ORIGINAL CONTRIBUTION

Evaluating the Effect of Intraoperative Near-Infrared Observation on Anastomotic Leakage After Stapled Side-to-Side Anastomosis in Colon Cancer Surgery Using Propensity Score Matching

Jun Watanabe, M.D., Ph.D.[1] Atsushi Ishibe, M.D., Ph.D.[2]
Hiroki Ohya, M.D.[1] Yusuke Suwa, M.D., Ph.D.[1]
Hirokazu Suwa, M.D.[3] Chikara Kunisaki, M.D., Ph.D.[1] Itaru Endo, M.D., Ph.D.[2]

1 Department of Surgery, Gastroenterological Center, Yokohama City University Medical Center, Yokohama, Japan
2 Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine, Yokohama, Japan
3 Department of Surgery, Yokosuka Kyosai Hospital, Yokosuka, Japan

BACKGROUND: Recent studies have clarified that near-infrared observation using indocyanine green has the advantage of evaluating perfusion of the anastomotic site, especially in rectal cancer surgery, resulting in a reduction in anastomotic leak.

OBJECTIVE: The aim of this study was to evaluate the efficacy of near-infrared observation for reducing the anastomotic leak after stapled side-to-side anastomosis in colon cancer surgery.

DESIGN: This was a retrospective propensity score case-matched study.

SETTINGS: The study was conducted at 3 institutions in the Yokohama Clinical Oncology Group.

PATIENTS: From January 2011 to December 2019, patients who underwent colon cancer surgery with stapled side-to-side anastomosis were included.

MAIN OUTCOME MEASURES: The main outcome was the percentage of anastomotic leak within 30 days after surgery.

RESULTS: A total of 1034 patients were collected. There were 532 patients who underwent near-infrared observation and 502 who did not. A total of 370 patients were matched to the near-infrared and non-near-infrared groups. In the near-infrared group, 12 patients (3.2%) were judged to have poor perfusion (4 patients) and no perfusion (8 patients), so the planned transection point was changed. There were no cases of anastomotic leak among these 12 patients. The anastomotic leak rates were 3.5% (13/370) in the non-near-infrared group and 0.8% (3/370) in the near-infrared group. The anastomotic leak and reoperation rates were significantly lower in the near-infrared group than in the non-near-infrared group (OR, 0.224; 95% CI, 0.063–0.794, $p = 0.001$; OR, 0.348; 95% CI, 0.124–0.977, $p = 0.036$).

LIMITATIONS: Although we reduced selection bias by performing propensity score matching, this was a retrospective study and was not randomized.

CONCLUSION: This large-scale case-matched study showed that assessing perfusion by near-infrared observation significantly reduced the anastomotic leak and reoperation rates after stapled side-to-side anastomosis in colon cancer surgery and may be better suited to colo-colonic anastomosis. **Video Abstract** at http://links.lww.com/DCR/B513.

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Correspondence: Jun Watanabe, M.D., Ph.D., Yokohama City University Medical Center, Department of Surgery, Gastroenterological Center, 4-57, Urafune-cho, Minami-ku, Yokohama, 232-0024. Japan. E-mail: nabe-jun@comet.ocn.ne.jp

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EVALUACIÓN DEL EFECTO DE LA OBSERVACIÓN INTRAOPERATORIA CON INFRARROJO CERCANO SOBRE LA FUGA ANASTOMÓTICA DESPUÉS DE UNA ANASTOMOSIS LATERO-LATERAL CON ENGRAPADORA EN LA CIRUGÍA DE CÁNCER DE COLON MEDIANTE EL EMPAREJAMIENTO POR PUNTAJES DE PROPENSIÓN

ANTECEDENTES: Estudios recientes han aclarado que la observación con infrarrojo

cercano con verde de indocianina tiene la ventaja de evaluar la perfusión del sitio anastomótico, especialmente en la cirugía de cáncer de recto, lo que resulta en una reducción de la fuga anastomótica.

OBJETIVO: El objetivo de este estudio fue evaluar la eficacia de la observación con infrarrojo cercano para reducir la fuga anastomótica después de una anastomosis latero-lateral con engrapadora en la cirugía de cáncer de colon.

DISEÑO: Este fue un estudio retrospectivo emparejado con puntaje de propensión.

AJUSTE: El estudio se llevó a cabo en tres instituciones del Grupo de Oncología Clínica de Yokohama.

