Risk Factor Analysis for Anastomotic Leakage after Lower Rectal Cancer Resection: A Retrospective Single-Center Study

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Abstract

Background We investigated the correlation between surgery-related factors and the incidence of leakage after low anterior resection (LAR) for lower rectal cancer.

Methods A total of 630 patients underwent colorectal surgery between 2011 and 2014 in our department. Of these, 97 patients (15%) underwent LAR, and are the subjects of this retrospective study. Temporary ileostomy was performed for each patient.

Results Anastomotic leakage occurred in 21 patients (21.7%). Univariate analysis showed that operative duration (p=0.0051), transanal hand-sewn anastomosis (p=0.0141), and operation procedure (p=0.0191) were significantly associated with the incidence of leakage. Multivariate analysis showed that underlying disease (p=0.044), transanal hand-sewn anastomosis (p=0.0188), and drain type (p=0.0251) were significantly associated with the incidence of leakage. The propensity score analysis results showed that closed drainage was associated with 6.3 times more postoperative blood loss (mls) in patients experiencing anastomotic leakage compared with open drainage, in the inverse probability of treatment-weighted analysis.

Conclusions Our results showed that underlying disease, transanal hand-sewn anastomosis, and the drain type may be risk factors for developing anastomotic leakage after LAR for lower rectal cancer. The notable finding was that the type of drainage was related to the incidence and volume of anastomotic leakage: open drainage was correlated with the incidence of leakage, and closed drainage was correlated with the volume of anastomotic leakage.

Background

Postoperative anastomotic leakage is a major complication after low anterior resection (LAR) for lower rectal cancer. Despite technical improvements and instrument developments, double-stapling anastomosis using circular staples and transanal anastomosis are relatively difficult. The incidence of anastomotic leakage after LAR is 3–27% [1, 2]. Anastomotic leakage significantly increases postoperative morbidity, requiring prolonged hospital stay and, in some patients, further surgical procedures [3], all of which affect patients’ quality of life. In patients with advanced cancer with lymph node metastasis, postoperative adjuvant chemotherapy may be delayed, which could lead to
an increased recurrence rate and a poorer prognosis. We previously experienced patients with continued anastomotic leakage after changing from open to closed drainage after LAR for lower rectal cancer.

In this study, we investigated the correlation between surgery-related factors, namely, the type of drain and the incidence of anastomotic leakage, after LAR for lower rectal cancer. Our previous experience suggested that the type of drain may be related to the incidence of postoperative complications. By clarifying these risk factors, we can improve patients’ outcomes to prevent the occurrence and severity of anastomotic leakage.

Methods
Between 2011 and 2014, 630 patients underwent colorectal surgery in our department, of which 149 patients had rectal cancer, excluding rectosigmoid cancer. This was a retrospective study of all 97 patients who underwent LAR (including intersphincteric resection and total colectomy) at our hospital from 2011–2014. Temporary ileostomy was performed in all patients, and no patients received preoperative chemoradiation. Informed consent was obtained from each patient before surgical resection, and the Institutional Review Research Committee for Human Subjects at Kurume University Hospital approved the study (no. 18197). Written informed consent was obtained from each of the subjects prior to enrollment in this study.

Data were extracted from the clinical records, including sex, age, underlying disease (namely, diabetes mellitus, hypertension, coronary artery disease, and renal dysfunction), body mass index (BMI), stage, preoperative albumin value, operation duration, blood loss volume, anastomosis method, lateral lymph node dissection, type of drainage, drainage volume, and any incidence of leakage. The drainage volume was calculated by measuring the total amount drained from the day of surgery until the day when the drain was removed, according to patients’ medical records.

The Clavien–Dindo classification system [4] was used for the definition of leakage and included Grade I complications. We confirmed anastomotic leakage by digital examination, anal-scopy findings, and enema imaging using an iodinated contrast agent.

The type of drain was divided into two types: open (Group O) and closed (Group C). Patients in Group
had both a 6-Fr. duple drain (Kaneka Medical Products, Osaka, Japan) and a 12-Fr. Penrose drain (Fuji Systems Corp., Tokyo, Japan), while those in Group C had a 19-Fr. J-VAC drainage system (Johnson & Johnson, New Brunswick, NJ) (Fig. 1). In all patients, we inserted the drains around the anastomosis site.

