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Indocyanine green fluorescence imaging to reduce the risk of anastomotic leakage in laparoscopic low anterior resection for rectal cancer: a propensity score-matched cohort study

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Abstract

Background Recent studies have shown the potential benefit of indocyanine green fluorescence imaging (ICG-FI) in lowering the anastomotic leakage (AL) rates by changing the surgical plan. The aim of this study was to evaluate the effect of ICG-FI on the AL rates in laparoscopic low anterior resection (LAR) for rectal cancer.

Methods From September 2014 to December 2017, data from patients who underwent laparoscopic LAR for rectal cancer were collected and analyzed. The primary endpoint was the AL rate within 30 days after surgery. The incidence of AL in patients who underwent ICG (ICG-FI group) was compared with that in patients who did not undergo ICG (non-ICG-FI group) using propensity score matching.

Results Data from 550 patients were collected from 3 institutions. A total of 211 patients were matched in both groups by the propensity score. ICG-FI shifted the point of the proximal colon transection line toward the oral side in 12 patients (5.7%). The AL rates of Clavien–Dindo (CD) grade ≥ II and ≥ III were 10.4% (22/211) and 9.5% (20/211) in the non-ICG-FI group and 4.7% (10/211) and 2.8% (6/211) in the ICG-FI group, respectively. ICG-FI significantly reduced the AL rate of CD grade ≥ II and ≥ III (odds ratio (OR) 0.427; 95% confidence interval (CI) 0.197–0.926; $p = 0.042$ and OR 0.280; CI 0.110–0.711; $p = 0.007$, respectively). The rate of reoperation was significantly lower (OR 0.192; CI 0.042–0.889; $p = 0.036$) and the postoperative hospital stay significantly shorter (mean difference 2.62 days; CI 0.96–4.28; $p = 0.002$) in the ICG-FI group than in the non-ICG-FI group.

Conclusions ICG-FI was associated with significantly lower odds of AL in laparoscopic LAR for rectal cancer.

Clinical trial The study was registered with the Japanese Clinical Trials Registry as UMIN000032654.

Keywords Indocyanine green · Colorectal surgery · Near infrared · Fluorescence image · Anastomotic leak · Rectal cancer

In colorectal surgery, anastomotic leakage (AL) is one of the most critical complications, occurring in 1%–20% of patients [1–4], and can worsen not only the short-term outcomes, such as the rate of reoperation and duration of hospitalization, but also the long-term outcomes, such as the rate of local recurrence and concurrent cancer-specific survival [5]. The risk factors for AL are a low-level anastomosis, male gender and preoperative chemoradiotherapy [1]. These factors are beyond the influence of the surgeon. Regarding the surgery-related factors affecting AL, three elements have been implicated: an incomplete anastomosis [6], anastomotic tension [7], and the anastomotic vascular perfusion [8–11].

Generally, the vascular perfusion to the anastomotic region is intraoperatively assessed by the surgeon. The criteria assessed are parameters such as active bleeding from the resection margin, palpable pulsation in the mesentery and a lack of discoloration [12]. However, these measures are subjective and highly unreliable, as demonstrated by

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Karliczek et al. [13]. Laser Doppler flowmetry and laser fluorescence angiography have been used as reliable intraoperative methods to assess the vascular perfusion [10, 12, 14, 15]. Near-infrared (NIR) fluorescence technology provides another objective and reliable method of evaluating the perfusion of the proximal and distal margin of resection [16]. This technique can be used to perform a real-time angiography during surgery to evaluate the perfusion of the anastomosis. The recent literature shows the potential benefit of fluorescence imaging with indocyanine green (ICG) in lowering AL rates by changing the surgical plan [17–26]. To our knowledge, however, there have been no randomized controlled trials or large-scale case-matched studies on this matter. Further research is needed to validate its efficacy in reducing the AL rate.

The aim of this study was to evaluate the effect of ICG fluorescence imaging (ICG-FI) on AL rates during laparoscopic low anterior resection (LAR) for rectal cancer compared to a propensity score-matched series of laparoscopic LAR performed without ICG-FI.

