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ORIGINAL ARTICLE

Visualization and quantification of anastomotic perfusion in colorectal surgery using near-infrared fluorescence

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Abstract

Background Anastomotic leakage (AL) is one of the most troublesome complications in colorectal surgery. Recently, near-infrared fluorescence (NIRF) imaging has been used intraoperatively to detect sentinel lymph nodes and visualize the blood supply at the region of interest (ROI). The aim of this study was to evaluate the role of visualization and quantification of bowel perfusion around the anastomosis using NIRF system in predicting AL.

Methods A prospective study was conducted on patients who had laparoscopic surgery for colorectal cancer at our institution. Perfusion of the anastomosis was evaluated with NIRF imaging after intravenous injection of indocyanine green (ICG). The time course of fluorescence intensity was recorded by an imaging analyzer We measured the time from ICG injection to the beginning of fluorescence (T_0), maximum intensity (I_{max}), time to reach I_{max} (T_{max}), time to reach I_{max} 50% ($T_{max_{1/2}}$) and slope (S) after the anastomosis.

Results Tumor locations were as follows; cecum: 2, ascending colon: 2, transverse colon: 7, descending colon: 1, sigmoid colon: 2, rectosigmoid colon: 3 and rectum: 6 (one case with synchronous cancer). All operations were performed laparoscopically. Four patients were diagnosed with or suspected to have AL (2 patients with grade B anastomotic leakage after low anterior resection, 1 patient with minor leakage in transverse colon resection and 1 patient needing re-anastomosis intraoperatively in transverse colon resection). T_0 was significantly longer in the AL group than in patients without AL (64.3 ± 27.6 and 18.2 ± 6.6 s, $p = 2.2 \times 10^{-3}$).

Conclusions Perfusion of the anastomosis could be successfully visualized and quantified using NIRF imaging with ICG. T_0 might be a useful parameter for prediction of AL.

Keywords Anastomotic leakage · Perfusion · Optical imaging · Fluorescence imaging · COLON/surg · RECTUM/surg

Abbreviations

AL	Anastomotic leakage
NIRF	Near-infrared fluorescence
ICG	Indocyanine green
UMIN-CTR	University Hospital Medical Information Network Clinical Trial Registry
FEEA	Functional end-to-end anastomosis
DST	Double stapling technique
SPIES	Storz Professional Image Enhancement system
ROI	Region of interest
ASA	American Society of Anesthesiologists
UICC TNM classification	The Union for International Cancer Control's tumor-node-metastasis classification
ISGRC	The International Study Group of Rectal Cancer

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Introduction

Anastomotic leakage (AL) is one of the most troublesome complications in colorectal cancer surgery. Delayed discovery of AL leads to prolonged contamination by luminal contents, and this can lead to severe sepsis, multiple organ failure and death. The reported incidence of AL in ileocolic, colocolic and colorectal/coloanal anastomoses is 1–4%, 2–3% and 5–19%, respectively [1]. Risk factors for AL are multiple, but a good blood supply to the anastomosis is a sine qua non for healing [2, 3]. The best way to reduce AL rate is intraoperative real-time detection of modifiable risk factors for AL and especially identification and correction of poor perfusion to the anastomosis. Chung reported a method of measuring blood flow in colonic anastomosis using laser Doppler velocimetry in 1987 [4]. More recently, near-infrared fluorescence (NIRF) imaging with indocyanine green (ICG) has been used for intraoperative visualization of blood supply to the bowel [5–12]. Diana et al. demonstrated in animal models that NIRF imaging can be used to clarify the vascularized/ischemic zone and this can be used to determine the anastomotic site [13–15].

We believe that quantitative evaluation of ICG imaging of colonic perfusion helps to reduce the risk of AL. Quantification of bowel perfusion, however, is not widely reported [16, 17]. In this study, we evaluated the role of NIRF imaging in predicting and reducing AL in colorectal cancer surgery.

Materials and methods

Patients

This is a prospective interventional study conducted on colorectal cancer patients who had colorectal resection at Wakayama Medical University Hospital between December 2014 and September 2015. These patients were not consecutive patients with colorectal cancer. We selected patients at high risk of AL, such as those with cancer in the transverse colon or rectum. All operations were performed laparoscopically. Tumor locations were as follows: cecum = 2, ascending colon = 2, transverse colon = 7, descending colon = 1, sigmoid colon = 2, rectosigmoid colon = 3 and rectum = 6 (above peritoneal reflection = 2, below peritoneal reflection = 4). One patient had synchronous cancers of the ascending and sigmoid colon.