PACIENTES: Desde enero de 2011 hasta diciembre de 2019, se incluyeron pacientes que se sometieron a cirugía de cáncer de colon con anastomosis latero-lateral con engrapadora.

PRINCIPALES MEDIDAS DE RESULTADO: El resultado principal fue el porcentaje de fuga anastomótica dentro de los 30 días posteriores a la cirugía.

RESULTADOS: Se recogió un total de 1034 pacientes. Hubo 532 pacientes que se sometieron a observación con infrarrojo cercano y 502 que no. Un total de 370 pacientes fueron emparejados con los grupos de infrarrojo cercano y no infrarrojo cercano. En el grupo de infrarrojo cercano, se consideró que 12 casos (3,2%) tenían mala perfusión (4 casos) y ninguna perfusión (8 casos), por lo que se cambió el punto de transección planificado. No hubo casos de fuga anastomótica entre estos 12 casos. Las tasas de fuga anastomótica fueron del 3,5% (13/370) en el grupo sin infrarrojo cercano y del 0,8% (3/370) en el grupo con infrarrojo cercano. Las tasas de fuga anastomótica y de reintervención fueron significativamente menores en el grupo con infrarrojo cercano que en el grupo sin infrarrojo cercano (razón de posibilidades 0,224, intervalo de confianza del 95% 0,063-0,794, $p = 0,001$; razón de posibilidades 0,348, intervalo de confianza del 95% 0,124 -0,977, $p = 0,036$, respectivamente).

LIMITACIONES: Aunque se redujo el sesgo de selección al realizar el emparejamiento por puntaje de propensión, este fue un estudio retrospectivo y no fue aleatorio.

CONCLUSIÓN: Este estudio de casos emparejados a gran escala demostró que la evaluación de la perfusión mediante la observación con infrarrojo cercano redujo significativamente la fuga anastomótica y las tasas de reintervención después de la anastomosis latero-lateral con engrapadora en la cirugía de cáncer de colon y puede ser más adecuada para la anastomosis colo-colónica. Consulte **Video Resumen** en http://links.lww.com/DCR/B513. *(Traducción—Dr. Gonzalo Hagerman)*

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KEY WORDS: Anastomotic leak; Colon cancer; Indocyanine green; Near-infrared; Vascular perfusion.

Anastomotic leakage (AL) occurs in 1% to 20% of patients undergoing colorectal surgery and is one of the most life-threatening complications.[1–4] Anastomotic leakage affects the surgical outcomes, eg, increasing the risk of reoperation and prolonging the hospital stay, as well as the long-term outcomes, eg, reducing the cancer-specific survival.[5] Anastomosis, such as stapled side-to-side anastomosis (SSSA), which is used for reconstruction in colon cancer surgery, is considered to have a lower incidence of AL than rectal cancer. In recent years, however, several reports with a large accumulation of unselected cases have led to higher AL rates, even in right colectomy, than previous studies. In these studies, the AL rate in colon cancer surgery has varied from 2.4% to 8.4%.[6–10] Studies of national databases have reported that the AL rate after colon cancer surgery has increased to 8.7%.[11]

Incomplete anastomosis, anastomotic tension, and anastomotic blood flow are possible causes associated with surgery for AL.[12–17] A surgeon evaluates the blood flow at the anastomosis during surgery by classical methods, such as pulsation of mesenteric blood vessels, active bleeding from the resection margin, and color change.[18] However, Karliczek et al[19] reported that these surgeon-based assessments are subjective and highly unreliable.

In recent years, near-infrared (NIR) observation using indocyanine green (ICG) has become available as an objective and reliable method of assessing intestinal blood flow. This technique can evaluate the perfusion of the proximal and distal margins of the resection in real-time during surgery when performing anastomosis.[20] Several reports have clarified that NIR observation has the potential advantage of evaluating vascular perfusion of the anastomotic site. An increasing number of reports have examined the usefulness of NIR observation, especially in rectal cancer surgery, finding that this approach reduces AL by allowing the planned resection line to be changed in cases with poor perfusion.[9,21–26] However, there have been no large case-matched comparative studies or randomized controlled trials concerning the potential benefits of NIR observation after SSSA in colon cancer surgery. Further research is needed to verify its reduction effect on AL.

In this study, we compared the effect of NIR observation on the AL rate after SSSA in colon cancer surgery using a propensity score-matched analysis.

