Evaluation of Colonic Perfusion for Colorectal Cancer Surgery Using Indocyanine Green Fluorescence Imaging

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Objective: Anastomotic leakage (AL) is one of the most serious postoperative complications in colorectal surgery. AL reportedly occurs in 5–10% of cases following colorectal surgery. Poor colonic perfusion is proceeded to be AL during mesenteric resection. The purpose of this study was to evaluate the clinical utility of assessing colonic perfusion with indocyanine green (ICG) fluorescence imaging.

Materials and Methods: The subjects comprised 47 patients who underwent colorectal surgery with double-stapling technique anastomosis between March 2015 and September 2016. We measured the time fluorescence first appeared after the ICG injection and the time until maximum fluorescence was measured. These were compared with other clinical findings that correlated with AL.

Results: The median first fluorescence time was 43 sec, and the median maximum fluorescence time was 92 sec. Based on the fluorescence imaging, the surgical team judged the proximal colon to be anastomosed insufficiently in 10 patients (21.2%). The median proximal change distance of the transection line was 12.5 mm (5–70). In all 47 patients, AL occurred in 6 patients (12.8%). Maximum fluorescence time (over 98 sec) was significantly longer in the AL group (p = 0.025).

Conclusions: The results of this study suggested that assessing colonic perfusion using ICG fluorescence imaging during colorectal surgery was clinical useful. It was considered that patients with elongation of fluorescence time should be careful of AL.

Key words: colorectal cancer, colorectal surgery, anastomotic leakage (AL), ICG fluorescence imaging, colonic perfusion

Introduction

Surgical resection is the first choice for the most of patients with colorectal cancer (CRC). However, surgical resection is often occurred to postoperative complications such as anastomotic stricture, abdominal abscesses, and anastomotic leakage (AL)\(^1\)\(^2\). AL is one of the most serious of postoperative complications and it occurs relatively frequently in the cases of the rectal cancer surgery. This complication is reported to occur with approximately 1.5% of colon cancer surgery and approximately 5–20% of rectal cancer surgery\(^3\). The colonic perfusion at anastomotic site is the one of most important cause of AL\(^4\). The only evaluation methods for colonic perfusion are several subjective methods such as verification of the marginal artery pulse by palpation and assessment of blood flow based on the color of the colon itself. Indocyanine green (ICG) fluorescence imaging, wherein the colon is exposed to near infrared rays after intravenous injection of ICG, has been
identified as means of assessing colonic perfusion. Some studies have also reported on its utility in evaluating colonic perfusion intraoperatively.\(^5\)-\(^14\) They have also been reported that colonic anastomosis after confirming favorable colonic perfusion with ICG fluorescence and photodynamic eye (PDE) can reduce the risk of AL in cases of esophageal cancer or CRC surgery.\(^15\)-\(^17\). We assessed the clinical utility of ICG fluorescence imaging in evaluating anastomotic site perfusion in cases of CRC surgery.

### Materials and Methods

1. **Patients**

The subjects comprised a series of 47 patients who underwent CRC surgery with double stapling-technique (DST) anastomosis in our department between March 2015 and September 2016. This study is retrospective observation. Patients with iodine contrast agent, medication, or food allergies were excluded.

The study protocol was approved by the institutional review board of Juntendo University Hospital, and was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry as UMIN000012432 (http://www.umin.ac.jp/ctr/index.htm). Written informed consent was obtained from all patients for the use of their clinical data.

2. **Surgical technique**

All patients underwent preoperative mechanical bowel preparation, and prophylactic antibiotics were administered perioperatively. That depended on surgeon whether laparoscopic surgery or open surgery.\(^18\)-\(^19\). Blood flow was generally managed by resecting the base of the inferior mesenteric artery (IMA). The left colic artery was preserved in some patients with early-stage cancer.\(^20\). Mobilization of the splenic flexure was performed according to intestinal length in patients who required this maneuver to avoid placing undue tension at the anastomotic site. After mobilizing the descending colon, tumor specific mesorectal excision was performed on the basis of the site of the tumor. After dissection of the mesorectum at the planned transection line, the distal side of the tumor was clamped and intestinal lavage was performed. Resection was performed using linear stapler. The colon was resected 10 cm proximally from the tumor, and the anvil head was attached to the proximal colon. The DST anastomosis was performed using with circular stapler. Selection of the size of circular stapler was at the discretion of the surgeon. The anastomotic site was confirmed with colonoscopy, and leak test was performed. Ileostomy or transanal drainage tube was placed in patient with anastomotic site close to the anal verge or with preoperative chemotherapy or chemoradiotherapy. Whenever the distal margin of the tumor was at or below the site of the peritoneal reflection or the tumor had depth of T3 or greater and preoperative diagnostic imaging suggested lateral lymph node metastasis (>7 mm), lateral lymph node dissection was performed. Among patients who had adhesions or invasion of adjacent organs, combined resection was also performed.