Materials and methods

This retrospective multi-institutional study was conducted to evaluate the AL rates after laparoscopic LAR for rectal cancer at three institutions of the Yokohama Clinical Oncology Group in Japan from September 2014 to December 2017. The study protocol was approved by the Ethical Advisory Committee of Yokohama City University Medical Center and the institutional review board of each participating hospital before the study was initiated. The study was registered with the Japanese Clinical Trials Registry as UMIN000032654 (http://www.umin.ac.jp/ctr/index.htm). Patient data were collected from clinical report forms. Eligibility criteria were (1) rectal cancer located within 15 cm from the anal verge with histologically proven adenocarcinoma or signet-ring cell carcinoma and (2) having undergone laparoscopic LAR. The exclusion criteria were (1) multiple primary cancers, (2) a history of treatment for other pelvic malignancy, (3) open or robotic surgery cases and (4) emergent cases.

The primary endpoint of this study was the rate of AL within 30 days after surgery. Secondary endpoints were the operative time, blood loss, postoperative complications, reoperation within 30 days after surgery, length of hospital stays, oncological clearance and the rate of changing the surgical plan.

The sample size was determined based on the chi-squared test with a significance level of 0.05 (2-sided) and a power of 0.80. Prior published data indicated that the AL rate among controls was 13% [27]. If the AL rate for the ICG-FI group was 5%, we estimated that 200 cases needed to be enrolled in each matched group.

Surgical procedure

During laparoscopic surgery, five ports are generally inserted: a 12-mm port in the umbilical region; 5-mm ports in the upper-right, left and lower-left quadrants; and a 12-mm port in the lower-right quadrant. A 12-mm umbilical trocar is used as a camera port for a rigid scope. Vessel ligation and colon or rectum mobilization are performed laparoscopically. To avoid contamination when specimen is removed, a wound protector is attached to the umbilical region in every case. We used an Endo GIA™ Universal (Medtronic, Minnesota, USA) or an Echelon™ 60 (Ethicon Endo-Surgery, OH, USA) stapler for distal colon transection. The anastomosis was performed with a double-stapling technique (DST) using an ILS™ device (Ethicon Endo-Surgery).

ICG-FI

The laparoscopic NIR camera system was provided by Karl Storz (D-Light P; Tuttlingen, Germany) and the Stryker Corporation (1588 AIM Platform; Michigan, USA). ICG was injected intravenously just before fluorescence observation. The dose of ICG administered was 0.25 mg/kg.

First, central side lymph node dissection with high tie vascular ligation of the inferior mesenteric artery was performed. After transection of the anal-side of the rectum, the specimen was extracted through the umbilical port, which was extended to about 3–5 cm. Just before proximal bowel resection, we injected ICG intravenously after the division of the mesentery at the level of planned transection and observed the vascular perfusion using the NIR camera system. If vascular perfusion via ICG-FI was well visualized within 60 s, it was judged to be good, and anastomosis was performed with the planned transection line (Fig. 1A, B). No vascular perfusion or perfusion times > 60 s was considered to indicate poor perfusion. In such cases, the transection line of proximal bowel was changed to a site with good vascular perfusion, and anastomosis was performed with the changed transection line (Fig. 1C, D).

Perioperative care

The duration of preoperative fasting was 2 h for liquids and 6–8 h for solids. During induction to anesthesia, one dose of prophylactic intravenous antibiotics (flomoxef; Shionogi, Osaka, Japan) was administered, and an additional dose was administered every 3 h during surgery.