MATERIALS AND METHODS

This retrospective, multicenter, case-matched study was conducted to evaluate the efficacy of NIR observation

for reducing the AL rate after SSSA in colon cancer surgery. From January 2011 to December 2019, consecutive patients who underwent radical resection of colon cancer were collected at 3 institutions of the Yokohama Clinical Oncology Group in Japan. The study was approved by the institutional review board for studies in humans of each participating hospital. Because of the retrospective nature of the study, written informed consent was not obtained. We used the opt-out approach to disclose the study information. This study was registered with the Japanese Clinical Trials Registry (UMIN-CTR000039977 (http://www.umin.ac.jp/ctr/index.htm)).

Patients were eligible if they 1) had histologically proven colon cancer; 2) had undergone D2 or D3 dissection according to the Japanese Classification of Colorectal Carcinoma; and 3) had undergone antiperistaltic SSSA, also known as functional end-to-end anastomosis.[27] The exclusion criteria were as follows: 1) a history of treatment for other abdominal malignancy; 2) reconstruction other than antiperistaltic SSSA (eg, handsewn anastomosis and triangle anastomosis using a linear stapler); 3) multiple primary cancers; and 4) emergent cases.

The main outcome was the percentage of AL within 30 days after surgery. Secondary outcomes were the duration of the operation, blood loss, perfusion time after ICG injection, additional resection rate, length of the additionally resected intestinal tract, postoperative complications, reoperation, mortality within 30 days after surgery, and length of the hospital stay.

The sample size was determined based on a χ^2 with a significance level of 0.05 (2-sided) and a power of 0.80. Based on previously published literature, in the patients who did not undergo NIR observation (non-NIR group), the post-SSSA AL rate was set at 5.5%.[6–11] We hypothesized that the AL rate in the patients who underwent NIR observation (NIR group) would decrease by 3.9% because the additional resection rate was 3.9% according to our institution data, resulting in an AL rate of 1.6%. Based on this setting, 352 cases in each matched group and 704 cases in both groups were estimated to be required for the sample size.

Surgical Procedure

All operations were overseen by doctors who were qualified based on the endoscopic surgical skill qualification system of the Japan Society for Endoscopic Surgery.[28] Six such doctors participated in this study. All participating surgeons had experience with more than 200 cases of laparoscopic surgery for colorectal cancer before selection of the first patient included in our study. One surgeon did not perform NIR observation in all cases.

Resection of the colon with D2 or D3 dissection was performed according to the Japanese Classification of Colorectal Carcinoma.[27] Approaches for colonic mobilization (medial-to-lateral and lateral-to-medial) were decided by the surgeon in charge. In laparoscopic surgery, a 12-mm port was inserted into the umbilical region as a camera port, and 5-mm ports were inserted into the upper right, left, lower right, and left quadrants, and the operation was generally performed through 5 ports. Lymph node dissection and colon or rectum mobilization, including ligation of the artery and vein, were all performed laparoscopically.

The proximal and distal intestinal tracts were separated with a stapler using an Echelon (Ethicon Endo-Surgery, Cincinnati, OH) or Endo GIA (Medtronic, Minneapolis, MN) device. After the specimen had been removed, antiperistaltic SSSA, termed functional end-to-end anastomosis, was performed extracorporeally using an Echelon or Endo GIA device. The anastomosis was standardized at 60 mm.

NIR Observation

The NIR camera system was provided by the Stryker Corporation (1588 AIM Platform; Kalamazoo, MI), Olympus Medical Systems Corporation (VISERA ELITE II; Tokyo, Japan), and Karl Storz (D-Light P; Tuttlingen, Germany). Just before NIR observation, ICG (0.25 mg/kg) was injected intravenously and then flushed with 20 mL of saline. In all cases, we performed a peripheral intravenous injection. Although a wide range of doses of ICG is set (0.04–0.3 mg/kg), we have been performing blood flow evaluations with a dose of 0.25 mg/kg.[26,29] Near-infrared observation was performed using a laparoscopic system extracorporeally. For such observation, it is necessary to shield the subject from sunlight and to douse room lights. Turning off all interior room lights makes it possible to perform NIR observation even extracorporeally.

