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ORIGINAL RESEARCH ARTICLE

Smoking and tumor obstruction are risk factors for anastomotic leakage after laparoscopic anterior resection during rectal cancer treatment

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Abstract:

Objectives: To clarify the surgical outcomes and risk factors for anastomotic leakage (AL) following laparoscopic anterior resection (Lap-AR) for the treatment of rectal cancer. Methods: We retrospectively reviewed the records of 175 consecutive primary rectal cancer patients who had undergone Lap-AR at our institution between April 2012 and November 2015. Patient, tumor, and surgical variables were analyzed using univariate analyses. Results: Of 175 patients, 116 were men (66.3%). All four patients who had AL (2.3%) were men and current smokers with heavy smoking histories. In three of the AL cases, preoperative total colonoscopy was impossible owing to tumor obstruction, and the other case had concomitant obstructive colitis after oral bowel preparation. Univariate analysis identified tumor size, tumor obstruction, and smoking history as factors significantly associated with AL development. Conclusions: Tumor size, tumor obstruction, and smoking history were risk factors for AL following Lap-AR for the treatment of primary rectal cancer.

Keywords:

anastomotic leakage, rectal cancer, laparoscopic surgery, smoking, tumor obstruction

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Introduction

Anastomotic leakage (AL) is one of the most severe complications related to colorectal cancer surgery. It contributes not only to postoperative morbidity and mortality, but also to local recurrence and poor prognosis[1-3)]. A recent systematic review and meta-analysis showed that laparoscopic anterior resection (Lap-AR) was associated with faster postoperative recovery, fewer complications, and better cosmetic results with equal oncologic results[4)]. In addition, the COlorectal cancer Laparoscopic or Open Resection (COLOR II) study group reported that laparoscopic surgery in patients with rectal cancer was associated with locoregional recurrence rates and disease-free and overall survival rates similar to those for open surgery[5)]. However, in clinical practice, Lap-AR is still one of the most difficult procedures in laparoscopic surgery. In addition, risk factors for AL following Lap-AR have not been fully delineated. Herein, we describe our clinical experience with Lap-AR and present an analysis of risk factors associated with AL using statistical analysis.

Methods

Study population and data collection

From June 2012 to November 2015, 175 consecutive patients underwent Lap-AR and anastomosis using the double-stapling technique (DST) during treatment for primary rectal cancer. Those who underwent simultaneous resection of other organs were excluded. Tumor location was classified based on its distance from the anal verge as follows: lower

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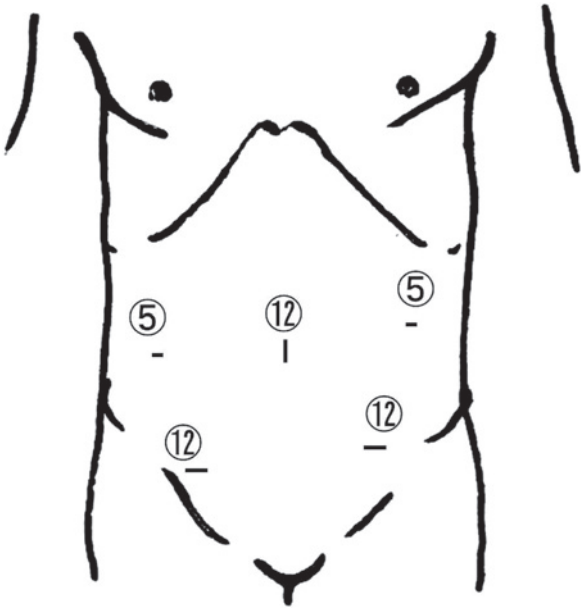

Figure 1. Port placement.
Numbers in circles represent port diameter in millimeters.