General procedures for laparoscopic colorectal surgery

The first port was inserted at the umbilicus for the scope, and the other four ports were inserted at right/left and upper/lower abdomen as is typical. A 30° rigid laparoscope was used in all procedures. After checking the cytology of washing fluid from the pouch of Douglas, we began with regional lymph node dissection and detection of regional arteries and veins (medial approach) using mainly ultrasonic laparoscopic coagulating shears. Regional arteries and veins were encircled, and these vessels were then clipped and divided. The section of the colon to be resected was sufficiently mobilized from the retroperitoneum and a small incision was then made to trim the small vessels around the planned anastomotic area. Functional end-to-end anastomosis (FEEA) was used in right hemicolectomy and transverse colon resection ($n = 9$, Table 1). In three transverse and descending colon cases, bowel anastomoses were performed by suture (one to revise an anastomosis at the operation). Double stapling technique (DST) was applied in sigmoidectomy and high/low anterior resection ($n = 11$). Air leakage tests were always performed in cases of left-sided anastomosis. Prophylactic drain insertion was not performed, but a drain was placed in the pouch of Douglas in cases of rectal cancer, at the operator's discretion ($n = 4$, Table 1). Diverting stoma were also fashioned at the operator's discretion, especially in cases of lower rectal cancer ($n = 6$, Table 1).

Procedures for intraoperative real-time NIRF

To detect the cancer from outside the serosa and to decide the colon cutting line, the area around the tumor is routinely preoperatively endoscopically marked using India ink. After the anastomosis, 5 mg/2 ml of ICG (Diagnogreen, Daiichi-Sankyo, Tokyo, Japan) was intravenously injected and observed via the laparoscope equipped for ICG-NIRF imaging (D-light P system, Karl Storz, Tuttlingen, Germany). The observation was 20 cm away from the proposed resection site and performed in Storz Professional Image Enhancement system (SPIES) SPECTRA A mode. The duration of evaluation of bowel fluorescence was 5 min. A merit of our method is that perfusion of bowel proximal and distal to the anastomotic area could be evaluated by one-time ICG injection.

Quantification parameters obtained from ICG-NIRF observation

The whole operation process including ICG-NIRF observation was recorded by laparoscopic record system to be used for quantification analyses. All time courses of fluorescence intensity were recorded by an image analyzer (ROIs software, Hamamatsu Photonics K.K., Hamamatsu, Japan). As shown in Fig. 1a, five points were set around the site of anastomosis on the bowel surface as the region of interest (ROI). A time curve of fluorescence intensity was created, we then evaluated the following factors, shown in Fig. 1b: the time from ICG injection to the beginning of fluorescence (T_0), maximum intensity (I_{max}), time to reach I_{max} (T_{max}), time to reach I_{max} 50% ($T_{max_{1/2}}$) and slope (I_{max}/T_{max}, S). The measurement points on this time curve were based on the

Table 1 Demographics of all 22 patients who underwent near-infrared fluorescence (NIRF) observation in bowel anastomosis