After lymph node dissection and transection of the proximal and distal side of the colon or ileum, we injected ICG intravenously just before SSSA reconstruction, and we performed NIR observation to evaluate the vascular perfusion. The vascular perfusion assessment was divided into 3 categories: good, poor (delayed fluorescence), and none (no fluorescence). If the time from the intravenous injection of ICG to the fluorescence of the intestinal wall at the anastomotic site was ≤60 seconds, the blood flow was judged to be good. If the fluorescence was observed for >60 seconds, it was determined to be poor perfusion, and if no fluorescence was observed, it was determined that there was no perfusion. When perfusion was good, anastomosis was performed at the planned line (Figs. 1A and B). In cases with poor or no perfusion, however, the plan was changed, and the intestinal tract was additionally resected at a site with good perfusion before anastomosis (Figs. 1C and D). The time from injection to fluorescence was measured by a doctor participating in the

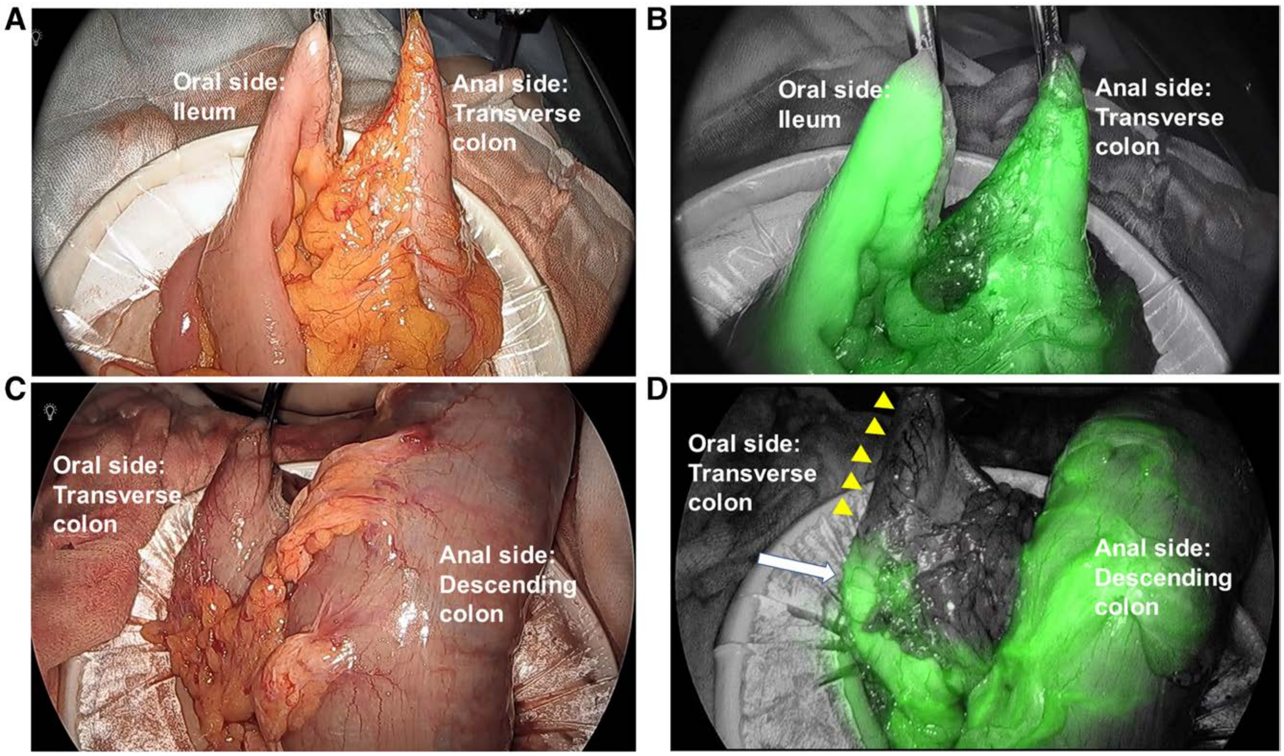

FIGURE 1. After transection of the oral and anal side of the colon or ileum, the specimen was extracted through the umbilical incision. Just before SSSA reconstruction, we injected ICG intravenously (A) and observed the vascular perfusion using the NIR camera system (B). If vascular perfusion via NIR observation was well visualized within 60 seconds for both the oral and anal side, it was judged to be good, and anastomosis was performed with the planned transection line. C, Another case. D, No vascular perfusion was observed at the level of the oral-side planned transection (yellow arrow). In this case, the transection line of the oral-side bowel was changed to a site with good vascular perfusion (white arrow), and anastomosis was performed with the changed transection line. ICG = indocyanine green; NIR = near-infrared; SSSA = stapled side-to-side anastomosis..

surgery using a timer. In the non-NIR group, there was no specific method used for the blood flow evaluation. Based on their personal experience, surgeons evaluated the blood flow in the intestinal tract by using classical methods, such as pulsation of the mesenteric blood vessels and color change.