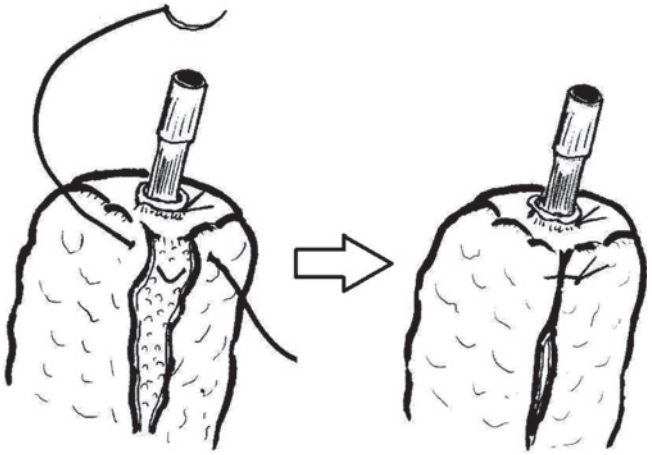

Figure 2. Reinforcing serosal suture after anvil placement.

(≤5 cm), middle (6-10 cm), and upper (11-15 cm). Distance was measured by digital examination and colonoscopy. Data for the following variables were collected retrospectively from medical records: age, sex, body mass index (BMI), distance from the anal verge, tumor obstruction (defined as the inability to perform preoperative endoscopic examination on the oral side of the tumor), smoking history, use of corticosteroids, the American Society of Anesthesiologists-Physical Status score (ASA score), previous history of laparotomy, history of diabetes, preoperative chemoradiotherapy (CRT), preoperative serum albumin level, operative duration, intraoperative blood loss, number of cartridges used for rectal transection, stoma creation, ligation level of the inferior mesenteric artery (IMA), lateral lymph node dissection (LLND), the use of a pelvic drain, the use of a transanal drain, leak test, maximum tumor diameter, Union for International Cancer Control (UICC) TNM (tumor/node/metastasis) stage, surgical complications and the length of hospital stay. All complications were classified, retrospectively, according to the Clavien-Dindo grading system[6] using medical records. The present study was conducted with the approval of the institutional review board at the University of Tokyo Hospital [approval number: 3252-(2)].

Preoperative CRT and LLND

Preoperative long-course CRT was indicated for a proportion of T3 and T4 tumors with anal borders located below the peritoneal reflection; however, it is important to note that the entire tumor was not necessarily located below the peritoneal reflection in each of these cases. LLND was indicated for a portion of T3 and T4 tumors with anal borders located below the peritoneal reflection and in cases with a suspected positive lateral lymph node, as advised by the Japanese guidelines for the treatment of colorectal cancer[7]. LLND was omitted for patients who did not have clinically positive lateral lymph node metastases and received preoperative CRT.

Surgical procedure

All patients, except those with tumor obstruction, underwent mechanical bowel preparation and received prophylactic antibiotics. A standard five-port technique was used[8] (Fig. 1). We routinely performed preoperative three-dimensional computed tomography (3D-CT) angiography and planned the ligation level of the IMA, taking the patient's blood flow and lymph node metastasis status into consideration. The splenic flexure was mobilized totally or partially, depending on the bowel length. Total or tumor-specific mesorectal excision was performed, depending on the tumor level, using a nerve-sparing technique. Colorectal anastomosis was performed using DST. Rectal transection was performed intracorporeally using a 60-mm or 45-mm endoscopic linear stapler, leaving an adequate margin, distal to the tumor. After placing the anvil in the proximal cut end of the colon, reinforcing serosal sutures were added to secure the ends of the serosa (Fig. 2). Intraoperative colonoscopy and leak tests were routinely performed to check the anastomosis (Fig. 3A). If the leak test was positive, re-anastomosis was performed (if possible) or additional sutures were added to the anastomotic site, and a covering stoma was created at the surgeon's discretion. Active bleeding from the anastomotic site was treated using an endoscopic clip or a transanal suture to achieve hemostasis (Fig. 3B, 3C). A pelvic drain was placed routinely in low- or middle-level anastomosis cases, and at the operator's discretion in high-level anastomosis cases. A multilumen transanal drain was placed routinely, except in a few early cases (Fig. 3D). A transanal drain was placed so that its tip did not touch the anastomotic site (Fig. 4). If deemed appropriate by the operator, drains were removed after the first defecation following the first meal. Surgical wounds were inspected daily, postoperatively, by surgeons and nurses, and surgical site infection (SSI) was diagnosed according to the guidelines from the Center for Disease Control and Prevention[9].