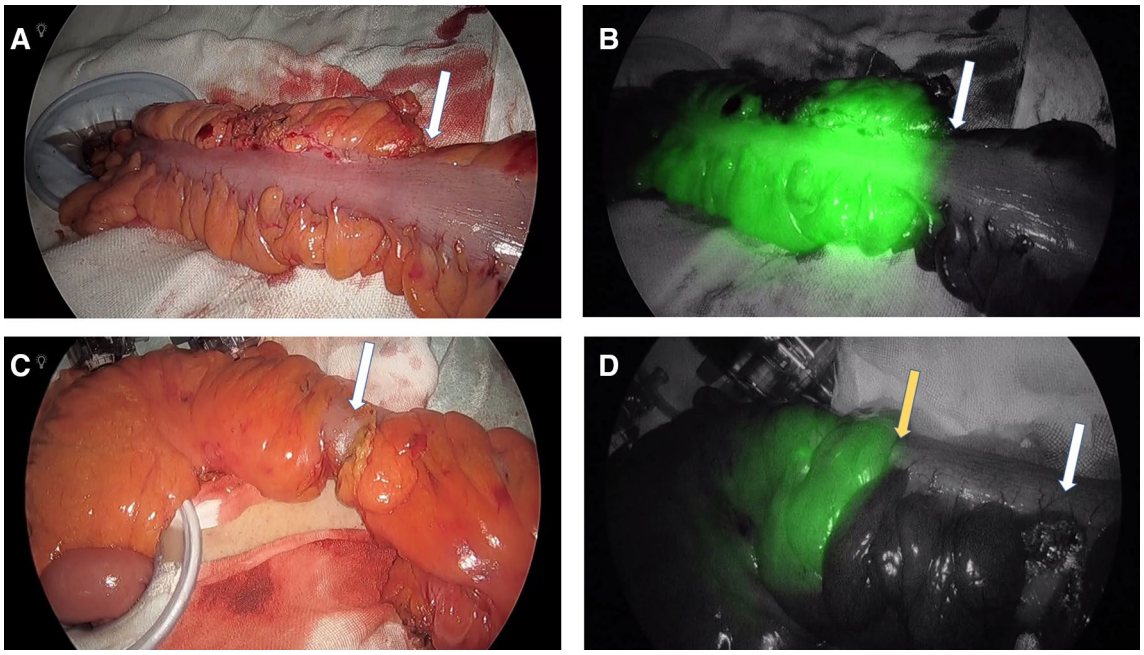

Fig. 1 After transection of the anal side of the rectum, the specimen was extracted through the umbilical incision. **A** Just before proximal bowel resection, we injected ICG intravenously after the division of the mesentery at the level of planned transection (white arrow) and **B** observed the vascular perfusion using the NIR camera system. If vascular perfusion via ICG-FI was well visualized within 60 s, it was judged to be good, and anastomosis was performed with the planned transection line (white arrow). **C** Another case. The white arrow indicates the planned transection line. **D** No vascular perfusion was observed at the level of planned transection (white arrow). In this case, the transection line of proximal bowel was changed to a site with good vascular perfusion (yellow arrow), and anastomosis was performed with the changed transection line. (Color figure online)

Postoperative oral liquid intake was usually authorized from the day following the surgery, and a normal diet was resumed on postoperative day 3. The intravenous catheter was removed when enteral feeding was adequate without nausea or vomiting.

Statistical analyses

Case matching was performed using the propensity score of five factors: age, sex, body mass index (BMI), tumor distance from anal verge and lateral pelvic lymph node dissection as described in the protocol. Nearest neighbor-matching without replacement within a caliper was used. According to the suggestion of Austin, the size of the caliper was set as 0.20 of the standard deviation of the logit of the estimated propensity score [28].

The data are presented as the median and variance. Statistical analyses were performed using the SPSS statistical software program (SPSS Inc., Chicago, IL, USA). Differences between categorical variables were tested using Pearson's Chi squared test. Differences between continuous variables were tested using the Mann–Whitney *U* test. All *p* values were two-sided, and values less than 0.05 were considered statistically significant.

Results

Data from 550 patients were collected from three institutions. ICG-FI was performed in 236 cases (ICG-FI group) and not performed in 314 cases (non-ICG-FI group). A total of 211 patients each were matched to the ICG-FI and non-ICG-FI groups using the propensity score (Fig. 1). The patient and tumor characteristics of the overall cohort and matched cases are presented in Table 1. Before matching, the age was older and the tumor height from the anal verge longer in the ICG-FI group than in the non-ICG-FI group. After matching, these results became more balanced with regard to the age and the tumor height from anal verge.