Near-infrared observation has been available since 2013 at institution A, since 2016 at institution B, and since 2017 at institution C. Near-infrared observation was not performed in any cases when NIR had not been introduced and was performed in most cases once it had been introduced. Even after NIR was introduced, NIR observation was not performed if NIR was not available during the surgery or if the patient had an iodine allergy.

Perioperative Care

Preoperative fasting times were 2 hours for liquids and 6 to 8 hours for solids. Before the induction of anesthesia, a prophylactic intravenous antibiotic (flomoxef; Shionogi, Osaka, Japan) was administered once, and additional doses were given every 3 hours during surgery. The nasogastric tube was removed immediately after surgery. Postoperative oral fluid intake was usually allowed the day after surgery, and normal diet was resumed 2 days after surgery.

Statistical Analyses

A propensity score matching was performed using the following 7 factors: sex, age, BMI, ASA physical status, tumor location, TMN stage, and surgical approach (open surgery/laparoscopic surgery). Based on these factors, we calculated the propensity score for receiving NIR observation for each patient with bivariate logistic regression. These propensity scores were used to match patients in the NIR group at a 1:1 ratio with those in the non-NIR group (caliper = 0.2). Although this study was a retrospective study, a study protocol had been developed before collecting cases. Therefore, propensity score matching was preplanned and was performed regardless of background factors.

The data are presented as the median and interquartile range (IQR). The SPSS Statistics 24 software program (SPSS Inc, Chicago, IL) was for the statistical analysis. Differences between categorical and continuous variables were tested using the Pearson χ^2 test and the Mann-Whitney *U* test. All *p* values were 2-sided, and values less than 0.05 were considered statistically significant.

RESULTS

A total of 1034 patients from 3 institutions were collected. There were 532 patients (NIR group) and 502 patients

TABLE 1. Patient and tumor characteristics

	Overall cohort			After matching		
Variable	*NIR group (n = 532)*	*Non-NIR group (n = 502)*	*p value*	*NIR group (n = 370)*	*Non-NIR group (n = 370)*	*p value*
Age, y[a]	74 (68–80)	73 (66–79)	0.487	72 (66–79)	72 (66–79)	0.606
Sex						
Male	273 (51.3)	268 (54.4)	0.533	187 (51.5)	187 (51.5)	1.000
Female	259 (48.7)	234 (46.6)		183 (49.5)	183 (49.5)	
BMI, kg/m^2 [a]	22.5 (20.2-24.8)	22.2 (20.0-24.6)	0.419	22.6 (20.4-24.8)	22.5 (20.5-24.7)	0.883
ECOG PS						
0	466 (87.6)	432 (86.1)	0.549	343 (92.7)	332 (89.7)	0.359
1	58 (10.9)	59 (11.8)		24 (6.5)	34 (9.2)	
2	7 (1.3)	7 (1.4)		3 (0.8)	4 (1.1)	
3	1 (0.2)	4 (0.8)		0 (0)	0 (0)	
ASA physical status						
I	56 (10.5)	71 (14.1)	0.074	56 (15.1)	56 (15.1)	1.000
II	409 (76.9)	384 (76.5)		312 (84.3)	167 (84.3)	
III	67 (12.6)	47 (9.4)		2 (0.5)	2 (0.5)	
Diabetes mellitus	121 (22.7)	113 (22.5)	0.941	78 (21.1)	77 (20.8)	0.928
Albumin, g/dL[a]	4.1 (3.8–4.4)	4.2 (3.8–4.4)	0.365	4.2 (3.8–4.4)	4.2 (3.9–4.5)	0.104
Tumor diameter, mm[a]	35.5 (20–50)	35.0 (22–50)	0.404	35.0 (20–50)	35.0 (20–50)	0.270
Tumor location						
Cecum	102 (19.2)	80 (15.9)	0.164	72 (19.5)	67 (18.1)	0.994
Ascending colon	208 (39.1)	227 (45.2)		143 (38.6)	145 (39.2)	
Transverse colon	139 (26.1)	111 (22.1)		95 (25.7)	97 (26.2)	
Descending colon	50 (9.4)	45 (9.0)		33 (8.9)	33 (8.9)	
Sigmoid colon	33 (6.2)	39 (7.8)		27 (7.3)	28 (7.6)	
UICC stage						
0–I	192 (36.1)	172 (34.3)	0.264	129 (34.9)	129 (34.9)	0.984
II	109 (20.5)	116 (23.1)		82 (21.9)	85 (23.0)	
III	191 (35.9)	163 (32.5)		135 (36.5)	131 (35.4)	
IV	40 (7.5)	51 (10.2)		25 (6.8)	25 (6.8)	
Preoperative treatment						
None	516 (97.0)	489 (97.4)	0.711	358 (96.8)	358 (96.8)	1.000
Chemotherapy	16 (3.0)	13 (2.6)		12 (3.2)	12 (3.2)	
Approach						
Open	4 (0.8)	99 (19.7)	<0.001	4 (1.1)	4 (1.1)	1.000
Laparoscopy	528 (99.2)	403 (80.3)		366 (98.9)	366 (98.9)	