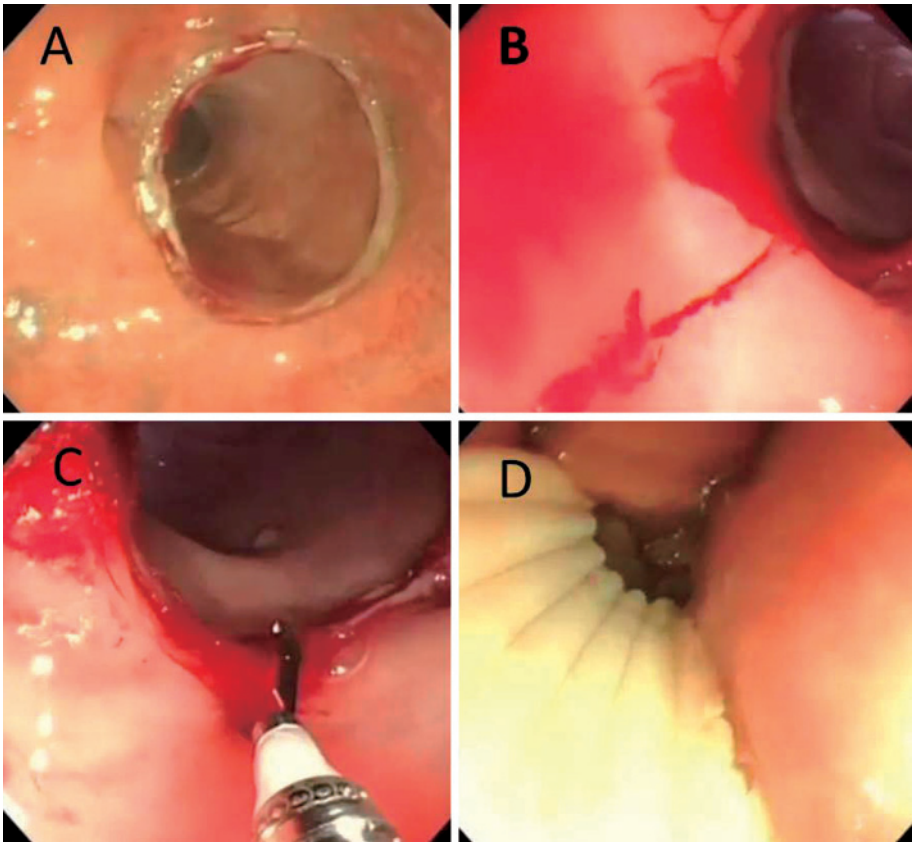

Figure 3. Intraoperative colonoscopy.
A) Normal anastomotic site without bleeding.
B) Bleeding from anastomotic site.
C) Hemostasis with an endoscopic clip.
D) Placement of multilumen transanal drain.

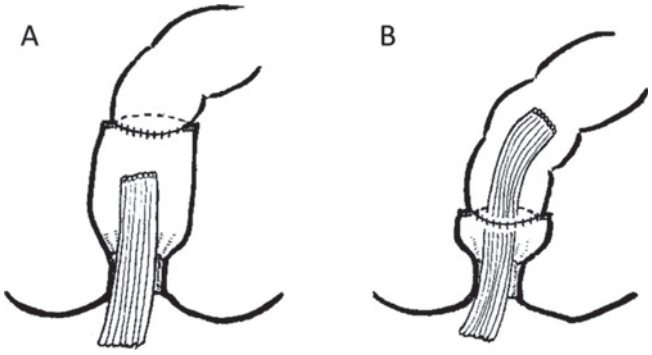

Figure 4. Placement of multilumen transanal drain.
A) High anastomosis.
B) Low anastomosis.