3. **ICG fluorescence imaging**

During extracorporeal operations, the mesentery

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**Figure 1**

A: PDE-neo\(^8\) (Hamamatsu Photonics, Shizuoka, Japan)
B: The camera was fixed at a site 15 cm perpendicular to the resected colon.
on the proximal side of the tumor and the marginal artery were prepared and the planned transection line determined. One stitch was sutured on the colon which was planned by resection line. The colon was arranged so that there was no twist. The camera, the PDE-neo® (Hamamatsu Photonics, Shizuoka, Japan), was fixed at a site 15 cm perpendicular to the colon (Figure-1) and 2 ml (0.25 mg/ml) of ICG was injected intravenously so that blood flow could be evaluated while observing ICG fluorescence. The parameters evaluated included the time from intravenous injection of ICG to the time until maximum fluorescence. In all cases, fluorescence time was determined intraoperatively by surgical team.

If fluorescence was noted up to the planned transection line or beyond the distal side, resection was performed along the planned resection line. For some cases in which sufficient fluorescence was not observed near the planned resection line, additional colon resection was performed by the side where fluorescence was observed (Figure-2).

4. Postoperative AL

When postoperative AL was suspected, computed tomography (CT), colonoscopy, and radiological examination were performed to reach definitive diagnosis. In patients who had received diverting stoma, colonoscopy was performed 7–10 days postoperatively to confirm the anastomotic site. AL was graded on the basis of guidelines published by the International Study Group of Rectal Cancer (ISGRC): grade A resulted in no change in patient management; grade B required active therapeutic intervention but was manageable without re-laparotomy; and grade C required re-laparotomy.

5. Parameters

The following clinicopathological factors were examined in this study. The patient factors included age, sex, body mass index (BMI) (kg/m²), smoking history (Brinkman Index: 400 or higher), presence/absence of diabetes, presence/absence of cardiovascular disease, oral administration of anticoagulants, preoperative American Society of Anesthesiologists (ASA) score, and preoperative treatment (chemotherapy: six courses of mFOLFOX6, chemoradiotherapy: S1 + radiation). The surgical factors included operative time, blood loss, left colic artery preservation, anastomotic diameter, number of staples used, placement of a transanal drainage tube, and with or without ileostomy. The tumor factors included maximum diameter (mm), location, depth, lymph node metastasis, and staging (UICC (International Union Against Cancer) 7th edition guidelines).

6. Statistical analysis

JMP version 13.0.0 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis, and a nonparametric chi-squared test and Mann-Whitney U test was performed. Items considered being risks factors for AL on the basis of the available literature were used as covariates. The level of statistical significance was set at p < 0.05.

Results

We investigated 47 patients (29 men, 18 women) with CRC, and the patient attributes were shown in Table-1. No complication clearly associated with ICG administration was observed such as allergy.

The median time until the start of fluorescence was 43 sec (range: 12–80 sec), and the median time until maximum fluorescence was 92 sec (range: 45–164 sec). In this study, the planned resection lines were changed in 10 patients. The median proximal change distance of the transection line was 12.5 mm (range 5–70 mm) (Table-2).

Postoperative AL occurred in 6 patients (12.8% of 47). Figure-2

A: Bowel perfusion under normal image. Yellow arrow indicates the point of initial planned transection line. B: Bowel perfusion under ICG fluorescence imaging. Red dotted line indicates the site of transection where fluorescence intensity was judged to be adequate intraoperatively. Note that the point of demarcation line determined by ICG fluorescence was moved more proximal compared with the initial planned transection line.
Those patients’ details were showed in Table-3. In 5 of 6 cases of AL, the time until maximum fluorescence exceeded the median time. Focusing on these results, when the evaluation was performed using the receiver operating characteristic curve and the cutoff value was set at 98 sec, the area under the curve reached a maximum value (area under the receiver operating curve = 0.776).