**Statistical analysis**

Continuous variables were presented as means and standard deviation and categorical variables as numbers and percentage. Independent-samples t-test was used for the analysis of differences between the two groups. All statistical analyses were performed using SAS ver. 9.4 (SAS Institute Inc., Cary, NC). A significant difference was defined as a p-value of less than 0.05.

Propensity score (PS) analysis was performed to confirm these findings. Because the population was unbalanced, the main analysis used an inverse probability of treatment weighted (IPTW) analysis in this study. Although the population was small, PS matching (PSM) was used.

**Results**

**Patients’ characteristics**

Table 1 summarizes the clinical background characteristics of the patients enrolled in this study. The median age was 64.2 years (range, 34–83 years); 76 (78.4%) patients were men, and 21 (21.6%) were women. The median BMI was 22.6 kg/m\(^2\), and an open drain was used in 56 patients (57.7%) and a closed drain in 41 patients (42.3%). The average drainage volume was 765 mls, the average preoperative albumin value was 3.93 g/dL, and 15 patients (15.5%) underwent lateral lymph node dissection while 82 patients (84.5%) did not. Forty-four patients (45.4%) had underlying disease (with duplicate cases), and 53 patients (54.6%) had no underlying disease.
Table 1
Clinical Background Characteristics of Patients enrolled in this Study

| Characteristic                      | (n = 97)                  |
|-------------------------------------|---------------------------|
| Age (years : mean ± SD)             | 64.2 ± 10.76              |
| Gender (male/female)                | 76 / 21                   |
| BD (positive / negative)            | 44 / 53                   |
| BMI (kg/m²: mean ± SD)              | 22.6 ± 3.45               |
| Blood loss (mls : mean ± SD)        | 316.0 ± 386.37            |
| Operative duration (mins : mean ± SD)| 363.0 ± 95.80            |
| Anast (DST / HS)                    | 59 / 38                   |
| Drain (open / close)                | 56 / 41                   |
| Alb (g/dl : mean ± SD)              | 3.93 ± 0.46               |
| Drainage volume (mls : mean ± SD)   | 765.0 ± 451.36            |
| LLD (+ / -)                         | 15 / 82                   |
| Operation (CAA, ISR / LAR, SLAR)    | 38 / 59                   |
| Stage (I + II / III + IV)           | 58 / 39                   |

BD: basal disease, BMI: body mass index, Anast: anastomosis, DST: double stapling technique, HS: Hand-sewn, LLD: lateral lymph node dissection, CAA: coloanal anastomosis, ISR: intersphincteric resection, SLAR: super low anterior resection, Alb: Albumin

We performed the following surgical procedures: LAR in 45 patients, super-low anterior resection in 14 patients, coloanal anastomosis in 6 patients, and intersphincteric resection in 32 patients. Fifty-nine patients (60.8%) underwent the double-stapling technique, and 38 patients (39.2%) underwent a hand-sewn technique for the anastomosis.

**Anastomotic leakage**

Anastomotic leakage occurred in 21 patients (21.7%), and none developed retrograde infection. The leakage-positive group constituted 21 patients, and the leakage-negative group constituted 76 patients (Table 2). We found no significant difference between the groups for age, sex, underlying disease, BMI, intraoperative blood loss volume, preoperative albumin, or lateral lymph node dissection. Although not significantly different, the drainage volume tended to be lower in Group C than in Group O. Significant differences were observed for operation duration (p=0.0026), the anastomosis method (p=0.0227), and the surgical procedure (p=0.0227).

Table 3 shows the results of the univariate and multivariate analyses of the risk factors for leakage in patients undergoing LAR. On univariate analysis, operative duration (p=0.0051), transanal hand-sewn anastomosis (p=0.0208), and the operation procedure (p=0.0191) were significantly associated with the incidence of leakage with LAR, and the leakage incidence was higher in patients with a long operative duration for LAR, and in those undergoing transanal hand-sewn anastomosis. On multivariate analysis, underlying disease (hazard ratio: (HR): 3.258, 95% confidence interval (CI):
1.032–10.283; p=0.044), transanal hand-sewn anastomosis (HR: 5.07, 95% CI: 1.31–19.632; p=0.0188), and drain type (HR: 4.311, 95% CI: 1.2–15.484; p=0.0251) were significantly associated with the incidence of leakage in patients undergoing LAR, and the leakage incidence with LAR was higher in patients with underlying disease, in those undergoing transanal hand-sewn anastomosis, and in those receiving closed drainage.