Statistical analysis

All statistical analyses were performed using JMP® Pro software, Version 11 (SAS Institute Japan, Ltd., Tokyo, Japan). In the univariate analysis of risk factors, either the Pearson chi-square test or the Fisher exact test was used for categorical variables based on the data points for each variable. The Mann-Whitney U test was used for continuous variables. A p value <0.05 was considered statistically significant.

Results

In total, 175 patients were enrolled in the analysis. Patient and tumor backgrounds are summarized in Table 1. Perioperative data are summarized in Table 2. In 64 patients (36.6%), rectal transection was performed using a single linear stapler cartridge. The remainder (63.4%) required two or more cartridges for rectal transection. Surgical complications and Clavien-Dindo classifications are summarized in Table 3. Seven patients (4.5%) developed superficial SSIs. Five patients (2.9%) developed a port-site hernia at the left lower port (i.e., the pelvic drain site) after the drain was removed, requiring sutures under local anesthesia. Four patients developed AL (2.3%); features of the four cases are summarized in Table 4; all patients were men and current smokers with a heavy smoking history (range, 30-60 packs/year), did not undergo CRT and underwent low ligation of the IMA. Three out of four patients had tumor obstruction, and the other developed obstructive colitis after oral bowel preparation. AL was observed on postoperative day 4 in two patients, and on postoperative days 6, and 9 in the other two patients. Three of four patients who experienced AL were treated conserva-

Table 1. Patient and Tumor Backgrounds.

	N=175
Age (years)	63 (36-87)
Body mass index (kg/m^2)	22.5 (15.8-32.4)
Male gender	116 (66.3%)
ASA score	
1	78 (44.6%)
2	92 (52.6%)
3	5 (2.8%)
Tumor location	
Upper	87 (49.7%)
Middle	61 (34.9%)
Lower	27 (15.4%)
TNM stage	
0	3 (1.7%)
I	50 (28.6%)
II	48 (27.4%)
III	62 (35.4%)
IV	12 (6.9%)
Tumor size (mm)	32 (3-200)
Preoperative chemoradiotherapy	23 (13.1%)

*Values are expressed as median (range) or number (%).
ASA: American society of anesthesiologists

Table 2. Surgical Results.

	N=175
Operative time (min) *	256 (128-605)
Blood loss (ml) *	10 (0-3350)
Cartridges for rectal transection	
1	64 (36.6%)
2	80 (45.7%)
≥3	31 (17.7%)
High tie of inferior mesenteric artery	40 (22.9%)
Lateral lymph node dissection	7 (4.0%)
Placement of pelvic drain	160 (91.4%)
Placement of transanal drain	167 (95.4%)
Diverting stoma	35 (20.0%)
Leak test positive	3 (1.7%)
Postoperative C-reactive protein (mg/dl)	4.5 (0.0-20.8)

*Values are expressed as median (range) or number (%).

Table 3. Complications.

	n	%
Total	33	18.9
Superficial surgical site infection	7	4.0
Anastomotic leakage	4	2.3
Intraabdominal abscess	1	0.6
Port site hernia	5	2.9
Urinary retention	5	2.9
Ileus	4	2.3
Pulmonary	2	1.1
Anastomotic bleeding	1	0.6
Cerebral infarction	1	0.6
Anemia	1	0.6
Enterocolitis	1	0.6
Jaundice	1	0.6
Clavien-Dindo classification		
Grade I	4	2.3
Grade II	16	9.1
Grade III	11	6.3
Grade IV	2	1.1

tively; however, the other required reoperation with general anesthesia and treatment in an intensive-care unit. The correlations between clinical variables and AL are summarized in Table 5. Results from the univariate analysis suggest that tumor size, tumor obstruction, current smoking, and smoking index were significantly correlated with AL.