Table 1: Patient and tumor characteristics (n=47)

| Characteristics                        | No. of patients |
|----------------------------------------|-----------------|
| Age (years)                            | 66 (38–86)      |
| Gender (Male/Female)                   | 29/18           |
| BMI (kg/m²)                            | 21.9 (15.0–31.4)|
| Brinkman Index ≥ 400                   | 11 (23.4%)      |
| Anticoagulant therapy                  | 11 (23.4%)      |
| Cardiovascular comorbidity             | 13 (27.7%)      |
| Diabetes                               | 11 (23.4%)      |
| ASA 1/2/3/4                            | 12/29/6/0       |
| Preoperative therapy *                 | 3 (6.3%)        |
| Tumor location (Sigmoid colon/Rectum)  | 33/14           |

Operative factors:
- Operation time (min): 266 (166–830)
- Operative blood loss (ml): 25 (5–210)
- Ligation of IMA (Low/High): 7/40
- Size of circular stapler (25 mm/29 mm): 7/40
- No. of firing staple cartridge (1/2/3): 32/15/0
- Transanal drain: 22 (46.8%)
- Covering ileostomy: 7 (14.9%)

Tumor factors (Oncological factors):
- Tumor size (mm): 40 (13–90)
- T-category (T1/T2/T3/T4): 7/6/28/6
- N-category (N1/N2/N3): 15/4/0
- UICC-TNM stage (I/II/III/IV): 9/19/15/4

*chemotherapy: 2 cases, chemoradiotherapy: 1 case

Table 2: ICG fluorescence imaging

| First fluorescence time (sec) | 43 (12–80) |
| Maximum fluorescence time (sec) | 92 (45–164) |
| Change of transection line (%) | 10 (21.2) |
| The median proximal change distance of the transection line (mm) | 12.5 (5–70) |

Table 3: Cases of Anastomotic leakage

| Case | 1 | 2 | 3 | 4 | 5 | 6 |
|------|---|---|---|---|---|---|
| Age (years) | 65 | 59 | 68 | 53 | 65 | 68 |
| Gender | M | F | M | M | M | M |
| Location | S | S | S | R | R | S |
| First fluorescence time (sec) | 60 | 55 | 34 | 18 | 43 | 50 |
| Maximum fluorescence time (sec) | 110 | 110 | 164 | 144 | 98 | 80 |
| Change of transection line | no | no | no | yes | no | no |
| Grade of anastomotic leakage | B | B | C | A | A | B |

S: Sigmoid colon, R: Rectum

Discussion

In recent years, several reports had indicated that intraoperative ICG fluorescence imaging was useful method for assessing organ perfusion. Some reports had focused on ICG fluorescence as the technique of evaluating colonic perfusion intraoperatively\(^5\)\(^-\)\(^14\). When ICG bound to a protein and an excitation light of 50–810 nm was applied, fluorescence with a peak of approximately 840 nm was produced. A near infrared camera could detect fluorescence emitted by ICG that had been injected

Table 3: Cases of Anastomotic leakage

- with a sensitivity of 0.83 and specificity of 0.68.

Patients were divided into two groups, depending on whether the time until maximum fluorescence was over 98 sec or not.

The AL rate in the group of under 98 sec was 3.4% (1/29), and that in the group of over 98 sec it was 27.8% (5/18).

In terms of the correlation between clinicopathological factors and AL, no significant difference was noted for any of the parameters in this study (Table-4). We found that AL was significantly more common in the group with results of over 98 sec which was the time until maximum fluorescence (p = 0.025). The risk factor of the time until maximum fluorescence being over 98 sec was the patients with preoperative therapy (p = 0.050) (Table-5).

