially, with the progressive increase in the aging population, the number of rectal cancer patients with cardiovascular vascular diseases is on the increase in clinical practice. We have recently reported that factors related to poor intestinal perfusion using ICG angiography include the use of anticoagulation drugs for cardiovascular diseases, in which the blood vessels throughout the body are damaged by arteriosclerosis [20]. In this study, multivariate analysis indicated lateral lymph node dissection as an independent risk factor of symptomatic AL following laparoscopic LAR (Table 5; $P = 0.011$). In our institution, laparoscopic total mesorectal excision (TME) with lateral lymph node dissection has been selectively performed to the rectal cancer patients with enlarged lateral pelvic lymph nodes (larger than 5 mm in diameter on MRI imaging). The learning curve of the surgical procedure for lateral lymph node dissection may possibly play a role in AL.

This study has some limitations. One limitation is its retrospective nature. The non-ICG group was drawn from the period of time before this technology was introduced. Another limitation is the limited number of patients. In addition, the assessment of ICG fluorescence intensity was subjective, and surgeon's visual interpretation for ICG fluorescence is sometimes difficult to judge whether intestinal perfusion is sufficient. Quantitative evaluation for ICG fluorescence could make assessment of anastomotic perfusion to be tailored for an individual patient. Owing to the multifactorial nature of AL, it is difficult to draw certain conclusions about the usefulness of ICG angiography. Further studies, including larger, multi-institutional, prospective, randomized controlled trials, are required to verify whether ICG angiography is beneficial in terms of causing a reduction in the rate of AL.

This is the first study to evaluate the effect of ICG angiography in laparoscopic LAR with DST anastomosis using a propensity score-matched analysis. From the data of this study, we conclude the following points. First, a revision of the transection site based on the intraoperative ICG angiography did not completely prevent AL. Next, hypoperfusion appearance was one of risk factors for AL. Intraoperative ICG angiography is useful for prediction of AL following laparoscopic LAR. Further studies are required to confirm the usefulness of intraoperative ICG angiography for AL reduction.

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Compliance with ethical standards

Conflict of interest Drs. Toshiaki Wada, Kenji Kawada, Nobuaki Hoshino, Susumu Inamoto, Mami Yoshitomi, Koya Hida, and Yoshiharu Sakai have no conflicts of interest or financial ties to disclose.

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 and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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