Case no.	Age (years)	Sex	BMI	ASA class	Smoking history	Tumor location	TNM stage	Radiation	Type of anastomosis	RBC transfusion	Drain insertion	Diverting stoma	Anastomotic leakage	Hospital stay (days)
1	81	F	16.7	2	–	Transverse	T3N1M0	–	Hand-sewn	–	–	–	–	8
2	73	F	19.5	2	–	Cecum	T2N0M0	–	FEEA	–	–	–	–	7
3	61	M	24.5	2	+	Rectosigmoid	T3N1M0	–	DST	–	+	–	–	11
4	63	F	22.9	2	–	Transverse	T3N0M0	–	FEEA	–	–	–	–	11
5	78	F	18.9	2	–	Sigmoid	T3N0M0	–	DST	–	–	–	–	7
6	85	F	23	3	–	Transverse	T3N1M0	–	FEEA	–	–	–	–	7
7	46	F	30.5	2	–	Rectosigmoid	T3N1M0	–	DST	–	+	–	–	7
8	82	F	16	3	–	Transverse	T4bN1M1a	–	FEEA	–	–	–	–	12
9	71	F	28.5	2	–	Rectosigmoid	T2N0M0	–	DST	–	–	–	–	7
10	62	F	22.6	2	–	Descending	T2N0M0	–	Hand-sewn	–	–	–	–	9
11	67	F	26.2	2	–	Transverse	T1N0M0	–	FEEA	–	–	–	–	7
12	62	M	18	2	+	Rectum	T3N0M0	+	DST	–	–	+	–	9
13	53	F	20.2	2	–	Rectum	T2N0M0	–	DST	–	–	+	–	7
14	46	F	23	2	+	Ascending	T2N0M0	–	FEEA	–	–	–	–	9
15	68	F	20.4	2	–	Rectum	T2N0M0	–	DST	–	+	–	–	8
16	70	F	23.1	2	–	Transverse	T3N1M0	–	FEEA	–	–	–	+	18
17	78	M	24.4	2	+	Rectum	T3N0M0	–	DST	–	–	+	+	7
18	72	M	22.2	2	+	Rectum	T2N0M0	–	DST	–	–	+	–	8
19	48	M	20.8	2	+	Rectum	T3N0M1a	–	DST	–	+	+	+	13
20	74	M	21.3	2	+	Sigmoid/ascending	S:T3N0M0 A:T4aN1M0	–	DST/FEEA	–	–	+	–	12
21	72	F	23.6	2	–	Transverse	T1N0M0	–	FEEA→hand-sewn	–	–	–	+*	7
22	60	M	26.2	2	+	Cecum	T1N1M0	–	FEEA	–	–	–	–	11

M male, *F* female, *RBC* red blood cell, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *FEEA* functional end-to-end, *DST* double stapling technique

*This case is presented in Fig. 4; re-anastomosis was performed after NIRF confirmation

