Strategy to Avoid Anastomotic Leakage in Laparoscopic Colorectal Resection Using the Indocyanine Green Fluorescence System

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**Purpose:** Anastomotic leakage (AL) in colorectal resections is often caused by insufficient blood flow to the stump. Injecting indocyanine green can help detect blood flow intraoperatively. In this study, we evaluated our original strategy using an indocyanine green fluorescence system to avoid AL.

**Methods:** We retrospectively evaluated 79 patients who underwent laparoscopic colorectal resection for colon cancer using a double-stapling technique. Blood flow in oral stumps was evaluated by measuring indocyanine green fluorescence time (FT). We investigated AL cases in detail and analyzed correlations between FT and risk factors for AL.

**Results:** Of the 79 patients, 7 (8.9%) developed AL. We divided patients by FTs: >60 seconds, 50 to 60 seconds, and <50 seconds. The AL rates were FT >60 seconds, 60%; FT 50 to 60 seconds, 10.3%; and FT <50 seconds, 2.2%. The AL rate of high-risk cases (with more than 2 risk factors) were calculated and we made our original strategy to avoid AL as the following. Further resection or diverting stomas were needed by the FT >60 seconds group, and by members of the FT 50 to 60 seconds group with ≥3 risk factors. The FT <60 seconds group needed no additional management.

**Conclusions:** Patients with delayed FT (>60 seconds, or 50–60 seconds with ≥3 risk factors) may need revision of the anastomosis (diverting stoma or additional resection) to avoid AL. Our original strategy may contribute to reduce AL in colorectal operations.

**Key words:** Blood flow evaluation – Indocyanine green fluorescence system – Colorectal resection – Anastomotic leakage
A nastomotic leakage (AL) is a life-threatening postsurgical complication that significantly increases rates of postoperative mortality and local recurrence and diminishes long-term cancer-specific survival in colon cancer patients. The reported incidence of AL is 3.6% to 11.6% after double-stapled anastomosis for rectal cancer.

Many factors reportedly increase the risk of AL in laparoscopic anterior resection (AR), including host factors such as male sex, body mass index ≥25 kg/m², American Society of Anesthesiologists score >2, tumor size >5 cm, and preoperative chemotherapy; and surgical factors, such as long surgical time, intraoperative transfusion/blood loss >100 mL, anastomosis distance from the anal verge <5 cm, and multiple staple firings.

To improve the AL rate in laparoscopic AR, assessment of intraoperative blood flow at the anastomotic site is important. Laser doppler flowmetry is reported to be a feasible method to evaluate intestinal ischemia, and thermography can be used to gauge gastric vascularization and gastric tube viability during esophagectomy.

The indocyanine green (ICG) fluorescence system has been used to assess organ blood flow intraoperatively, and it is reportedly useful for evaluating anastomotic perfusion and detecting transection lines in colorectal surgery.

We are using the ICG system to improve the AL rate in patients with colon cancer. We used the Hyper Eye Medical System (HEMS; Mizuho Medical Co Ltd, Tokyo, Japan), which can visualize blood and lymphatic vessel with near-infrared light (760–780 nm). Intravenously injected ICG emits light with a peak wavelength of 800 to 850 nm and clearly shows circulatory vessels. We have been evaluating blood flow at anastomotic sites by measuring the fluorescence time (FT) of oral stumps, and have investigated the relationship between FT and AL.

In laparoscopic AR, diverting stomas are sometimes created to prevent AL and septic complications. However, the role of diverting stomas is still controversial; they affect patients’ quality of life, and sometimes develop their own complications. However, diverting stomas may be beneficial for selected patients.

We retrospectively investigated the relationship between AL and stump FT in 79 patients who underwent colorectal resection using double-staple technique for colon cancer. This study analyzed a new strategy for avoiding AL in laparoscopic colorectal resection by evaluating colon blood flow intraoperatively.

