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Time required for indocyanine green fluorescence emission for evaluating bowel perfusion in left-sided colon and rectal cancer surgery

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Abstract

Background Indocyanine green fluorescence imaging (ICG-FI) has been reported to be useful in reducing the incidence of anastomotic leakage (AL) in colectomy. This study aimed to investigate the correlation between the required time for ICG fluorescence emission and AL in left-sided colon and rectal cancer surgery using the double-stapling technique (DST) anastomosis.

Methods This retrospective study included 217 patients with colorectal cancer who underwent left-sided colon and rectal surgery using ICG-FI-based perfusion assessment at our department between November 2018 and July 2022. We recorded the time required to achieve maximum fluorescence emission after ICG systemic injection and assessed its correlation with the occurrence of AL.

Results Among 217 patients, AL occurred in 21 patients (9.7%). The median time from ICG administration to maximum fluorescence emission was 32 s (range 25–58 s) in the AL group and 28 s (range 10–45 s) in the non-AL group ($p < 0.001$). The cut-off value for the presence of AL obtained from the ROC curve was 31 s. In 58 patients with a required time for ICG fluorescence of 31 s or longer, the following risk factors for AL were identified: low preoperative albumin [3.4 mg/dl (range 2.6–4.4) vs. 3.9 mg/dl (range 2.6–4.9), $p = 0.016$], absence of preoperative mechanical bowel preparation (53.8% vs. 91.1%, $p = 0.005$), obstructive tumor (61.5% vs. 17.8%, $p = 0.004$), and larger tumor diameter [65 mm (range 40–90) vs. 35 mm (range 4.0–100), $p < 0.001$].

Conclusion The time required for ICG fluorescence emission was associated with AL.

Keywords ICG · Indocyanine green · Colorectal cancer · Anastomotic leakage · Double stapling technique · Bowel perfusion

Anastomotic leakage (AL) after colorectal cancer surgery, one of the most feared postoperative complications, can increase the length of hospital stay, local recurrence rate, and mortality rates [1–3]. Previous studies have identified risk factors for AL. Among the various factors, anastomotic perfusion has been recognized as one of the most important [4–11]. Various subjective methods for assessing anastomotic perfusion have been developed, including bowel serosal color, palpable pulsation, peristaltic movement, and active bleeding from marginal arteries [12–15]. The main drawback of such subjective assessments is their low-quality metric, with bias in each surgeon's perception. In comparison, the assessment of anastomotic perfusion using indocyanine green fluorescence imaging (ICG-FI) has been reported to be potentially more useful and reproducible in recent years, owing to its clear-cut representation and affordability [16–24]. However, it is essential to note that ICG-FI is still a subjective evaluation based on the perception of the operating surgeon, which introduces potential bias in the assessment.

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ICG is a fluorophore that responds to near-infrared (NIR) irradiation by absorbing light from 790 to 805 nm and remitting it at an excitation wavelength of 835 nm [25]. NIR fluorescence technology with ICG is a safe, simple, and cost-effective method to assess bowel perfusion [20, 21, 24]. Although several studies have reported that ICG fluorescence prevents AL by changing the transection line, evaluation criteria, and methodology using ICG-FI have not yet been established in clinical settings [16–24]. AL can occur even in patients with good bowel perfusion.

Quantitative assessment using ICG-FI currently lacks widespread adoption, and multiple authors have reported the need for a quantitative and stable metric. D'Urso et al. reported that fluorescence-based enhanced reality (FLER) is helpful in assessing bowel perfusion [26]. FLER is a software-based analysis system that displays the dynamic evolution of fluorescent signals. Although useful, it is not widely accepted in routine clinical practice because of the need for special machinery and the complexity of the procedure.

A previous study configured additional transection criteria of perfusion times of > 60 s [20]. Therefore, we focused on the time required for ICG fluorescence to assess anastomotic perfusion in a clinical setting. This study aimed to investigate the correlation between the required time for ICG fluorescence emission and AL in left-sided colon and rectal cancer surgery using the double-stapling technique (DST) anastomosis.