The operative outcomes are summarized in Table 2. The operative time, blood loss, vessel ligation level, lateral lymph node dissection, diverting stoma, length of proximal margin, length of distal margin and number of lymph nodes harvested were similar between the two groups. The median time for perfusion fluorescence after ICG injection was 35 s (range 20–180 s). ICG-FI shifted the point of the proximal colon transection line toward the oral side in 12 patients (5.7%). The median distance from the planned transection line was 6.5 cm (range 2–45 cm). There were 2 anastomotic leaks in the 12 patients in whom a change in the surgical

Table 1 Patient and tumor characteristics

Variable	Overall cohort			After matching		
	ICG-FI group ($n=236$)	Non-ICG-FI group ($n=314$)	p value	ICG-FI group ($n=211$)	Non-ICG-FI group ($n=211$)	p value
Age (years)[a]	67 (34–92)	65 (34–89)	<0.001	66 (34–92)	66 (36–89)	0.893
Gender						
Male	140 (59.3)	192 (61.1)	0.665	128 (60.7)	131 (62.1)	0.764
Female	96 (40.7)	122 (38.9)		83 (39.3)	80 (37.9)	
BMI (kg/m^2)[a]	22.1 (15.6–36.4)	22.5 (14.5–32.9)	0.211	22.3 (15.6–36.4)	22.4 (14.5–31.6)	0.921
PS						
0	222 (94.1)	290 (92.4)	0.487	199 (94.3)	197 (93.4)	0.676
1	11 (4.7)	19 (6.1)		10 (4.7)	12 (5.7)	
2	2 (0.8)	5 (1.6)		1 (0.5)	2 (0.9)	
3	1 (0.4)	0 (0)		1 (0.5)	0 (0)	
ASA physical status						
I	41 (17.4)	50 (15.9)	0.758	40 (19.0)	31 (14.7)	0.378
II	183 (77.5)	244 (77.7)		162 (76.8)	167 (79.1)	
III	12 (5.1)	20 (6.4)		9 (4.3)	13 (6.2)	
Diabetes mellitus	54 (22.9)	65 (20.7)	0.539	47 (22.3)	49 (23.2)	0.816
Albumin (g/dL)[a]	4.3 (1.3–5.3)	4.3 (2.8–5.2)	0.054	4.3 (1.3–5.3)	4.3 (2.8–5.2)	0.914
Tumor diameter (mm)[a]	35.0 (0–100)	35.0 (0–130)	0.479	35.0 (0–100)	35.0 (0–130)	0.268
Tumor height from anal verge (cm) [a]	10.0 (2.5–15.0)	8.0 (2.0–15.0)	<0.001	10.0 (2.5–15.0)	10.0 (3.0–15.0)	0.938
Stage						
0–I	79 (33.5)	119 (37.9)	0.404	76 (36.0)	70 (33.2)	0.478
II	63 (26.7)	79 (25.2)		51 (24.2)	63 (29.9)	
III	68 (29.2)	95 (30.3)		61 (28.9)	61 (28.9)	
IV	25 (10.6)	21 (6.7)		23 (10.9)	17 (8.1)	
Preoperative treatment						
None	192 (81.4)	249 (79.3)	0.549	169 (80.1)	162 (76.8)	0.407
Chemotherapy	44 (18.6)	65 (20.7)		42 (19.9)	49 (23.2)	

Values in parentheses are percentages, unless indicated otherwise

ICG-FI indocyanine green fluorescence imaging, *BMI* Body Mass Index, *PS* performance status, *ASA* American Society of Anesthesiologists

[a]Values are median (range)

plan occurred based on ICG-FI. Two cases were treated with conservative antibiotics treatment (CD grade 2).