| Case | 1 | 2 | 3 | 4 | 5 | 6 |
|------|---|---|---|---|---|---|
| Age (years) | 65 | 59 | 68 | 53 | 65 | 68 |
| Gender | M | F | M | M | M | M |
| Location | S | S | S | R | R | S |
| First fluorescence time (sec) | 60 | 55 | 34 | 18 | 43 | 50 |
| Maximum fluorescence time (sec) | 110 | 110 | 164 | 144 | 98 | 80 |
| Change of transection line | no | no | no | yes | no | no |
| Grade of anastomotic leakage | B | B | C | A | A | B |
### Table 4  Risk factors of AL

|                      | AL (n = 6) | No leak (n = 41) | p-value  |
|----------------------|------------|------------------|----------|
| Age                  | 65 (53–68) | 65 (38–86)      | 0.644    |
| Gender               | Male/Female| 5/1              | 24/17    | 0.384    |
| BMI 25 or more       | yes/no     | 1/5              | 8/33     | 1.000    |
| Brinkman Index ≥400  | yes/no     | 2/4              | 9/32     | 0.614    |
| Anticoagulant therapy| yes/no     | 2/4              | 9/32     | 0.614    |
| Cardiovascular comorbidity | yes/no  | 2/4              | 11/30    | 1.000    |
| Diabetes             | yes/no     | 3/3              | 8/33     | 0.131    |
| ASA                  | 1.2/3.4    | 6/0              | 35/6     | 1.000    |
| Preoperative therapy | yes/no     | 1/5              | 2/39     | 0.343    |
| Tumor location       | S/R        | 4/2              | 11/30    | 1.000    |
| Operation time (min) | 297.5 (261–410) | 263 (166–830)   | 0.138    |
| Operative blood loss (ml) | 25 (20–50) | 25 (5–210)     | 0.586    |
| Ligation of IMA      | Low/High   | 1/5              | 6/35     | 1.000    |
| Size of circular stapler (mm) | 25 mm/29 mm | 5/1              | 35/6     | 1.000    |
| Transanal drain      | yes/no     | 2/4              | 20/21    | 0.670    |
| Covering ileostomy   | yes/no     | 2/4              | 6/35     | 0.081    |
| Tumor size (mm)      | 36.5 (18–90) | 40 (13–86)     | 0.836    |
| T-category           | 1.2/3.4    | 1/5              | 12/29    | 1.000    |
| Lymph node metastasis| yes/no     | 2/4              | 17/24    | 1.000    |
| First fluorescence time (sec) |        |                  |          |
| Maximum fluorescence time over 98 sec | yes/no | 5/1              | 13/28    | 0.025    |
| Change of transection line | yes/no  | 1/5              | 9/32     | 1.000    |

### Table 5  Risk factors the time until maximum fluorescence being over 98 sec

|                      | 98 sec or less | 98 sec or more | p-value  |
|----------------------|----------------|---------------|----------|
| Age                  | 65.6           | 64.4          | 0.878    |
| Gender               | Male/Female    | 15/14         | 14/4     | 0.122    |
| BMI 25 or more       | yes/no         | 6/23          | 3/15     | 1.000    |
| Brinkman Index ≥400  | yes/no         | 6/23          | 5/13     | 0.726    |
| Anticoagulant therapy| yes/no         | 6/23          | 5/13     | 0.726    |
| Cardiovascular complications | yes/no | 7/22          | 6/12     | 0.521    |
| Diabetes             | yes/no         | 6/23          | 5/13     | 0.726    |
| ASA                  | 1.2/3.4        | 6/0           | 35/6     | 0.384    |
| Preoperative therapy | yes/no         | 0/29          | 3/15     | 0.050    |
| Tumor location       | S/R            | 21/8          | 13/15    | 1.000    |
| Operation time (min) | 303            | 289           | 0.457    |
| Operative blood loss (ml) | 44.7          | 38.8          | 0.502    |
| Ligation of IMA      | Low/High       | 4/25          | 3/15     | 1.000    |
| Tumor size (mm)      | 36.5           | 40            | 0.250    |
| T-category           | 1.2/3.4        | 6/23          | 7/11     | 0.199    |
| Lymph node metastasis| yes/no         | 12/17         | 7/11     | 1.000    |
into the body to produce real-time visualization of the blood vessels. Since this was a relatively simple process that allowed comparatively deep internal observations with very few side effects, this technique was highly advantageous for use intraoperatively\textsuperscript{13} -\textsuperscript{14}. Moreover, as minimally invasive procedure it was being utilized in a wide range of fields including cardiovascular surgery\textsuperscript{23} and breast cancer sentinel lymph node biopsy\textsuperscript{24}. In the field of gastrointestinal surgery, ICG fluorescence imaging had been reported to be useful for evaluating blood flow in the esophagus\textsuperscript{16} -\textsuperscript{17} and colon\textsuperscript{5} -\textsuperscript{14}. Kumagai \textit{et al.} used ICG fluorescence imaging to assess perfusion of reconstructed gastric tubes during esophageal cancer surgery\textsuperscript{25}. Their study focused on the time from ICG intravenous injection until contrast was observed in the reconstructed gastric tube. After the intravenous injection of ICG, they measured the time from contrast entry into the right gastroepiploic artery base to contrast entry into the left gastroepiploic artery terminal branch and the gastric tube tip. They reported that there was a strong possibility of necrosis in the gastric tube in patients that contrast time over 90 sec. They also reported that the portion required at least 60 sec of contrast time to prevent AL. Our study also investigated fluorescence as a function of time. We found that a significant difference with the time until maximum fluorescence cutoff value such as 98 sec. The determination of organ contrast completion was left to a surgeon’s subjective judgment. It had been reported that differences may arise among testers. Wada \textit{et al.} assessed blood flow using luminosity analysis software (ROIs) in cases of left colon cancer\textsuperscript{13}. Although the time until maximum fluorescence tended to be a useful parameter, no significant difference was found. On the other hands, the first fluorescence time was not related to AL in this study. Wada \textit{et al.} also reported the first fluorescence time was not related to AL\textsuperscript{13}.