Discussion

AL is one of the most severe complications related to colorectal cancer surgery. It contributes not only to postoperative morbidity and mortality, but also to local recurrence and poor prognosis[1-3]. In the early days of Lap-AR, rates of AL were relatively high, ranging from 8.6% to 17%[10-12]. The rate of AL in the present study was 2.3%, which is among the lowest of recently reported rates[13-16]. Univariate analyses showed that smoking, tumor size, and tumor obstruction were significantly correlated with AL occurrence.

The association between cigarette smoking and AL has been reported; specifically, both current smoking[17,18] and a high smoking index are associated with AL[19,20]. The mechanism through which smoking affects AL is still unclear; however, involvement of a decrease in mucosal blood flow has been reported[21-23]. In the present study, the four patients who experienced AL were current smokers and had heavy smoking histories. Interestingly, both the smoking index (packs/year) and the proportion of current smokers were significantly higher among patients in the AL group. Surgeons should pay attention to patients' smoking habits, because it is potentially modifiable, even at their first visit. However, the length of smoking cessation necessary to reduce AL is still debatable. Sørensen et al. conducted a randomized controlled trial (RCT) and reported that two weeks of smoking cessation was not enough to reduce complications after colorectal resection[24]. On the other hand, a recent meta-analysis showed that at least three to four weeks of smoking cessation reduced wound-healing complications[25]. Regardless, given the potential adverse effects of smoking on perioperative cardiovascular and pulmonary events other than AL, and the known long-term benefits of smoking cessation, it is important for clinicians to encourage their surgical patients to stop smoking, irrespective of the time of their visit.

Tumor size is a well-known risk factor of AL after low anterior resection[26]; in the limited working-space of the pelvis, a large tumor size adversely affects the ease of rectal division and anastomosis. Furthermore, larger tumors naturally tend to be accompanied by tumor obstruction. In the present

Table 4. Anastomotic Leakage Cases.

Case number	1	2	3	4
Sex	Man	Man	Man	Man
Age (years)	75	59	64	48
Body mass index (kg/m^2)	25.4	23.6	21.8	25.2
Tumor location (anal verge, cm)	14	12	7	8
Preoperative colonoscopy findings	obstruction	obstruction	obstruction	obstructive colitis
Current smoking	yes	yes	yes	yes
Smoking index (Packs/year)	60	40	44	30
Laparotomy history	no	yes	no	no
Diabetes	yes	no	yes	no
Use of corticosteroid	no	no	no	no
Other comorbidity	COPD, HT	CKD, HT	HT	-
Preoperative albumin (g/dl)	4.0	3.2	3.6	4.1
Preoperative chemoradiotherapy	no	no	no	no
ASA score	2	2	2	1
Operative time (min)	234	357	378	605
Blood loss (ml)	6	200	150	3350
Inferior mesenteric artery (high tie/low tie)	low	low	low	low
Cartridges for rectal transection	2	3	3	2
Lateral lymph node dissection	no	no	no	yes
Diverting stoma	no	yes	no	no
Postoperative day of anastomotic leakage diagnosis (day)	9	6	4	4
Treatment of anastomotic leakage	conservative	re-operation	conservative	conservative
Duration of pelvic drainage (day)	32	63	42	40
Duration of transanal drainage (day)	7	69	26	32
Duration of hospital stay (day)	42	71	55	42
Tumor size (mm)	48	52	200	65
TNM stage	IIA	IIIB	IIIC	IVA
Tumor	3	4a	4a	3
Node	0	1b	2b	2c
Metastasis	0	0	0	1a