The postoperative complications are shown in Table 3. In the ICG-FI group, the complication rates of Clavien–Dindo (CD) grade ≥ II were significantly lower than in the non-ICG-FI group ($p=0.001$). The AL rates of CD grade ≥ II and ≥ III were 10.4% (22/211) and 9.5% (20/211) in the non-ICG-FI group and 4.7% (10/211) and 2.8% (6/211) in the ICG-FI group, respectively. ICG-FI was associated with significantly lower odds of AL of CD grade ≥ II and ≥ III in laparoscopic LAR for rectal cancer. The odds ratio (OR) (95% confidence interval [CI]; p value) was 0.427 (0.197–0.926; $p=0.042$) and 0.280 (0.110–0.711; $p=0.007$) in the complication rates of CD grade ≥ II and ≥ III, respectively. The rate of reoperation was significantly lower (OR 0.192; CI 0.042–0.889; $p=0.036$) and the postoperative hospital stay significantly shorter (mean difference 2.62 days; CI 0.96–4.28; $p=0.002$) in the ICG-FI group than in the non-ICG-FI group.

Discussion

This multicenter, propensity score-matched cohort study showed that ICG-FI significantly reduced the rate of AL of CD grade ≥ II and ≥ III and reoperation during laparoscopic LAR for rectal cancer. Recent studies have described the potential utility of ICG-FI in reducing AL rates by changing the surgical plan [25]. Furthermore, ICG-FI was shown to be safe and feasible in colorectal surgery [25]. However, most of these previous studies were retrospective case series and cohort studies without case

Table 2 Operative Outcomes

Variable	ICG-FI group ($n=211$)	Non-ICG-FI group ($n=211$)	p value
Operative time (min)[a]	219 (128–719)	214 (89–760)	0.24
Blood loss (ml)[a]	10 (0–1774)	10 (0–1120)	0.894
Vessel ligation level			
High ligation of IMA (proximal to left colic takeoff)	190 (90.0)	184 (87.2)	0.358
Low ligation (distal to left colic takeoff)	21 (10.0)	27 (12.8)	
Anastomosis level from anal verge (cm)[a]	7.0 (1.0–12.5)	6.0 (1.0–12.5)	0.4
Lateral LN dissection	45 (21.3)	47 (22.3)	0.814
Double-stapling technique	211 (100)	211 (100)	1
Autonomic nerve preserving	200 (94.8)	200 (94.8)	1
Diverting ileostomy	107 (50.7)	110 (52.1)	0.77
Proximal margin (cm)[a]	15.0 (1.0–55.0)	14.5 (5.0–62.0)	0.797
Distal margin (cm)[a]	3.0 (0.5–9.0)	3.0 (0.5–12.0)	0.127
Number of LN dissection[a]	19 (2–58)	21 (6–72)	0.114
Dietary intake (day)[a]	3 (2–14)	3 (2–32)	0.203
The perfusion time after ICG injection (second)[a]	35 (20–180)		
Changing the surgical plan by ICG-FI	12 (5.7)	–	–
Distance from planned transection (cm)[a]	6.5 (2–45)	–	–

Values in parentheses are percentages, unless indicated otherwise

ICG-FI indocyanine green fluorescence imaging, *IMA* inferior mesenteric artery, *LN* lymph node

[a]Values are median (range)

Table 3 Postoperative complication

Variable	ICG-FI group ($n=211$)	Non-ICG-FI group ($n=211$)	p value
Postoperative complication (POD < 30)			
Clavien–Dindo grade II ≥	34 (16.7)	64 (30.3)	0.001
Clavien–Dindo grade III ≥	16 (7.6)	27 (12.8)	0.107
Anastomotic leakage (POD < 30)			
Clavien–Dindo grade II ≥	10 (4.7)	22 (10.4)	0.042
Clavien–Dindo grade III ≥	6 (2.8)	20 (9.5)	0.007
Anastomotic bleeding (POD < 30)	4 (1.9)	1 (0.5)	0.372
Wound infection (POD < 30)	5 (2.4)	4 (1.9)	0.736
Reoperation (POD < 30)	2 (0.9)	10 (4.7)	0.036
Mortality (POD < 30)	0 (0.0)	0 (0.0)	–
Length of hospital stay (POD) (day)[a]	9 (4–77)	12 (4–73)	0.002

Values in parentheses are percentages, unless indicated otherwise

ICG-FI indocyanine green fluorescence imaging, *POD* postoperative day

[a]Values are median (range)

matching [25]. This is the first study evaluating the effect of ICG-FI on AL rates during laparoscopic LAR for rectal cancer in a large-scale propensity score-matched study.