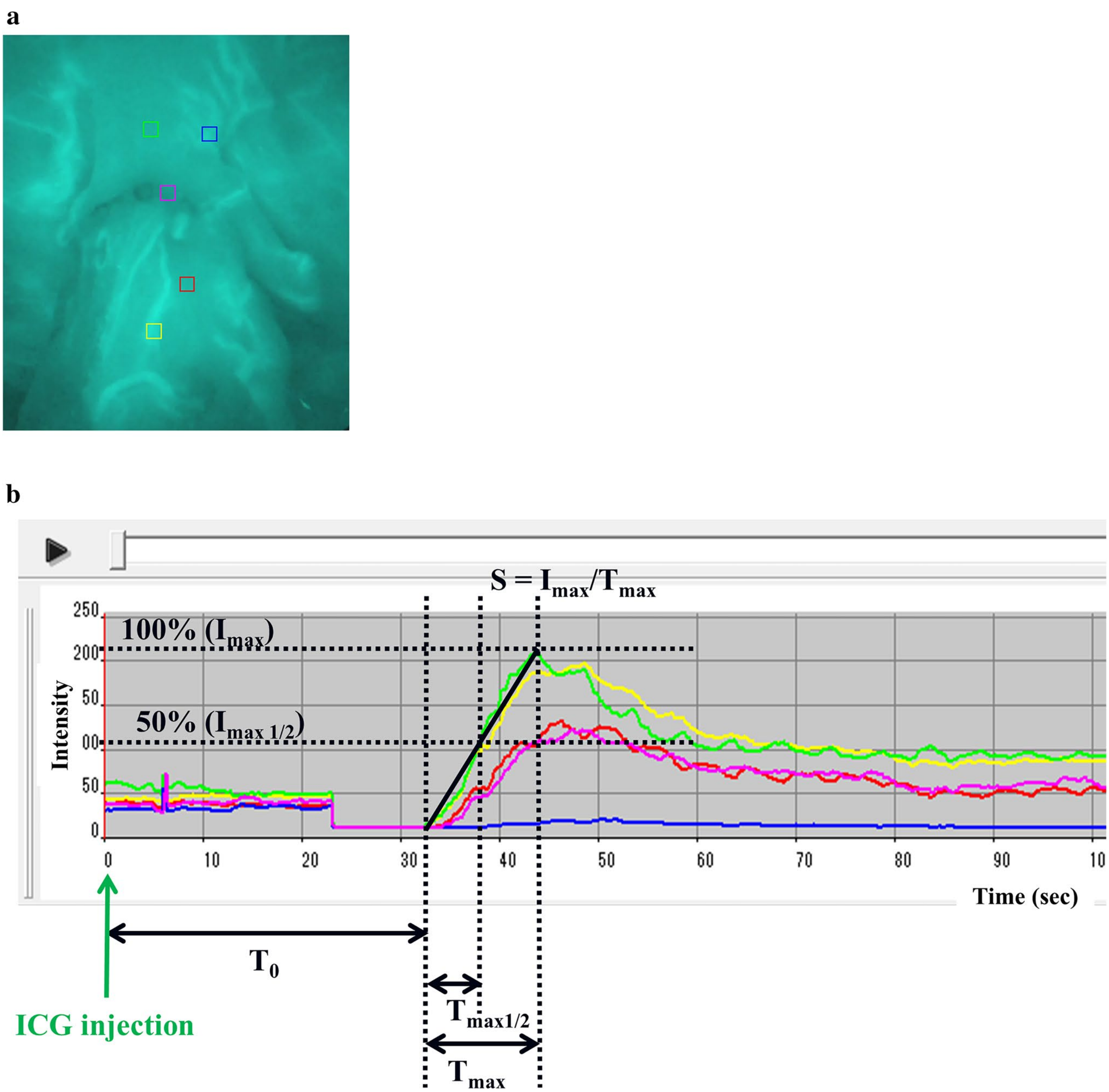

Fig. 1 Setting for the measurement of bowel perfusion using near-infrared fluorescence (NIRF) observation. **a** Five points were set around the site of anastomosis on the bowel surface as the ROI (region of interest). Obtained values were averaged at five points of ROI. **b** Time curve of fluorescence intensity. Parameters were as follows: time from ICG injection to the beginning of fluorescence (T_0), maximum intensity (I_{max}), time to reach I_{max} (T_{max}), time to reach I_{max} 50%($T_{max_{1/2}}$), and slope (I_{max}/T_{max}, S)

previous report by Igari et al. [18]. Obtained values were averaged at five points of ROI.

Statistical analysis

To evaluate the factors related to AL, we checked the following factors: age, sex, height, weight, body mass index (BMI), patient history to evaluate American Society of Anesthesiologists (ASA) risk factors and smoking history. Tumor factors were: tumor location and The Union for International Cancer Control's tumor-node-metastasis (UICC TNM) classification and preoperative radiation (±). Operative factors were: type of anastomosis (hand-sewn/FEEA/DSA), red blood cell transfusion (±), drain insertion (±), diverting stoma (DS) (±), anastomotic leakage (±) and postoperative hospital stay (days). Anastomotic leakage was defined in reference to the International Study Group of Rectal Cancer (ISGRC) grading system [19]. Each parameter was compared between AL and non-AL groups by Wilcoxon–Mann–Whitney test as a continuous variable. These statistical calculations were performed using JMP® Pro 13 (SAS Institute Japan, Tokyo, Japan). $P<0.05$ was defined as a statistically significant value in this study.

Results

Patient characteristics

There were 22 patients (7 males and 15 females). Patients, tumors and perioperative characteristics are shown in Table 1. Median age was 69 years (range 46–85 years) Median body mass index was 22.8 kg/m^2 (range 16.0–30.5 kg/m^2). There were 20 patients in American Society of Anesthesiologists (ASA) class 2 and only 2 in ASA class 3 (because of diabetes and a history of myocardial infarction). There were 8 patients with a history of smoking, 2 of whom developed AL. The UICC TNM stage was as follows: T1 = 9 patients, T2 = 5 patients, T3 = 7 patients, T4 = 2 patients (one patient had double cancer: sigmoid and ascending colon cancer). There were no severe postoperative complications except for AL. Median hospital stay was 8 days (range 7–18 days).

Quantification parameters from intensity curve of fluorescence imaging

In this study, AL occurred in 3 patients. Figure 2 shows typical perfusion patterns of no AL (Case No. 14) and AL (Case No. 16) after ICG injection. In the non-AL case, fluorescence around the anastomosis had already emerged at 30 s after ICG injection (Fig. 2b). In the AL case, fluorescence did not emerge, even at 60 s (Fig. 2i), though it was finally observed 72 s after ICG injection (Fig. 2j). There was a significantly longer time between ICG injection and T_0 in AL than in the no AL group (64.3 ± 27.6 and 18.2 ± 6.6 s, $p = 2.2 \times 10^{-3}$). Conversely, there were no differences between no AL and AL cases in $I_{\max}$ or time course ($T_{\max}$ and $T_{\max_{1/2}}$). All parameters observed with NIRF imaging are shown in Table 2. There was no difference in fluorescent pattern according to tumor location. Confirmed by one-way plot, all of the cases $T_0 > 40$ s belonged to AL group (Fig. 3).