Patients and methods

Study design and patients

We retrospectively analyzed the database of our hospital. The inclusion criteria were as follows: patients with colorectal cancer; surgery for left-sided colon and rectal surgery, including open and minimally invasive surgery (laparoscopic/robotic-assisted); and DST anastomosis with ICG-FI guidance between November 2018 and July 2022. The exclusion criteria were simultaneous resection of other organs and a history of allergic reactions to ICG or iodine. Patients who underwent combined resection of other organs owing to direct invasion were included in the study (Fig. 1). This study was approved by the Institutional Review Board of the Ageo Central General Hospital (Approval No.: 1062). All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the 1964 Declaration of Helsinki and its later versions. The requirement for informed consent was waived owing to the retrospective observational design.

Study endpoints

The primary endpoint was the correlation between the time required for ICG fluorescence emission and AL occurrence. The secondary endpoint was to determine the ICG emission time after which the risk of AL was higher and to identify

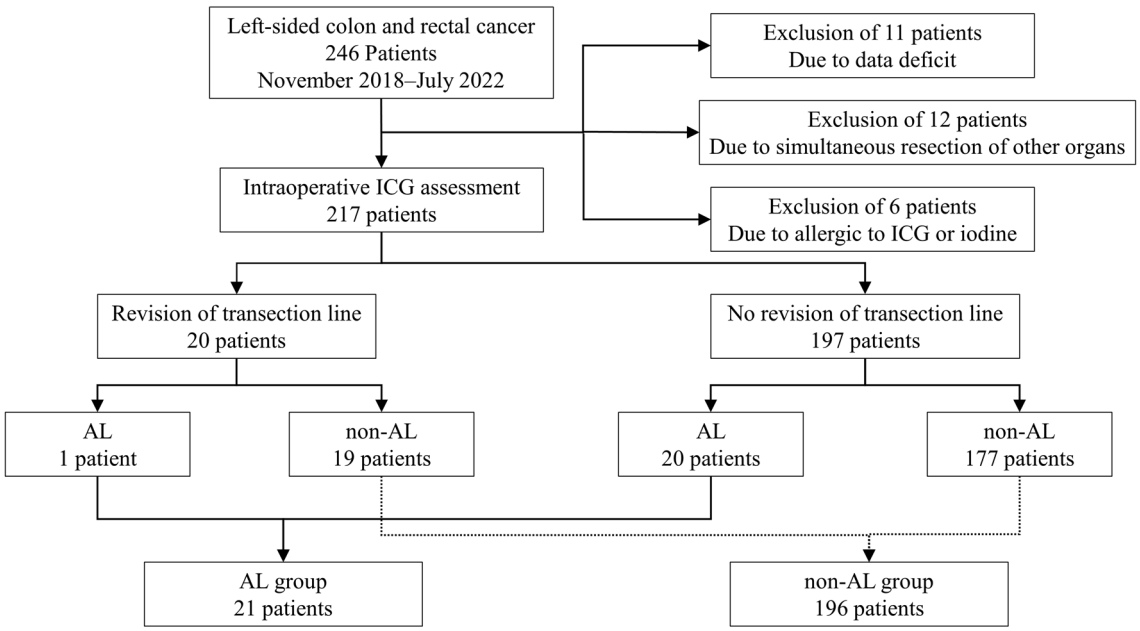

Fig. 1 Flow diagram of patients in this study

the risk factors for AL in patients with ICG fluorescence times exceeding this threshold.

AL was defined as any disruption of the anastomosis confirmed by computed tomography (CT) and/or water-soluble contrast enema. In all patients with AL, CT was performed after the patients showed any clinical symptoms, such as fever, abdominal pain, or the presence of stool-containing ascites through the drainage tube. Asymptomatic AL was not included because routine CT scans and contrast enemas were not performed postoperatively at our institution. The severity of complications was classified according to the Clavien–Dindo [CD] classification.