Values in parentheses are percentages, unless indicated otherwise.
ECOG PS = Eastern Cooperative Oncology Group performance status; NIR = near-infrared; UICC = The Union for International Cancer Control.
[a]Values are median (interquartile range: 25th–75th percentile).

(non-NIR group). Before matching, significant difference was observed between the 2 groups in terms of the surgical approach (Table 1). After propensity score matching, all covariates were balanced, and no statistically significant differences were noted between the NIR (n = 370) and non-NIR (n = 370) groups (Table 1). Table 1 shows the patient and tumor characteristics of the entire cohort and the matched cases. Ileostomy was constructed in cases where the risk of AL was high due to malnutrition or heavy steroid use.

Table 2 shows the operative outcomes and postoperative complications. There were no significant differences in the operative time, blood loss, or rate of transfusion, lymph node dissection (D3/D2), ileocolonic anastomosis/colo-colonic anastomosis, or diverting ileostomy between the NIR and non-NIR groups. The median time from ICG injection to fluorescence observation of the intestinal wall was 25 seconds (IQR 20–30 seconds). In the NIR group, 12 patients (3.2%) were judged to have poor perfusion (4 patients) and no perfusion (8 patients), so the planned transection point was changed, and additional resection was performed. The details of the 12 patients in whom the planned transection point was changed and additional resection was performed are as follows: the surgical procedures were ileocolic resection in 1 patient (proximal side 1), right hemicolectomy in 3 patients (distal side 3), left hemicolectomy in 2 patients (proximal side 1, distal side 1), partial colectomy (descending colon) in 4 patients (proximal side 2, distal side 2), and sigmoidectomy in 2 patients (proximal side 1, distal side 1); and the additional transection sites were ileum in 1 patient, transverse colon in 7 patients, descending colon in 2 patients, and sigmoid colon in 2 patients. The median length of the additionally resected intestinal tract was 4.0 cm (IQR 3.0–5.8 cm).

TABLE 2. Operative outcomes and postoperative complication

Variable	NIR group (n = 370)	Non-NIR group (n = 370)	p value
Operative time, min[a]	182 (154–223)	175 (146–213)	0.078
Blood loss, mL [a]	5 (0–8)	5 (0–25)	0.215
Transfusion	5 (1.4)	3 (0.8)	0.725
Lymph node dissection			
D3	273 (73.8)	261 (70.5)	0.367
D2	87 (26.2)	109 (29.5)	
Stapled functional end-to-end anastomosis	370 (100)	370 (100)	1.000
Ileocolonic anastomosis	260 (70.3)	274 (74.1)	0.251
Colo-colonic anastomosis	110 (29.7)	96 (25.9)	
Perfusion time after ICG injection, s[a]	25 (20–30)	–	–
Changing the surgical plan by ICG-FI	12 (3.2)		
Nonfluorescence	8 (2.1)		
Delayed fluorescence	4 (1.1)		
Surgical procedure			
Ileocolonic anastomosis	4 (1.1)		
Ileocolic resection	1 (proximal side 1) (0.3)	-	-
Right hemicolectomy	3 (distal side 3) (0.8)		
Colo-colonic anastomosis	8 (2.2)		
Left hemicolectomy	2 (proximal side 1, distal side 1) (0.5)		
Partial colectomy (descending colon)	4 (proximal side 2, distal side 2) (1.1)		
Sigmoidectomy	2 (proximal side 1, distal side 1) (0.5)		
Additional transection site			
Ileum	1 (0.3)		
Transverse colon	7 (1.9)		
Descending colon	2 (0.5)		
Sigmoid colon	2 (0.5)		
Distance from planned transection, cm[a]	4.0 (3.0–5.8)	-	-
Postoperative complication (POD<30)			
Clavien-Dindo grade II ≧	44 (11.9)	48 (13.0)	0.656
Clavien-Dindo grade III ≧	13 (3.5)	20 (5.4)	0.213
Anastomotic leakage (POD<30) Total	3 (0.8)	13 (3.5)	0.011
Ileocolonic anastomosis	2/260 (0.8)	7/274 (2.6)	0.109
Colo-colonic anastomosis	1/110 (0.1)	6/96 (6.3)	0.035
Anastomotic bleeding (POD<30)	3 (0.8)	1 (0.3)	0.316
Wound infection (POD<30)	10 (2.7)	15 (4.1)	0.309
Reoperation (POD<30)	5 (1.4)	14 (3.8)	0.036
Mortality (POD<30)	0 (0.0)	1 (0.3)	0.317
Length of hospital stay (POD), days [a]	7 (6–8)	7 (6–9)	0.256