Case No. 21 was a remarkable case in which postoperative AL could be avoided because it was identified by NIRF imaging (Fig. 4). A tumor was located in the transverse colon and thought to be suitable for laparoscopic transverse colon resection. Inspection of the anastomosis did not reveal any problems (surface color or tension) but when NIRF imaging was used to confirm perfusion, no fluorescence was seen at the proximal side of the colocolic anastomosis. In this case, re-anastomosis was performed, and the patient had no complications. In some other AL cases, there was late fluorescence (prolongation of T_0: cases 16, 17 and 19). We, therefore, performed re-anastomosis only in case No. 21.

Discussion

In this study, we demonstrated that patients with AL had longer T_0 than those without AL. Notably, all cases had AL when T_0 was over 40 s. This factor might, therefore, be the most sensitive predictor of AL.

In the past decade, there have been many reports on the effectiveness of NIRF imaging after anastomosis in gastrointestinal surgery including colorectal surgery [5–12], esophagectomy [20–23] and emergency colorectal surgery [24]. Using NIRF imaging with ICG, mesenteric vessels and related bowel perfusion can now be observed. Whether in open or laparoscopic surgery, intraoperative assessment of NIRF can contribute to reduction of the risk of AL and observation of real-time NIRF can become an important part of colorectal surgery [3].

Wada et al. reported that lower $F_{\max}$ (we have used the term '$I_{\max}$') might be a predictor of AL using PDE-neo (Hamamatsu Photonics K.K., Hamamatsu, Japan) as an open NIRF detector in 2017 [17]. The current study is, to the best of our knowledge, the first to target quantification of bowel perfusion using a laparoscopic NIRF detector. We also demonstrated the importance of T_0 using the quantification parameters from the intensity curve of fluorescence imaging. In this study, $I_{\max}$ was not such an important predictor of AL, in contrast to Wada's suggestion. We analyzed $I_{\max}$ data from our results and hypothesize that it is susceptible to respiratory fluctuation, especially in laparoscopic surgery. We, therefore, thought that $I_{\max}$ was an unstable factor, and an unreliable indicator of AL.

Checking T_0 by means of NIRF is easy, non-invasive and it has precise parameters that are easy to gather and has the potential to be measured in real time at operation. We previously reported that the AL rate in rectal surgery was 13% in our hospital [25], and we will investigate whether a new prediction system using NIRF T_0 reduces our leak.

Our study is limited by the small number of participants, so further studies such and randomized control trials, are needed [26]. Diverting stoma is currently recommended to reduce the risk of AL in rectal surgery [27]. If T_0 parameter is established for general application in clinical use and consensus is obtained for its use in AL prediction, we may not need to create a diverting stoma for patients who do not really require it.