Surgical procedure and perfusion assessment

Except for patients with risk for bowel obstruction, all patients underwent preoperative mechanical bowel preparation. After arterial dissection, total mesorectal or complete mesocolon excision was performed, and the distal end of the rectum was transected using a linear stapler. The splenic flexure was mobilized only when excessive tension was applied to the anastomotic site. The specimen was extracted through an umbilical port or a laparotomy incision. The transection line of the proximal colon was determined by dissecting the mesentery and ligating the marginal artery and vein extracorporeally. Outside the abdomen, the colon was placed naturally to prevent tension on the vessels. ICG (12.5 mg per body: 25 mg of ICG dissolved in 10 ml of water, 5 ml was used) was injected through a peripheral venous catheter, followed by a 20 ml bolus of saline.

After ICG injection, the IR mode of either the da Vinci Xi system (Firefly, Intuitive Surgical, Sunnyvale, CA, USA), VISERA ELITE II (OLYMPUS, Shinjuku, Japan) or the Image1 S System (KARL STORZ SE & Co. KG, Tuttlingen, Germany) was used to visualize the watershed between the perfused bowel and ICG fluorescence emission in the proximal colon and non-perfused bowel in the distal colon. The camera was fixed at approximately 5 cm from the bowel, and the lights in the operating room were completely turned off to exclude external light. The time was recorded from the point of a bolus injection of saline after ICG administration to the point when perfusion of the proximal colon was considered at maximum by the two surgeons. The maximum was defined as the point at which the vascular perfusion of the proximal colon was well visualized and would not lighten any further. The number of the seconds elapsed at the point of reaching the maximum was recorded, followed by a brief observation period to confirm no further increase in brightness.

If ICG fluorescence was poorly emitted in the planned resection site, the transection line of the proximal colon was changed to the physiological watershed border (Fig. 2). Anastomosis was performed with DST using a circular stapler (25 mm ILS or Powered Circular, Ethicon Endo-Surgery, OH, USA). After the completion of anastomosis, a standardized air-leak test was performed using a colonoscopy. An ileostomy or transanal drainage tube was placed if the anastomotic site was close to the anal verge or if the patient received preoperative chemotherapy. A pelvic drainage tube was placed in all the patients.