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HT, hypertension
ASA: American society of anesthesiologists

study, tumor size in the obstruction group (n=21) was significantly larger than that in the non-obstruction group (n= 154) (median, 65 [range: 28-200] vs. 30 [range: 3-100] mm, respectively; p<0.0001). With tumor obstruction, mechanical bowel preparation becomes difficult and solid stool often remains inside the colon, proximal to the tumor, increasing the possibility of intraoperative contamination. In addition, the proximal colonic wall becomes edematous, inhibiting wound healing at the anastomotic site. Furthermore, some patients with tumor stenosis also have obstructive colitis, in which ulceroinflammatory lesions occur in the colon, proximal to an obstructing or potentially obstructing lesion[27]. In fact, one of our AL cases developed obstructive colitis after oral bowel preparation (Table 4, case 4). In cases of tumor obstruction, anastomosis must be performed carefully to avoid contamination, especially when solid stool is present inside the proximal colon. It is also important to carefully inspect the proximal colonic wall for obstructive colitis, which, if present, may require resection of the colon, up to the point of normal colonic mucosa. Another AL case had extensive solid stool inside the proximal colon; despite the placement of a diverting stoma, clinical AL occurred, requiring reoperation and treatment in an intensive-care unit (Table 4, case 2). In clinical practice, because of the potential for AL in patients with tumor obstruction or large tumors, and among those who are current smokers or those who have heavy histories of cigarette smoking, Lap-AR should be carefully considered as a treatment for rectal cancer.

Adequate blood flow is also essential for successful anastomosis. We routinely perform 3D-CT angiography and plan the ligation level of the IMA. In principle, we preserve the left colic artery (i.e., low ligation of IMA) unless lymph node metastasis at the root of the IMA is suspected, or a high tie is required for sufficient mobilization of the proximal colon. In a systematic review and meta-analysis, high vs. low ligation level of the IMA had no influence on AL or survival, but the need for a randomized controlled trial was emphasized[28]. Moreover, to promote adequate blood flow during division of the proximal colic mesentery, an attempt is made to avoid injury to the vasa recta. After placing an anvil in the proximal cut end of the colon, reinforcing serosal sutures were added to keep the serosa attached (Fig. 2).

Table 5. Univariate Analysis of Risk Factors for Anastomotic Leakage.

Variables		Leakage (+) n=4	Leakage (-) n=171	Univariate P value
Age (years)		61 (48-75)	63 (36-87)	0.865
Body mass index (kg/m^2)		24.4 (21.8-25.4)	22.4 (15.8-32.4)	0.287
Preoperative albumin		3.8 (3.2-4.0)	4.0 (2.2-4.9)	0.171
Tumor size (mm)		58 (48-200)	31 (3-100)	0.024
Sex	Male	4 (100%)	0 (0%)	0.300
Tumor location	Lower	0 (0%)	27 (15.8%)	0.637
	Middle	2 (50%)	59 (34.5%)	
	Upper	2 (50%)	85 (49.7%)	
Tumor obstruction	Yes	3 (75%)	18 (10.5)	0.005
Current smoking	Yes	4 (100%)	39 (22.8%)	0.003
Smoking index (Packs/year)		42 (30-60)	7 (0-160)	0.019
Laparotomy history	Yes	1 (25%)	47 (27.5%)	1.000
Diabetes	Yes	2 (50%)	34 (19.9%)	0.188
Use of corticosteroid	Yes	0 (0%)	2 (1.2%)	1.000
Preoperative chemoradiotherapy	Yes	0 (0%)	23 (13.5%)	1.000
ASA score	1	1 (25%)	77 (45.0%)	0.667
	2	3 (75%)	89 (52.1%)	
	3	0 (0%)	5 (2.9%)	
Cartridges for rectal transection	1	0 (0%)	64 (37.4%)	0.180
	2	2 (50%)	78 (45.6%)	
	≥3	2 (50%)	29 (17.0%)	
High tie of inferior mesenteric artery	Yes	0 (0%)	40 (23.4%)	0.575
Lateral lymph node dissection	Yes	1 (25%)	6 (3.5%)	0.152
Leak test	Positive	0 (0%)	3 (1.75%)	1.000
TNM stage	0	0 (0%)	3 (1.8%)	0.328
	I	0 (0%)	50 (29.2%)	
	II	1 (25%)	47 (27.5%)	
	III	2 (50%)	60 (35.1%)	
	IV	1 (25%)	11 (6.4%)	
Operative time		367 (234-605)	255 (128-602)	0.049
Blood loss		175 (6-3350)	10 (0-500)	0.033

*Values are expressed as median (range) or number (%).