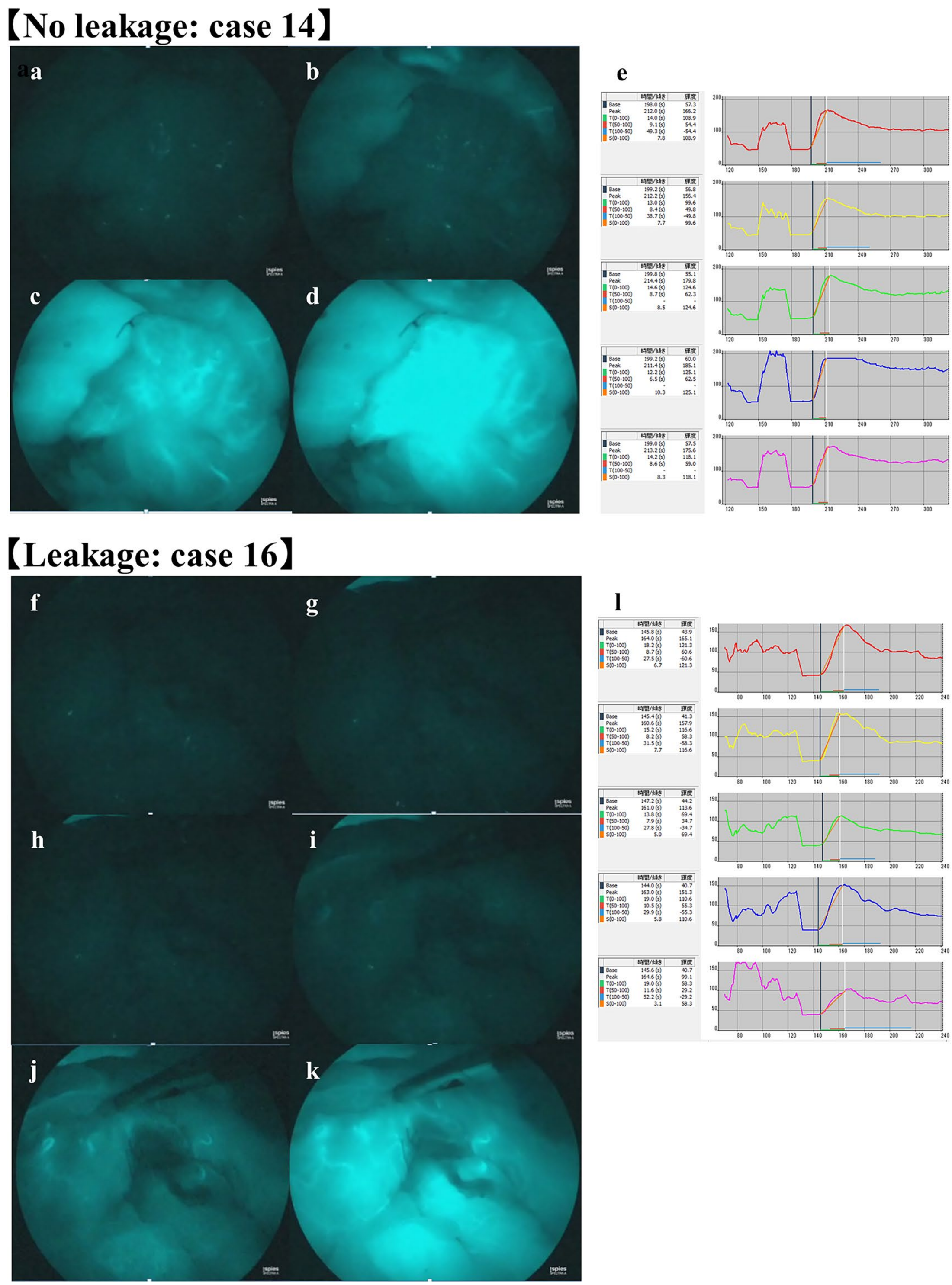

Fig. 2 Typical perfusion patterns of no AL (Case No. 14) and AL (Case No. 16). **a**–**f** no AL examples; **a** time of ICG injection (0 s). **b** Twenty seconds after ICG injection. **c** Fluorescence had already emerged at 30 s after ICG injection. **d** Forty seconds after ICG injection. **e** Time curve of fluorescence intensity after ICG injection. **f**–**l** AL examples; **f** time of ICG injection (0 s). **g** Thirty seconds after ICG injection. **h** Fluorescence had not emerged, even at 60 s after ICG injection. **i** Fluorescence emerged at 72 s after ICG injection. **j** Eighty seconds after ICG injection. **k** Ninety seconds from ICG injection. **l** Time curve of fluorescence intensity after ICG injection

Table 2 Parameters obtained from near-infrared fluorescence imaging

	Leakage group ($n = 4$)	No leakage group ($n = 18$)	P value
T_0 (s)	64.3 ± 27.6	18.2 ± 6.6	2.2×10^{-3}**
T_{max} (s)	26.4 ± 8.4	18.6 ± 6.2	0.09
$T_{max_{1/2}}$ (s)	13.3 ± 4.9	7.8 ± 2.9	0.12
I_{max}	79.9 ± 28.5	87.6 ± 33.2	0.42
S	3.4 ± 2.0	5.5 ± 2.8	0.27

**< 0.01

Conclusions

Bowel perfusion around the anastomotic area can be successfully visualized and quantified using NIRF imaging Prolonged T_0 might be a useful parameter for predicting AL in colorectal surgery.