Patients and Methods

This study retrospectively included 79 patients with colon cancer who underwent laparoscopic colorectal resection using a double-staple technique at Tokushima University Hospital from 2012. Blood flow was evaluated in oral stumps after small-incision laparotomies, using umbilical ports, with ICG (Diagnogreen, Daiichi Sankyo Co Ltd, Tokyo, Japan) and the HEMS. The study protocol was approved by the Institutional Review Board of Tokushima University Hospital (No. ToCMS 3215-2). And the work has been reported in line with the PROCESS criteria.

Blood flow evaluation

After the intraabdominal procedure, the rectum was resected with a linear stapler, and a small laparotomy was performed at the umbilical site. As an extra-abdominal procedure, the mesentery was dissected, and the tumor was resected. The area was tightened with a purse-string suture, and an anvil was placed in the oral sigmoid colon. We injected 7.5 mg of ICG intravenously and evaluated blood flow in the oral stump by measuring FT using the HEMS. The FT was defined as the time from ICG injection to the point when the oral stump was most strongly fluorescent in the monitor. End-to-end anastomosis was performed by the double-stapling technique. The air leak test was routinely performed in all cases; if any tissue showed leakage, it was sutured laparoscopically. Diverting stomas were not created in these 79 patients. All patients in the validation group were given transanal drains.

Risk factors for AL

We investigated associations between AL and FT of oral stumps, and between other risk factors for AL. We examined the risk factors described in the introduction and other well-known factors, including male sex, body mass index ≥25 kg/m², tumor size >5 cm, diabetes mellitus, steroid administration, and such surgical risk factors as operative time ≥300 minutes, intraoperative blood loss ≥100 mL, and ≥3 staple firings.

Statistical analysis

Surgical data were compared using Student t test. P < 0.05 was considered significant. All statistical analysis was performed using statistical software (JMP 14.0.0, SAS Institute Inc, Cary, North Carolina).
Results

All patients’ FTs are plotted in Fig. 1. Of the 79 patients, 7 (8.9%) developed AL. Their FTs were 71, 62, 55, 52, 50, and 45 seconds; 1 patient showed no fluorescence. The AL rate was 60% in the FT >60 seconds group and 5.4% in the FT <60 seconds group.

We had 4 patients who experienced AL but whose FT was <60 seconds (Table 1). The FTs for patients 1 to 3 were 55, 52, and 50 seconds, respectively; these patients had some host or surgical risk factors. Patient 1 had 2 surgical risk factors (long operation, multiple staples) due to obesity (body mass index, 29.9); however, patients 2, 3, and 4 had few surgical risk factors.

Table 1  Details of patients with AL whose FT was <60 seconds

| Case | FT, s | Sex | BMI   | Tumor size, cm | Other factors | Operative time, min | Blood loss, mL | Firings |
|------|-------|-----|-------|----------------|---------------|---------------------|----------------|---------|
| 1    | 55    | M   | 29.9  | None           |               | 321                 | 10             | 3       |
| 2    | 52    | M   | 17.6  | 1.2            | Steroids      | 232                 | Minimal        | 1       |
| 3    | 50    | M   | 25.8  | 2.8            | DM            | 291                 | Minimal        | 1       |
| 4    | 45    | F   | 19.9  | 4.0            | Poor preparation | 200                | minimal        | 1       |

BMI, body mass index; DM, diabetes mellitus

*Host and surgical risk factors are shown. Bold indicates high risk factor.

We then defined high-risk patients (for AL) as those with ≥2 risk factors. In the FT 50 to 60 seconds group, 44.8% (13 of 29) of the patients were high risk, compared with 17.8% (8 of 45) in the FT <50 seconds group. Among the high-risk patients, the AL rate was 23.1% (3 of 13) in the FT 50 to 60 seconds group, but 0% in the FT <50 seconds group (Fig. 2).

We then considered how these results affect the indication for diverting stomas. If diverting stomas were created in all patients in the FT >60 seconds group and all patients in the FT 50 to 60 seconds group with ≥2 risk factors, the total AL rate would decrease from 8.9% (7 of 79 patients) to 1.3% (1 of 79 patients). However, this would produce a huge false-positive rate—stomas in patients who do not need them—of 34.5%. However, if diverting stomas were created in all patients in the FT >60 seconds group and all patients in the FT 50 to 60 seconds group with ≥3 risk factors, the AL rate would decrease from 8.9% to 2.6% (2 patients) and the false-positive rate to a more acceptable 6.9% (2 of 29 patients).