Values in parentheses are percentages, unless indicated otherwise.
FI = fluorescence imaging; ICG = indocyanine green; NIR = near-infrared; POD = postoperative day.
[a]Values are median (interquartile range: 25th–75th percentile).

There were no cases of AL among the 12 patients that received additional bowel resection based on the results of NIR observation.

Regarding postoperative complications, the AL rates were 3.5% (13/370) in the non-NIR group and 0.8% (3/370) in the NIR group. Near-infrared observation significantly reduced the AL rate after SSSA in colon cancer surgery. The OR (95% CI; p value) was 0.224 (0.063–0.794; $p = 0.011$) for the AL rate. Anastomotic leakage occurred in 9 cases (1.7% 9/534) of ileocolonic anastomosis and 7 cases (3.4% 7/206) of colo-colonic anastomosis ($p = 0.151$). Near-infrared observation reduced the ileocolonic anastomosis rate from 2.6% to 0.8% and the colo-colonic anastomosis rate from 6.3% to 0.1%. Near-infrared observation significantly reduced the AL rate in colo-colonic anastomosis ($p = 0.035$). In total, AL occurred in 16 patients. In the non-NIR group, 13 patients were treated for AL (reoperation, 9 patients; CT-guided drainage, 2 patients; and conservative treatment with antibiotics, 2 patients), whereas in the NIR group, 3 patients were treated (reoperation in all).

The rate of reoperation was significantly lower (OR, 0.348; 95% CI, 0.124–0.977; $p = 0.036$) in the NIR group than in the non-NIR group.

DISCUSSION

This study showed that assessing the perfusion by NIR observation using ICG significantly reduced the AL

rate and rate of reoperation after SSSA in colon cancer surgery. Recent studies have shown that NIR observation can be used to objectively assess vascular perfusion safely, especially in rectal surgery, and is especially useful for reducing the AL rate by removing additional sections of intestinal tract with poor perfusion.[9,21–26] Two randomized controlled trials have been reported targeting the left-sided colon and rectum.[30,31] However, most of these previous studies have focused mainly on rectal cancer and had a small sample size. This is the first study to evaluate the efficacy of NIR observation on the post-SSSA AL rates in colon cancer surgery using propensity score matching.

In recent years, several reports with a large accumulation of unselected cases and nationwide series have described elevated AL rates in patients with colon cancer, ranging from 2.4% to 8.7%.[6–11] Although these rates seem very high, our study also showed that the non-ICG-fluorescence imaging group had a 3.5% incidence of AL. This result was similar to that of a previous unselected relatively large case series.

In the present study, NIR observation reduced the AL rate by 2.7% in SSSA for colon cancer. Regarding whether or not NIR observation needs to be performed in all cases because of the associated 2.7% reduction in AL, the "number needed to treat (NNT)" is used as a measure of the magnitude of therapeutic effect.[32] In the matched cohort of this study, the NNT for reducing AL was 1/0.027 (= 37.0), which means that NIR observation needs to be performed in 37 cases to prevent AL in 1 case. Furthermore, in the prematched cohort, the AL rate was the 4.0% (20/502) in the non-NIR group and 0.8% (4/532) in the NIR group. The NNT of the prematched population for reducing AL was 1/0.032 (= 31.25), which means that NIR observation needs to be performed in 31 cases to prevent AL in 1 case. The cost of the ICG dye used for NIR observation per patient in Japan is $6 US. This should be considered against a report from the United States that treating AL costs $20,000 US per patient.[33] Furthermore, AL increases the risk of mortality and a prolonged hospital stay as well as the risk of systemic and local recurrence.[3,5,34] Regarding the details of additional resection cases observed by NIR, the transverse colon accounted for a large proportion of intestinal sites that had undergone additional resection due to poor or no blood flow (58.3%, 7/12). In addition, the small intestine was reported as the site in 1 case, and 66.7% (8/12) of cases had colo-colonic anastomosis, so NIR observation was considered to be more effective in cases of colo-colonic anastomosis in which the transverse colon was involved.