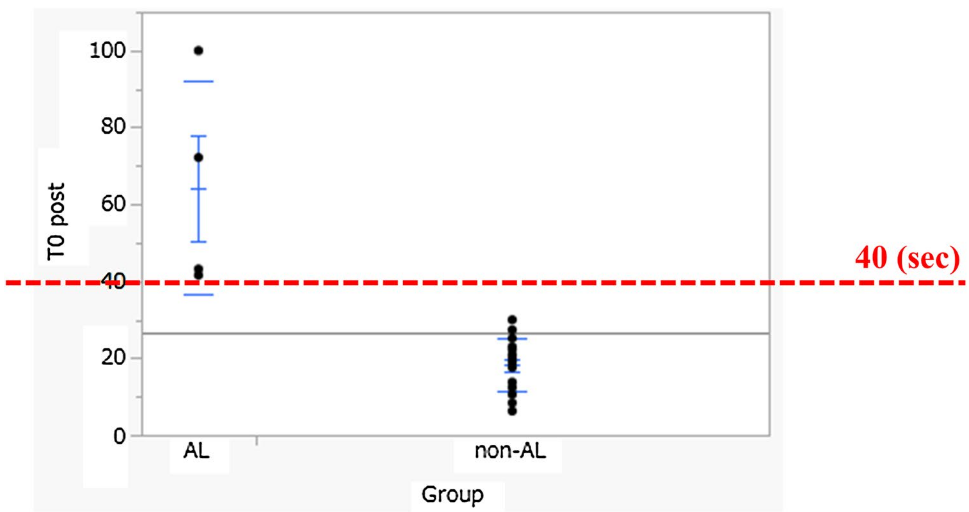

Fig. 3 One-way plot of T_0 comparing AL and no AL groups. Forty seconds might be a good indicator for prediction of AL

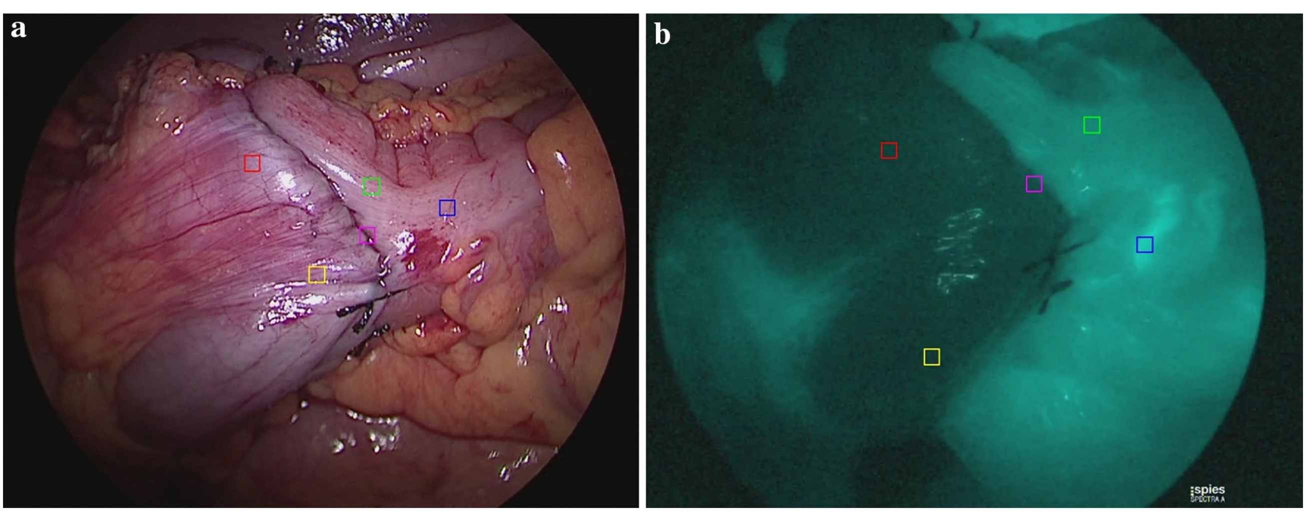

Fig. 4 Case No. 21 postoperative AL could be avoided by use of NIRF imaging. **a** Laparoscopic observation in usual light. **b** Fluorescence of oral side bowel never emerged after anastomosis

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol was approved by Wakayama Medical University Ethical Committee (approval number: 1418) and registered on University Hospital Medical Information Network (UMIN) Clinical Trial Registry (UMIN-CTR, UMIN000022876).

Informed consent Written informed consent was obtained from all participants included in this study.

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