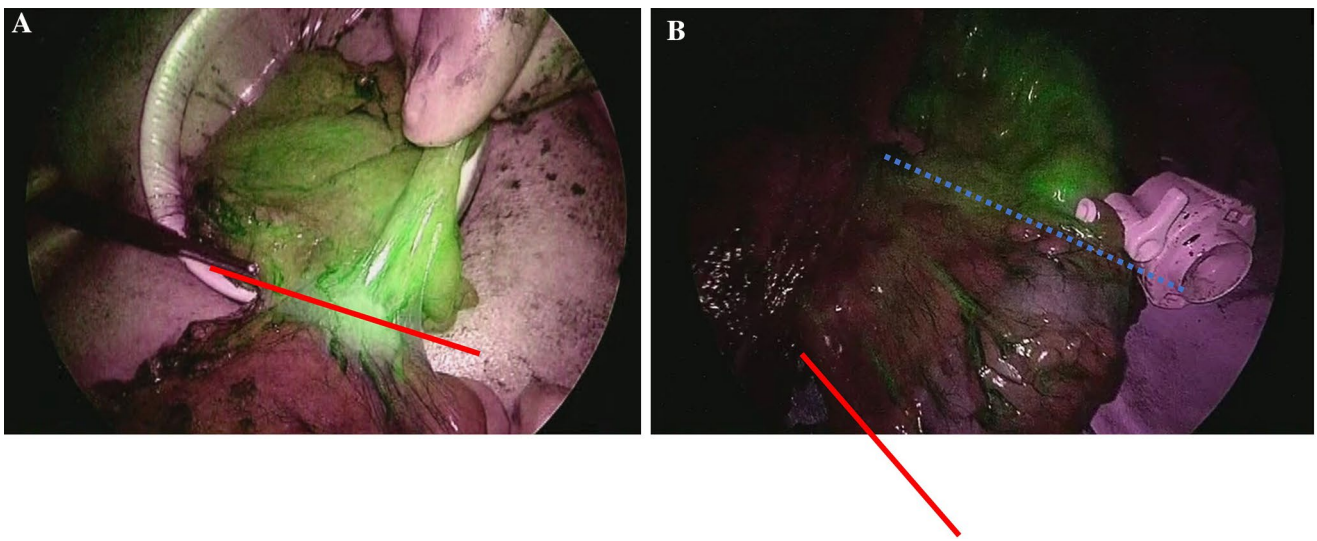

Fig. 2 Intra-operative findings of ICG fluorescence demarcation. After dissecting the mesentery and ligating the marginal arteries and veins, ICG was injected intravenously. The red line represents the planned transection. We recorded a required time to fluorescence emission at maximum in areas with good vascular perfusion after ICG systemic injection. **A** Fluorescence perfusion with ICG-FI corresponded to the planned transection line. **B** The transection line was changed to a more proximal site (blue line) based on fluorescence perfusion using ICG-FI

Postoperative care

The postoperative diet was restarted from lunch on the day after surgery. Blood test data were recorded on postoperative days (POD) #1 and 4. If the blood test data on POD #4 were satisfactory, the drainage tube was removed after confirmation of stool passage.

Statistical analysis

Categorical variables are reported as numbers and percentages, and continuous variables are reported as medians and ranges. The chi-square test or Fisher's exact test was used to compare categorical variables between the two groups, and the Wilcoxon rank-sum test was used to compare continuous variables. Differences were considered statistically significant at two-tailed $p < 0.05$. A receiver operating characteristic (ROC) curve was used to identify the cut-off for the incidence of AL using the time required for perfusion fluorescence after ICG injection as a marker of sensitivity and specificity. Statistical analysis was performed using the JMP® software, version 16.1.0 (SAS Institute Inc., Cary, NC, USA).

Results

During the study period, 217 patients with left-sided colon and rectal cancer who underwent resection with DST anastomosis were analyzed. We classified all patients into two groups: the AL group ($n = 21$, 9.7%) and the non-AL group ($n = 196$, 90.3%). Patient and tumor characteristics are shown in Table 1.

An obstructive tumor was defined as the inability to pass through the endoscope preoperatively. Obstructive tumors were observed more frequently (47.6% vs. 25.5%; $p = 0.041$) in the AL group. The proportion of patients who underwent mechanical bowel preparation was lower (66.7% vs. 89.3%; $p = 0.01$) in the AL group. The tumor diameter was larger (60.0 mm vs. 40.0 mm; $p = 0.047$) in the AL group. Additionally, rectal cancer diagnoses were higher in the AL group ($p = 0.005$). The operative outcomes are summarized in Table 2. Operative time was longer in the AL group (383 vs. 275 min; $p = 0.003$). Of the 21 patients in the AL group, 3 required antibiotic treatment (CD grade II), 8 required exchange of drainage tubes (CD grade IIIa), and 10 required construction of ileostomy or colostomy (CD grade IIIb). No mortality was observed in this study.

The evaluation of proximal colon perfusion is presented in Table 3. The median time required for maximum perfusion fluorescence was significantly longer in the AL group [32 s (range 25–58 s)] than in the non-AL group [28 s (range 10–45 s)] ($p = 0.0002$). The cut-off value for the incidence of AL was determined using the ROC curve to be 31 s (AUC, 0.745). Additionally, 20 patients (9.2%) with poor fluorescence emission required revision of the transection line. Of these 20 patients, only one developed AL, whereas the remaining 19 did not.

Patient and tumor characteristics with ICG fluorescence times of ≥ 31 s are presented in Table 4. Compared with those in the non-AL group, patients in the AL group had a lower preoperative albumin level [3.4 mg/dl (range 2.6–4.4) vs. 3.9 mg/dl (range 2.6–4.9), $p = 0.016$], higher incidence of obstructive tumor (61.5% vs. 17.8%, $p = 0.004$), a lower rate of mechanical bowel preparation (53.8% vs. 91.1%; $p = 0.005$), and larger tumor diameter [65 mm (range 40–90) vs. 35 mm (range 4.0–100), $p < 0.001$].