In previous reports, the ICG dose ranged widely, from 2.5 mg to 25 mg, and a standard ICG dose has yet to be established.[24,35] In the present study, the dose of ICG was set at 0.25 mg/kg (12.5 mg at 50 kg), and, in all cases, it was possible to observe the fluorescent signal of vascular perfusion well. We believe that it is best to assess the blood flow just before the anastomosis, ie, after transecting the intestine. If this evaluation is made before the transection of the intestinal tract, intestinal transection would be performed after the blood flow evaluation, and the blood flow might consequently deteriorate by this additional operation. For example, if the cut site is shifted by 1 cm, the blood flow may deteriorate.

Previous reports have shown that additional intestinal resection due to changing the planned transection line based on ICG-fluorescence imaging was performed in 6.5% of patients in the PILLAR II trial,[21] 16% in the report of Wada et al,[23] and 7.4% in a recent meta-analysis of 5 articles.[24] The time from ICG injection to fluorescence at the planned transection lines has been reported to range from 29 to 44 seconds.[9,23,26,36] One factor that affects the fluorescence time of ICG is the cardiac output, which is calculated as the stroke volume × heart rate. Therefore, the heart rate affects the ICG fluorescence time. A normal cardiac output is 2.6 to 4.2 $L \cdot min^{-1} \cdot m^{-2}$. In the present study, we did not measure the cardiac output. According to the Forrester classification, a cardiac output of less than 2.2 $L \cdot min^{-1} \cdot m^{-2}$ is classified as a low stroke rate, because the patient can easily fall into a hypoperfusion state. Assuming a cardiac output of 4.2 $L \cdot min^{-1} \cdot m^{-2}$, the median time to intestinal fluorescence in the present study was calculated to be 25 seconds (IQR 20–30). Even assuming a low cardiac output of 2.2 $L \cdot min^{-1} \cdot m^{-2}$, the time to fluorescence was calculated to be 48 seconds (IQR 38–57). Therefore, if the fluorescence is delayed by more than 60 seconds, the blood flow is judged to be poor.

Although standard additional excision criteria based on the ICG fluorescence time have yet to be established, we have used this criterion thus far to identify cases with a poor blood flow and have obtained relatively good results.[26,29] In the present study, we set "no fluorescence signal" or "delayed fluorescence signal (>60 seconds)" as the criteria for additional resection. Twelve of the present patients (3.2%) needed to have the incision line shifted to an adequately fluorescent portion, and there were no cases of AL among these 12 patients. In cases of perfusion times >60 seconds, the transection line of the bowel was shifted to a site with good vascular perfusion, and anastomosis was performed with the new transection line, so whether AL would have occurred if anastomosis had been performed without changing the transection line of the proximal bowel is unknown.

Regarding fluorescence quantification, automatic analysis software programs have recently been developed to allow for more accurate and objective quantification. The utility of fluorescence quantification for preventing AL has also been reported.[23,37] However, the diagnostic criteria for quantification are not well defined, and none of the currently available laparoscopic NIR systems can quantify the fluorescence signal.

This study has 2 limitations. First, NIR has been available since 2013 at institution A, since 2016 at institution B, and since 2017 at institution C. Near-infrared observation was not performed in any patients when NIR had not been introduced and was performed in most patients once it had been introduced. Even with propensity score matching, this selection bias cannot be eliminated because this was not a randomized controlled trial. In addition, although the patients in this study were treated by well-experienced surgeons, there was a possibility that improved surgical techniques reduced AL, because the controls were historical and the NIR group was a more recent case. Second, the laparoscopic NIR observation system used was not unified due to the use of 3 types of systems for fluorescence observation. The results of this study do not definitively confirm the benefits of NIR observation for reducing AL, and multicenter, phase III, randomized trials will be required to verify the efficacy of NIR observation for reducing AL rates in colon cancer surgery. However, the authors believe that this report provides useful results that will lead to future research.

CONCLUSION

In conclusion, this large-scale case-matched study showed that assessing the perfusion by NIR observation significantly reduced the AL rate and rate of reoperation after SSSA in colon cancer surgery and may be better suited to colo-colonic anastomosis.

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