Preoperative treatment tended to be a factor in the time to reach maximum fluorescence exceeding 98 sec. The reason for this remains unclear as no large-scale studies have investigated this topic among patients who have undergone preoperative treatment and few data are available on the topic. However, it has been reported that AL tends to be common in such cases\textsuperscript{26}. When radiotherapy is performed, chronic intestinal wall fibrosis and vascular arteriosclerotic changes cause microangiopathy\textsuperscript{27} -\textsuperscript{28}. Whereas when chemotherapy is performed, oxaliplatin causes reactive oxygen species to be produced, which damage epithelial cells and upregulate matrix metalloproteinases 2 and 9, causing microangiopathy resulting from a loss of endothelial cells and invasion by blood cell components\textsuperscript{29} -\textsuperscript{30}. This may affect the anastomotic site in the colon, causing fluorescence time to be prolonged.

In cases of maximum fluorescence requiring over 98 sec, surgeons should consider the way of the reduce risk of AL, such as transanal drainage tube placement\textsuperscript{31}, prophylactic ileostomy, or implementing splenic flexure mobilization and additional resection to achieve sufficient perfusion from the middle colic artery left branch. Future study should reveal which way was the best for the reduce risk of AL.

This study had several limitations. As various factors other than anastomotic site perfusion were related to AL\textsuperscript{26}, an objective evaluation with unified patient conditions needed to be conducted. Our sample size was small. A study in larger population needed to be performed. In addition, remaining distal side colonic perfusion was not evaluated because this ICG system is an extracorporeal operation. Venous return failure can also be involved in AL. Evaluation of arterial perfusion was not comprehensive. There was no report using ICG fluorescence imaging to evaluate venous return. However, ICG fluorescence imaging could theoretically be used to evaluate venous return according to contrast disappearance time. We found that the contrast intensity did not decrease for at least several minutes after contrast injection. Further research was needed to investigate the evaluation of venous congestion.

After DST anastomosis, AL was more common in cases wherein maximum fluorescence with ICG fluorescence imaging took over 98 sec. Intraoperative ICG fluorescence imaging prevented the AL by evaluating anastomotic site blood flow. It is anticipated that further improvements and the accumulation of more case data will make it possible to apply this technique in colorectal cancer surgery to ensure greater safety and fewer complications.
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Authors’ contributions

Study concept and design, S. Motegi, KT; data acquisition, S. Motegi, SK, SI, MT, YK; analysis and interpretation of data, S. Motegi, SK, K. Sugimoto; drafting of the manuscript, S. Munakata, YT; critical revision of the manuscript, K. Sakamoto. All authors read and approved the final manuscript.

Conflicting interest statement

The authors declare that there are no conflicts of interest.

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