We performed propensity score analysis to confirm these findings. Because the population was imbalanced, we used an inverse probability of treatment-weighted (IPTW) analysis in the main analysis. Although the population was small, we used propensity-score matching. Table 4 shows the propensity score analysis results (unadjusted HR: 2.161, p=0.1235; adjusted by IPTW, HR: 6.315, p<0.0001; propensity-score matching: HR: 5, p=0.1738). The IPTW analysis revealed a significant difference between results using an open drain compared with results using a closed drain: closed drainage was associated with a 6.315 times higher incidence of postoperative leakage than open drainage. In the propensity-scored matched analysis, the number of patients receiving open vs closed drainage was imbalanced, so the number of patients to be examined decreased when matching was performed, and no significant difference was observed. Table 5 shows that the average drainage volume was 954 mls in Group O and 507 mls in Group C, indicating that the drainage volume was significantly greater in the open-drain group than in the closed-drain group (p< 0.001).

Table 2. Clinical Background Characteristics of Patients with, and Those without Leakage in this Study

Leakage
|                          | Positive (n=21) | Negative (n=76) | p-value |
|--------------------------|----------------|-----------------|---------|
| Age (years : mean ± SD)  | 65.81 ± 8.80   | 63.737 ± 11.2   | 0.43    |
| Gender (Male/Female)     | 17 / 4         | 59 / 17         | 1       |
| BD (Positive / Negative) | 13 / 8         | 31 / 45         | 0.13    |
| BMI (kg/m²: mean ± SD)   | 23.51 ± 2.40   | 22.38 ± 3.67    | 0.18    |
| Blood loss (mls: mean ± SD) | 325.71 ± 378.3 | 313.89 ± 388.6 | 0.88    |
| OP time (mins: mean ± SD) | 418.04 ± 89.7  | 348.01 ± 92.3   | 0.00    |
| Anast (DST / HS)         | 8 / 13         | 51 / 25         | 0.02    |
| Drain (Open / Close)     | 9 / 12         | 47 / 29         | 0.13    |
| preoperative Alb (g/dL: mean ± SD) | 3.91 ± 0.42 | 3.94 ± 0.48    | 0.85    |
| Drainage volume (mls: mean ± SD) | 688.95 ± 449.9 | 785.68 ± 452.3 | 0.38    |
| LLD (+ / -)              | 3 / 18         | 12 / 64         | 1       |
| OP (CAA, ISR / LAR, SLAR)| 13 / 8         | 25 / 51         | 0.02    |
| Stage (I+II / III+IV)    | 11 / 10        | 47 / 29         | 0.46    |

BD: basal disease, BMI: body mass index, OP: operation, Anast: anastomosis, DST: double stapling technique, HS: Hand-sewn, LLD: lateral lymph node dissection, CAA: coloanal anastomosis, ISR: intersphincteric resection, SLAR: super low anterior resection, Alb: Albumin

Table 3. Univariate and Multivariate Analyses for Leakage in Patients with LAR
| Factor                  | OR   | 95%CI          | P value | OR     | 95%CI          |
|------------------------|------|----------------|---------|--------|----------------|
| Sex                    |      |                |         |        |                |
| Male                   | 1    |                |         |        |                |
| Female                 | 0.817| 0.242-2.754    | 0.7439  |        |                |
| Age /years             | 1.019| 0.972-1.069    | 0.4343  |        |                |
| Basal disease          | 2.359| 0.874-6.364    | 0.0901  | 3.258  | 1.032-10.283   |
| BMI                    | 1.099| 0.955-1.265    | 0.1862  |        |                |
| Blood loss (mls)       | 1    | 0.999-1.001    | 0.8848  |        |                |
| Operative duration (mins) | 1.008| 1.002-1.013    | 0.0051  | 1.007  | 1-1.013        |
| Anast                  |      |                |         |        |                |
| DST                    | 1    | 1              |         |        |                |
| Hand sewn              | 3.521| 1.289-9.617    | 0.0141  | 5.07   | 1.31-19.632    |
| Drain                  |      |                |         |        |                |
| Open                   | 1    | 1              |         |        |                |
| Closed                 | 2.161| 0.811-5.76     | 0.1235  | 4.311  | 1.2-15.484     |
| preoperative Alb       | 0.905| 0.321-2.558    | 0.8513  |        |                |
| Discharge volume mls   | 1    | 0.998-1.001    | 0.3844  |        |                |
| LLD performed          | 0.889| 0.226-3.494    | 0.8661  |        |                |
| Stage                  |      |                |         |        |                |
| I + II                 | 1    |                |         |        |                |
| III + IV               | 1.473| 0.557-3.9      | 0.4352  |        |                |
| OP                     |      |                |         |        |                |
| CAA/ISR                | 1    |                |         |        |                |
| LAR/SLAR               | 0.302| 0.111-0.822    | 0.0191  |        |                |