Regarding the dose of ICG, no standard dosage has yet been established, and dosages ranging from 2.5 to 25 mg have been reported [17–24, 26, 29–33]. In the present study, 0.25 mg/kg (12.5 mg at 50 kg) was used, and fluorescence observation was possible with good contrast in all cases.

Previous studies have been published regarding shifting the planned transection line [17–26]. Jafari et al. reported that the resection margin was changed in 6.5% of cases in the PILLAR II trial [19], and Wada et al. reported that it was changed in 16% of cases [24]. A recent meta-analysis of five articles on left-sided colorectal surgery reported that the planned anastomotic level was changed in 7.4% of cases (41 of 555 patients in the ICG-FI group) [25]. In the present study, the transection line had to be shifted

more proximally to an adequate fluorescent portion in 12 cases (5.7%). We considered additional transection criteria of no vascular perfusion and perfusion times > 60 s via ICG-FI in our study. No standard additional excision criteria by ICG-FI have yet been established. According to previous reports, the perfusion time to fluorescence after ICG injection at the planned transection line is reported to range from 29 to 44 s [17, 24, 34]. In the present study, the perfusion time to fluorescence after ICG injection was 35 s. However, in cases of perfusion times > 60 s, the transection line of the proximal bowel was shifted to a site with good vascular perfusion, and anastomosis was performed with the new transection line, so whether or not AL would definitely have occurred if anastomosis had been performed without changing the transection line of the proximal bowel is unknown.

Furthermore, the quantitative definition of adequate or inadequate pre-anastomosis perfusion is poorly defined, as none of the laparoscopic ICG-FI systems available at present are able to quantify the fluorescent signal. Automated analysis software programs have been recently developed for a more precise and objective quantification. Although some experimental studies have suggested that fluorescence quantification can effectively detect the ischemic zones in animal models, the cutoff value necessary to judge ischemia was not guided by quantification in these studies [35, 36].

When measuring the magnitude of the therapeutic effect, the most practical measure is "number needed to treat (NNT)" [37]. In this study, since NNT is 1 / 0.06 = 16.7, it means that we prevent anastomotic leak (AL) of one patient by using ICG in 16.7 patients. The cost for ICG dye is 6$ per patient in Japan. In contrast, AL represents over 20.000$ per patient in the USA [32]. AL also increases the mortality risk and the length of hospital stay [3]. Moreover, AL has been associated with reduced long-term cancer-specific survival and a greater risk of systemic and local recurrence [5, 38]. We think that ICG-FI has enough cost effectiveness and therapeutic effect.

There are several limitations associated with this study. First, although the perfusion of the oral-side bowel of the anastomotic site was assessed, the anal-side rectum was not assessed. Second, the vascular perfusion was observed using two kinds of laparoscopic NIR observation systems. Third, this was a retrospective study and not randomized or controlled, although selection bias was reduced by propensity score matching. The results of this study do not provide definitive proof of the benefits of ICG-FI on AL reduction. Thus, further multi-institution, phase III, randomized studies are needed to confirm whether or not ICG-FI can reduce the AL rate in laparoscopic rectal surgery. However, the authors believe that the findings of the present study will provide a firm foundation for future studies.

Conclusion

In conclusion, ICG-FI was associated with significantly lower odds of AL of CD grade ≥ II and ≥ III, lower rate of reoperation and reduced hospital stay in laparoscopic LAR for rectal cancer according to our multicenter, propensity score-matched cohort study. A phase III, randomized controlled study is planned to further evaluate the true clinical significance of ICG-FI on AL reduction.

Compliance with ethical standards

Disclosures Jun Watanabe, Atsushi Ishibe, Yusuke Suwa, Hirokazu Suwa, Mitsuyoshi Ota, Chikara Kunisaki, and Itaru Endo have no conflicts of interest or financial ties to disclose.

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