Discussion

The present study revealed that the prolonged time required for maximum ICG fluorescence emission is associated with the incidence of AL. Recent studies have concluded that navigation using ICG-FI evaluation can assist in achieving a decrease in AL [16–24, 27]. However, to date, there is little consensus or recommendation focusing on the impact of the time required for ICG fluorescence visualization on AL. Our study addressed this clinical question in a user-friendly manner for colorectal surgeons worldwide. The main drawback of the present study was the subjective perception of the maximum emission by one or two surgeons. The main strength of the present study is that only affordable agents and settings were used in our ICG-FI method, which may provide more practicality compared to previous studies that used dedicated software or technicians [26, 27].

To prevent AL, precise assessment of bowel perfusion at the anastomotic site is crucial. Beyond traditional toolless methods of evaluating tissue perfusion, such as bowel serosal color, there are several machinery methods, such as Doppler ultrasound, transabdominal laser Doppler flowmetry, oxygen spectroscopy, and quantitative analysis using software [12–15]. However, these methods are not widely used because of the difficulty and complexity of procedures in routine clinical practice. ICG was introduced by Fox et al. in 1960 [25] and is currently used for various diagnostic indications, such as assessing perfusion in cardiothoracic, hepatobiliary, transplant, and plastic surgery. Both fluorescence imaging and ICG are considered feasible and safe [28–31]. This procedure is easy to apply with a simple procedure using a NIR camera system after ICG injection.

Previous studies have suggested that ICG fluorescence guidance leads to a change in the planned transection line and a reduction in AL [16–24]. In this study, the transection line was changed to a well-perfused area in 20 (9.2%) patients. Although it may have prevented 19 of these 20

Table 1 Patient and tumor characteristics

Variable	AL group ($N=21$)	Non-AL group ($N=196$)	p value
Sex, *n* (%)			0.81
Male	15 (71.4)	132 (67.3)	
Female	6 (28.6)	64 (32.7)	
Age (years)	70 (40–84)	72 (33–92)	0.38
BMI (kg/m^2)	21.5 (18.1–31.0)	23.0 (15.1–38.4)	0.3
ASA physical status			0.64
I	2 (9.5)	26 (13.3)	
II	15 (71.4)	147 (75.0)	
III	4 (19.0)	23 (11.7)	
Diabetes mellitus	7 (33.3)	35(17.9)	0.14
Preoperative albumin (g/dl)	3.8 (2.6–4.9)	3.9 (2.2–5.2)	0.31
Obstructive tumor	10 (47.6)	50 (25.5)	0.041*
Mechanical bowel preparation	14 (66.7)	175 (89.3)	0.01*
Tumor diameter (mm)	60.0 (8–90)	40.0 (4–110)	0.047*
UICC-TNM pStage			0.52
0–I	4 (19.0)	56 (28.6)	
II	7 (33.3)	51 (26.0)	
III	6 (28.6)	67 (34.2)	
IV	4 (19.0)	22 (11.2)	
Preoperative treatment			0.61
None	21 (100)	187 (95.4)	
Chemotherapy	0 (0)	9 (4.6)	
Location of the tumor, *n* (%)			0.005*
Sigmoid colon	5 (23.8)	86 (43.9)	
Rectalsigmoid colon	4 (19.0)	67 (34.2)	
Ra	11 (52.4)	34 (17.3)	
Rb	1 (4.8)	9 (4.6)	

The *Ra* rectum above the peritoneal reflection nearly corresponds to that between the superior and middle rectal valves. The *Rb* rectum below the peritoneal reflection nearly corresponds to that below the middle rectal valve