Anast: anastomosis, LLD: lateral lymph node dissection, BMI: body mass index, DST: double stapling technique, CAA: coloanal anastomosis, OP: operation ISR: intersphincteric resection, SLAR: super low anterior resection, Alb: Albumin

Table 4. Propensity Score Analysis
| Method  | Category | n   | OR  | 95%CI       | P value |
|---------|----------|-----|-----|-------------|---------|
| Unadjusted | Open     | 97  | 1   |             |         |
|          | Closed   | 2.161 | 0.811 | 5.76     | 0.1235  |
| IPTW     | Open     | 96  | 1   |             |         |
|          | Closed   | 6.315 | 3.008 | 13.256   | <0.0001 |
| Matching | Open     | 32  | 1   |             |         |
|          | Closed   | 5   | 0.492 | 50.831   | 0.1738  |

IPTW: inverse probability of treatment weighted

Table 5. Average Drained Volume (mls) Analyses in this Study

| Type of drain | Group-O | Group-C |
|---------------|---------|---------|
| Group-O       | 56 cases (57.7%) | 41 cases (42.3%) |
| Average drained volume (mL) | 954 ± 437.4 | 507 ± 328.0 |

O: open drain, C: close drain

Discussion

Anastomotic leakage is a major complication after lower rectal surgery and is associated with postoperative morbidity, mortality, functional defects, and oncological outcomes [5, 6]. Several risk factors have been reported for anastomotic leakage after open LAR [7–11], and recently, studies have also examined the risk factors for anastomotic leakage after laparoscopic LAR [12–21]. The devices and technique used for laparoscopic LAR differ from those used in open LAR, suggesting that the risk factors for anastomotic leakage also may differ between laparoscopic and open LAR. According to these studies, the anastomotic level, number of linear staples, sex, smoking, alcohol intake, previous abdominal surgery, preoperative chemoradiotherapy, tumor location, stage, operative duration, blood loss volume, transfusion, and precompression before firing are reported risk factors for anastomotic leakage after LAR. In the present study, our analysis of potential risk factors suggested that patients
with underlying disease, those undergoing transanal hand-sewn anastomosis, and those receiving closed drains may be at higher risk for anastomotic leakage.

In some studies, intraoperative blood loss volume was a reported independent risk factor for anastomotic leakage [17–19, 21, 22]. In the present study, we found no significant difference regarding blood loss volume as a continuous variable. This suggested that anastomotic leakage did not occur directly because of bleeding, and intraoperative blood loss volume was likely to be a surrogate for surgical difficulty.

The duration of surgery was also considered a risk factor in some studies [23–25]. Our study also confirmed that patients with a longer surgical duration had a higher incidence of anastomotic leakage. Prolonged surgery may be caused by lower surgical skill or poor exposure of the surgical field secondary to pelvic stenosis or a large tumor. In addition, a decrease in blood perfusion caused by prolonged anesthesia may also increase the risk of developing anastomotic leakage.

Previous studies reported that diabetes mellitus was a risk factor for anastomotic leakage [26, 27], which our results confirmed (Table 3). The reasons type 2 diabetes mellitus increase the risk of anastomotic leakage may be as follows: insufficient blood supply to the anastomosis secondary to microcirculatory disorders, insufficient glycogen stores, and delayed tissue healing secondary to hyperglycemia. These results suggest that patients with type 2 diabetes mellitus require good blood glucose control before surgery to reduce the risk of anastomotic leakage post-LAR. However, other studies have found that diabetes was not a risk factor for anastomotic leakage [16, 28].

Sánchez-Guillén et al. reported the perioperative risk factors for anastomotic leakage and for 60-day morbidity and mortality after ileocolic anastomosis (stapled vs hand-sewn). The authors’ multivariate analysis showed the following independent risk factors for major anastomotic leak: male sex (P = 0.014, odds ratio (OR): 2.9), arterial hypertension (P = 0.048; OR: 2.29), and perioperative transfusions (P < 0.001, OR: 2.4 per liter). The overall 60-day complication rate was 27.3%. Male sex (31.3% vs female 22.3%, P = 0.02, OR: 1.7), diabetes (P = 0.03, OR: 2.0), smoking habit (P = 0.04, OR: 1.8), and perioperative transfusions (P < 0.001, OR: 3.3 per liter) were independent risk factors for postoperative morbidity [29]. These results were consistent with our underlying disease results, which
suggested that the presence of underlying disease was associated with anastomotic leakage.