ASA: American society of anesthesiologists

These surgical procedures are difficult to quantify, but we believe they are important for accomplishing successful anastomosis.

Number of linear staple cartridges used for intracorporeal rectal transection may also affect the success of anastomosis, although the negative impact of multiple stapler firings on AL is debatable[15,29]. Okuda et al. reported a high single-staple resection rate of 98% (99/101), and only a 1% AL rate (1/101)[16]. In the present study, 36% of transections used a single staple cartridge. On the other hand, two or more cartridges were required in the four cases that experienced AL. In addition, a slight tendency for multiple firings was observed among patients in the AL group; however, this finding was not significant (p=0.18, Table 5). An analysis of additional cases may clarify this association. We do not always exclude the possibility of multiple firings, because it is sometimes necessary to ensure an adequate distal margin or because of a narrow pelvis. Nevertheless, careful confirmation of anastomotic integrity is required after anastomosis as described below.

We routinely perform intraoperative colonoscopy and leak tests after anastomosis; when air leak is positive, we perform re-anastomosis (if possible) or place additional sutures at the anastomotic site, and a covering stoma is created at the surgeon's judgement. In the present study, only three cases (1.7%) showed positive findings on the leak test. In these cases, additional transanal sutures and a covering stoma were added, and no clinical AL occurred. Although intraoperative endoscopy has not been reported to reduce AL[30], we still recommend endoscopic assessment of circular-stapled anastomosis as a routine procedure in rectal surgery since it is not a complicated or time-consuming procedure and does not increase the risk for AL, but rather has potential benefits for reducing AL and postoperative bleeding[31].

Other risk factors for AL after laparoscopic anterior resection include male sex, preoperative CRT, obesity, and low rectal tumor[14,15,32,33]. With regard to these factors, our study showed no significant difference between the AL and non-AL groups; however, this might be attributable to the small

number of AL cases. LLND was not a risk factor for AL in the present study. Several studies have suggested that a longer operative duration and excessive blood loss are risk factors of AL (367 vs. 255 min, p=0.049 and 175 vs. 10 mL, p=0.033, respectively)[14,34,35]; we also found that these variables were correlated with the occurrence of AL. However, these surgical factors are not preoperatively modifiable or predictable, instead, we think that they are consequences of difficult, potentially high-risk operations, rather than risk factors. Nevertheless, they may help determine if a protective stoma should be created to reduce severe complications in case AL occurs[36].

Limitations of our study include the relatively low proportion of cases with low-level tumors and those that received CRT. This could be because we introduced robotic surgery for rectal cancer at the same time as laparoscopic surgery, cases classified as low-rectal or those that received CRT may have preferred robotic surgery instead of laparoscopic surgery. Differences between surgical procedures in Japan and those in Western countries may also be associated with reduced use of CRT. As for the racial difference, the population of obese patients was also apparently lower than that in Western countries; the median BMI in the current study population was 22.5 kg/m^2. These differences in patients and surgical backgrounds may have contributed to the low rate of AL identified in the present study. As the average BMI varies between races, some may argue that these results may not be applicable to all Western people. However, smoking status and tumor size are less variable between races, thus our results are indeed notable, even among the Western population. Moreover, obtained risk factors such as smoking habit, tumor size, and obstruction, are important, irrespective of racial differences, as they are potentially modifiable by the cessation of smoking or the promotion of early detection via cancer screening. As a result, these factors should be universally considered to ensure the safety and success of Lap-AR.

In conclusion, tumor size, tumor obstruction, and smoking history were identified as risk factors for AL following Lap-AR with anastomosis involving DST for primary rectal cancer. Surgeons should pay close attention to these factors, suggest preoperative smoking cessation, and consider creating a diverting stoma to reduce severe complications in AL cases.

Conflicts of Interest

The authors declare that there are no conflict of interest.

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