Values are presented as mean, median value (range), or number (%) of patients

*Statistically significant ($p < .05$)

patients from developing ALs, one patient in whom the transection line was changed and another 20 patients with acceptable perfusion emission who did not need plan revisions developed ALs. AL occurred even in patients who did not require plan revisions; thus, we focused on the time required for ICG fluorescence in areas with good vascular perfusion. The time required for perfusion fluorescence was significantly prolonged in the AL group. Although the median difference is only 4 s, if you actually measure the time, you will recognize a clear distinction between the non-AL and AL groups, including the time when the dye uptake begins. Although it may be challenging to fully implement it initially, regular time measurements make it easy to determine whether the time required for ICG fluorescence is faster or slower. Therefore, assessing bowel perfusion while measuring the time is highly beneficial. Furthermore, if the ICG fluorescence time exceeds 31 s, there could be a significant increase in the risk of AL.

Previous reports have identified various risk factors for AL other than anastomotic vascular perfusion, such as sex, tumor location, anastomotic tension, and preoperative chemoradiotherapy [4–11]. Thus, other factors may have contributed to AL in patients without plan revisions. We further investigated 58 patients with a time required for perfusion fluorescence of ≥ 31 s to identify risk factors for AL and found that low preoperative albumin level, tumor obstruction, and larger tumor diameter were significantly associated with AL. Although AL in these patients may be difficult to prevent, severe complications can be avoided by performing diverting ileostomy. Importantly, these four parameters (ICG perfusion time, albumin level, presence of tumor obstruction, and tumor diameter) can be determined

Table 2 Perioperative outcomes

Variable	AL group ($N=21$)	Non-AL group ($N=196$)	p value
Operative time (min)	383 (230–665)	275 (124–830)	0.003*
Blood loss (ml)	30 (8–220)	20 (3–1464)	0.25
Operative procedure, n (%)			0.13
Laparoscopic	11 (52.4)	140(71.4)	
Robot-assisted	8 (38.1)	44 (22.4)	
Open	2 (9.5)	12 (6.1)	
Vessel ligation level			1
High ligation of IMA	17 (81.0)	161 (82.1)	
LCA preservation	4 (19.0)	35 (17.9)	
Operative procedure, n (%)			0.005*
Sigmoidectomy	5 (23.8)	86 (43.9)	
High anterior resection	1 (4.8)	44 (22.4)	
Low anterior resection	14 (66.7)	56 (28.6)	
Super low anterior resection	1 (4.8)	10 (5.1)	
Diverting ileostomy	6 (28.6)	37 (18.9)	0.39
Transanal drainage tube	14 (66.7)	93 (47.4)	0.11

Values are presented as mean, median value (range), or number (%) of patients

*Statistically significant ($p<.05$)

during the pre- or intra-operative period so that surgeons can take AL-preventing measures such as diverting ileostomy. In theory, ICG-FI could help prevent AL by changing the planned transection line in some cases as well as avoiding severe complications in patients with pre/intra-operatively known risk factors.

The dose of ICG used in colonic surgery is not well defined. According to previous studies, the ICG dose ranges from 2.5 to 25 mg [16–24, 31]. In the present study, 12.5 mg was used because it is simple and easy to use half of the dissolved solution (25 mg of ICG/10 ml of distilled water). The dosage used in this study was adequate to assess bowel perfusion and fluorescence time. However, it should be noted that administering a standard dose ICG may result in variability in the concentration of ICG per kg body weight, which represents a potential bias and limitation of the present study. Furthermore, we did not observe any side effects in our patient cohort. However, standardization of administration protocols, including the dose of ICG, should be addressed in future well-controlled studies.