Several studies reported that tumor location and distance from the anal verge are risk factors for LAR [13-17, 20]. Choi et al. reported that the anastomotic leakage rate was 10 times higher when the anastomotic region was located within 5 cm of the anal verge in a series of 156 patients undergoing LAR without double stapling [15]. It is hypothesized that tumor location and distance from the anal verge may reflect technical difficulties and affect anastomotic tension and blood supply. In the present study, there was a statistically significant difference between double-stapling and hand-sewn anastomosis, in the multivariate analysis. Therefore, we concluded that these were likely risk factors for anastomotic leakage.

Our results showed that the type of drain was related to anastomotic leakage after LAR. To our knowledge, these results have not been reported previously and are considered important findings. An open drain can be used for effective long-term drainage, but the possibility of retrograde infection is a concern. In contrast, a closed drain is less likely to be associated with retrograde infection, but obstruction is a problem. Although some reports described a risk of retrograde infection in patients receiving open drainage [30-32], none have reported the related frequency or any diagnostic criteria. In the present study, no retrograde infection occurred in patients receiving open drainage. Within the pelvis, a peritoneal defect sometimes occurs after resecting the rectum. Therefore, it is well known that reabsorption of the effusion decreases, and the risk of infection increases, predisposing to abscess formation, and there is a high possibility that this leads to leakage.

Because efficient fluid drainage is important, we consider it necessary to carefully consider which type of drain to use in digestive surgery. Surprisingly, in the propensity-score analysis, closed drainage had a 6.315 times higher risk of postoperative leakage than open drainage. This finding is impressive and important, and statistically meaningful.

The limitations of this study must be addressed. The major limitations are the single-institution, retrospective design, and the small number of patients. In fact, the anastomotic rate in this study was a slightly higher percentage (21.7%) compared with other studies. This is likely because many patients had advanced disease, in this study. Moreover, many patients had Rb-positive lesions, which
may have caused selection bias. Additionally, we excluded patients receiving preoperative chemotherapy or chemoradiotherapy, because of our department’s treatment policy. These limitations should be considered when evaluating the results in our study. A prospective study involving multiple institutions with a unified definition of anastomotic leakage and standardized procedures is needed. However, to our knowledge, no studies have collected and analyzed drainage data in patients undergoing lower rectal surgery; therefore, our findings are noteworthy, particularly because our study provides actual data supporting the theory.

Conclusion
Anastomotic leakage is a multifactorial complication that occurs after LAR. Patients’ characteristic cannot be changed, but several technique steps and devices can be used to avoid this complication. We demonstrated that in patients with anastomotic leakage after LAR, leakage volume was higher in patients with underlying disease, in those undergoing transanal hand-sewn anastomosis, and in patients receiving closed drainage. Our results suggested that it is necessary to determine the need for a drain and to select the drainage method by comprehensively assessing the surgical procedure and the patient’s condition.

Abbreviations
BMI
body mass index, LAR:low anterior resection, IPTW:inverse probability of treatment-weighted, HR, hazard ratio, CI, confidence interval, OR, odds ratio

Declarations
Ethics approval and consent to participate
The Institutional Review Research Committee for Human Subjects at Kurume University Hospital approved the study (no. 18197). Written informed consent was obtained from each of the subjects prior to enrollment in this study.

Consent for publication
Not applicable

Availability of data and materials
After publication of the primary findings, the de-identified and completely anonymised individual
participant-level dataset will be posted on the UMIN-ICDR website (http://www.umin.ac.jp/icdr/index-j.html) so that it can be accessed by qualified researchers.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

TK designed the study; TK, SN, KM, TM, TO, TI, FF, and YA collected data; TM reviewed patient’s histology; TK, SN, KM analyzed the data, reviewed the chart, and interpreted the data; TK wrote the paper. All authors have read and approved the manuscript.

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Figures
Figure 1

(A) Open drains. (a) Duple drain (6 Fr.); (b) Penrose drain (12 Fr.); (c) combining (a) and (b) into a single drain. (B) Closed drain. J-VAC drainage system (19 Fr.) (Johnson & Johnson, New Brunswick, NJ).