A schematic showing our strategy to decrease AL rate is shown in Fig. 3. Patients whose FT is <50 seconds need no additional management; those whose FT is >60 seconds may need diverting stomas, or an additional resection toward tissue where FT is >60 seconds; and those whose FT is 50 to 60 seconds need no additional management if patients, more detailed evaluation may be needed to control AL.

We had 4 patients who experienced AL but whose FT was <60 seconds (Table 1). The FTs for patients 1 to 3 were 55, 52, and 50 seconds, respectively; these patients had some host or surgical risk factors. Patient 1 had 2 surgical risk factors (long operation, multiple staples) due to obesity (body mass index, 29.9); however, patients 2, 3, and 4 had few surgical risk factors.

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A schematic showing our strategy to decrease AL rate is shown in Fig. 3. Patients whose FT is <50 seconds need no additional management; those whose FT is >60 seconds may need diverting stomas, or an additional resection toward tissue where FT is >60 seconds; and those whose FT is 50 to 60 seconds need no additional management if
they have $\leq 2$ host or surgical risk factors, but should be considered for diverting stomas or further resection if they have $\geq 3$ risk factors.

Discussion

Anastomotic leakage is a serious, often life-threatening complication in colorectal surgery. Patients with major AL often need peritoneal lavage and drainage, and diverting stomas. Disease-free survival for patients with AL is also shorter than for patients with no AL.\textsuperscript{16} Despite improved devices and surgical techniques, the AL rate is still high.

Understanding and reducing host and surgical risk factors for AL are critical to reducing their incidence. As a surgical technique, precompression before firing for staple formation is reported to help decrease the likelihood of AL.\textsuperscript{17,18}

Although diverting stomas are sometimes created in AR patients, their role is still controversial. They can reportedly prevent AL,\textsuperscript{19,20} thus reducing reoperations. A prospective, randomized, multicenter trial of stoma indications reported that diverting loop ileostomies should be fashioned in rectal cancer patients with anastomoses below 6 cm, particularly in male patients.\textsuperscript{21} In contrast, another report found that diverting stomas were not significantly related to symptomatic AL.\textsuperscript{22} These contrasting reports indicate how unclear criteria for creating diverting stomas are.

Sufficient blood flow is critical in healing gastrointestinal anastomosis. Several methods are used to evaluate intestinal perfusion: doppler ultrasound, laser doppler flowmetry, tissue oxygen tension, angiography, and oxygen spectroscopy.\textsuperscript{23–25}

However, these methods have some problems, such as the need for technical skill and lack of reproducibility. The ICG fluorescence imaging system has been used to assess intraoperative blood perfusion in cardiovascular surgery, neurosurgery, reconstructive surgery, gastrointestinal surgery,\textsuperscript{26,27} and, as we show here, intestinal surgery. It is a relatively simple, reproducible technology for assessing tissue blood flow.

This is the first report of the relationship between FT and AL. In conjunction with other risk factors for AL, FT can be part of a useful and easily measured set of criteria for diverting stomas. To know patients’ risk factors before surgery is very important because AL may occur especially in patients with multiple risk factors even when the blood flow at the anastomosis is enough.

This study has some limitations. We defined FT as the time from ICG injection to the time when the stump was most strongly fluorescent in the monitor. Measuring FT may vary among different surgical staff, so more objective methods of measuring FT may be needed. Quantitative assessment of intesti-
nal perfusion by measuring ICG intensity is reportedly useful\(^\text{11}\) and is being examined further at our institution.

Another limitation is that we evaluated the FT only in oral stumps. Evaluation of anal stumps is difficult in the minilaparotomy field. We are currently using laparoscopic ICG systems to evaluate oral stumps and other colon sections during various procedures. In laparoscopic evaluation, FT of anal stumps was almost under 60 seconds (data not shown).

In conclusion, intraoperative evaluation of blood flow using an ICG fluorescence system, considered with relevant risk factors, is an easy method to identify and help manage patients at risk for AL after anterior resections.

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