Our study has several limitations. First, this was a single-center retrospective study. Thus, it may have been subject to selection bias. Multivariate analysis of the risk factors for AL was not available in the present study because of the small number of patients with AL. Further studies, including larger, well-controlled, or randomized controlled studies, are warranted to eliminate this bias. Second, the assessment of peak ICG perfusion was based on the subjective perception of surgeons. This subjective evaluation introduces potential bias in the results, as the outcomes are not objectively reproducible or verifiable. However, it is worth noting that either or both surgeons with a common understanding attend all operations, which enhanced the reliability of the assessments made in this study. Third, bowel perfusion was observed using the three NIR camera systems. However, these systems are relatively new and have been optimized for detecting ICG fluorescence emission. Therefore, we believe its effect on our study results is minimal in the modern era. Fourth, we did not assess the rectal stump perfusion. There are various risk factors for AL other than bowel perfusion; therefore, ICG evaluation alone is insufficient to reduce AL. However, we believe that ICG may help surgeons improve the quality of colonic surgeries.

Conclusion

In conclusion, our findings show that the time required for perfusion fluorescence was significantly prolonged in the AL group. Indeed, patients with an ICG fluorescence time ≥ 31 s were significantly more likely to develop postoperative AL. Furthermore, among these patients, those undergoing left-sided colon and rectal cancer surgery who have low preoperative albumin, presence of obstructive tumor, absence of preoperative mechanical preparation, or larger tumor diameter are at higher risk of AL. If the time required for ICG

Table 3 Evaluation of the perfusion demarcation of the proximal colon

Variable	AL group ($N=21$)	Non-AL group ($N=196$)	p value
Revision of the transection line according to ICG-FI	1 (4.8)	19 (9.0)	0.7
The perfusion time after ICG injection (s)	32 (25–58)	28 (10–45)	< 0.001*
The perfusion time after ICG injection (s)			< 0.001*
≤ 30 s	8 (38.1)	151 (77.0)	
≥ 31 s	13 (61.9)	45 (23.0)	

Values are presented as the mean and median value (range) of patients

*Statistically significant ($p<.05$)

Table 4 Patient and tumor characteristics with ICG fluorescence time of ≥ 31 s

Variable	AL group ($N=13$)	Non-AL group (N = 45)	p value
Sex, *n* (%)			0.29
Male	8 (61.5)	35 (77.8)	
Female	5 (38.5)	10 (22.2)	
Age (years)	70 (57–84)	72 (42–86)	0.4
BMI (kg/m^2)	20.3 (18.1–31.0)	23.1 (17.5–38.3)	0.075
ASA physical status			0.88
I	1 (7.7)	6 (13.3)	
II	10 (76.9)	34 (75.6)	
III	2 (15.4)	5 (11.1)	
Diabetes mellitus	6 (46.2)	8(17.8)	0.062
Preoperative Albumin (g/dl)	3.4 (2.6–4.4)	3.9 (2.6–4.9)	0.016*
Obstructive tumor	8 (61.5)	8 (17.8)	0.004*
Mechanical bowel preparation	7 (53.8)	41 (91.1)	0.005*
Tumor diameter (mm)	65.0 (40–90)	35.0 (4–100)	< 0.001*
UICC-TNM pStage			0.29
0–I	1 (7.7)	13 (28.9)	
II	5 (38.5)	10 (22.2)	
III	4 (30.8)	16 (35.6)	
IV	3 (23.1)	6 (13.3)	
Preoperative treatment			1
None	13 (100)	45 (100)	
Chemotherapy	0	0	
Location of the tumor, *n* (%)			0.17
Sigmoid colon	3 (23.1)	15 (33.3)	
Rectalsigmoid colon	4 (30.8)	20 (44.4)	
Ra	6 (46.2)	7 (15.6)	
Rb	0 (0)	3 (6.7)	

Values are presented as mean, median value (range), or number (%) of patients

*Statistically significant ($p < .05$)

fluorescence emission is validated as a predictive factor in the future, ICG-FI would be a promising decision-making tool for surgeons to reduce the incidence of AL.

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Declarations

Disclosures Chie Hagiwara, Taiga Wakabayashi, Atsuko Tsutsui, Junichi Sakamoto, Shohei Fujita, Yoshiki Fujiyama, Nobuhiko Okamoto, Kenji Omura, Takeshi Naitoh, and Go Wakabayashi have no conflicts of interest or financial ties to disclose.

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