Efficacy of side-to-end anastomosis to prevent anastomotic leakage after anterior resection for rectal cancer

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Abstract. The present study aimed to investigate whether side-to-end anastomosis could provide an improved surgical outcome, such as lower anastomotic leakage rate, compared with end-to-end anastomosis, following anterior resection for rectal and rectosigmoid cancer. This retrospective study included 162 patients with rectal cancer who underwent elective anterior resection between January 2012 and October 2019 at a single institution. Patients with double cancers or colonic J-pouch were excluded. Anastomotic leakage was defined clinically and radiologically. Side-to-end anastomosis was introduced in the International University of Health and Welfare Mita Hospital in January 2017. Side-to-end anastomosis was performed in 63 patients, while end-to-end anastomosis was performed in 99 patients. Tumors tended to be located lower in the rectum in the side-to-end anastomosis group than in the end-to-end anastomosis group. No significant differences were observed in other patient characteristics. The incidence of anastomotic leakage was significantly lower in the side-to-end anastomosis group than in the end-to-end anastomosis group (3/63, 4.8% vs. 18/99, 18.2%, respectively, P=0.02). No significant differences were observed in the incidence rates of other complications. Univariate and multivariate analyses revealed that a smoking habit (P=0.04) and side-to-end anastomosis (P=0.02) were significantly associated with anastomotic leakage. In conclusion, side-to-end anastomosis using a double-stapling technique following anterior resection for rectal cancer may prevent anastomotic leakage.

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Introduction

Anterior resection (AR) for rectal and rectosigmoid (RS) cancer has become a standard procedure, thus improving oncological and surgical outcomes because of advances in surgical strategy and perioperative management. Despite these advances, anastomotic leakage (AL) is an important complication that occurs during the acute phase after AR; the anastomotic leakage rate, regardless of temporary stoma use, varies from 2% to 15% among reports (1-3).

AL is associated with poor functional outcome, reduced quality of life, and prolonged hospital stay, as well as with poor oncological outcomes (e.g., morbidity, mortality, and recurrence rate) (4-7). Patient-related and operative factors have been reported in many studies as risk factors for the development of AL (8). For example, male sex, body mass index (BMI), level of anastomosis, absence of a diverting stoma, use of neoadjuvant therapy, and absence of a trans-anal tube have been reported as risk factors (8-13). Many of these factors remain controversial; however, surgical techniques related to blood flow, pressure, and tension at the anastomosis site play important roles in prevention of AL (14-18).

Blood flow is reportedly better at the antimesenteric border than at the end of the colon (14); moreover, blood flow at the anastomotic site is associated with AL (14-18). Therefore, blood flow at the side-to-end anastomotic site can be better than that at the end-to-end anastomotic site, and a side-to-end anastomosis can reduce the rate of AL after AR. The principle of a side anastomosis in gastrointestinal surgery is well recognized; it is considered a standard technique for esophagojejunal anastomosis. However, this approach is much less frequently used in colorectal surgery; few studies have directly compared side-to-end anastomosis and end-to-end anastomosis (19-21).

In our hospital, side-to-end anastomosis with a trans-anal double-stapling technique has been performed since

January 2017 as the preferred procedure to prevent AL, along with a trans-anal tube and intraoperative indocyanine green fluorescence angiography (ICG-FA). The purpose of this study was to investigate whether side-to-end anastomosis could provide better surgical outcomes, compared to end-to-end anastomosis, following AR for rectal and RS cancer. In addition, this study identified factors associated with AL using univariate and multivariate analyses.

Materials and methods

Patients. This single-center retrospective observational clinical trial at International University of Health and Welfare Mita Hospital enrolled 178 patients with rectal and RS cancer who had undergone elective AR from January 2012 to October 2019. To examine the association between anastomosis type and surgical outcome, three patients with double cancers, eight patients with a colonic J-pouch, and five patients with trans-anal hand-sewn anastomoses were excluded. Therefore, 162 patients were included in this study; all underwent anastomosis with the application of a trans-anal double-stapling technique. Of the 162 patients, 63 underwent side-to-end anastomosis following AR. The flow chart of patient inclusion criteria is shown in Fig. 1. Patient characteristics and surgical outcomes were recorded. The descriptions and diagnoses of the cancers were performed in accordance with the Japanese classification of colorectal cancer. The treatment policy was decided in accordance with the Japanese Society for Cancer of the Colon and Rectum 2019 guidelines for the treatment of colorectal cancer. This study was approved by the institutional review board of the International University of Health and Welfare Mita Hospital (approval no. 5-19-41).

Surgical procedure. Anterior resections were performed by a laparoscopic or open approach. Blood vessels were ligated, lymph nodes were dissected, and the colon and rectum were mobilized; the rectum was then resected with a linear stapler at the anal side of the resection range. In the laparoscopic approach, the intestine was pulled out from an elongated umbilical incision wound; the oral side of the resection range was then determined. Either side-to-end or end-to-end anastomosis was performed (Fig. 2). Side-to-end anastomosis was considered the preferred approach beginning in January 2017; however, end-to-end anastomosis was typically applied when tension at the anastomosis site was expected to be high, as determined by the surgeons. In the side-to-end anastomosis group, the anvil of the circular stapler was inserted into the lumen of the open end; the antimesenteric wall of the intestine was then stapled approximately 3-4 cm from the open end. The open end was stapled with the same stapler. In the end-to-end anastomosis group, the anvil of the circular stapler was fixed at the open end. The splenic flexure was often mobilized to avoid tension at the anastomosis site in both groups, as determined by the surgeons. Following anastomosis, a drain was placed near the anastomosis region. The need for intraoperative ICG-FA, stoma diversion, or trans-anal tube placement was determined by the surgeons. A charge-coupled device camera (HyperEye Medical System™; HEMS, Mizuho) was used for ICG-FA, following dissection of the intestine. The anesthesiologist injected 0.25 mg/kg ICG, followed by flash-injection of 10 ml of saline. When fluorescent labeling at the intended dissection site was poor, the site was modified to a well-perfused proximal site, as determined by the surgeons.

Definition of postoperative complications. Postoperative complications included AL, ileus, and surgical site infections defined as Grade II or higher, according to the Clavien-Dindo classification. The definition of AL was both clinical (i.e., fever, abdominal pain, drain contents, and enhanced inflammatory response) and radiological (i.e., computed tomography scan and contrast enema study). AL in this study included peritonitis due to leakage from any staple line or a pelvic abscess near the anastomosis region, with or without a proven defect in the intestinal wall of the anastomosis, as verified by both clinical and radiological investigations. Patients with AL in this study included those who were diagnosed during their initial hospital stay or after discharge. Leakage verified by either clinical or radiological investigations was not included.

Perioperative management. Mechanical bowel preparation was performed 1 and 2 days before surgery. Sodium picosulfate hydrate (5 ml; sodium picosulfate solution 0.75%) was used 2 days before surgery. Magnesium citrate (100 g; MAGCOROL P) and sodium picosulfate hydrate (5 ml; sodium picosulfate solution 0.75%) were used 1 day before surgery. Patients were only permitted to drink clear liquid after mechanical bowel preparation. No chemical bowel preparation was performed.

Patients were permitted to drink clear liquids on the day of surgery. The trans-anal tube was removed on day 3 after surgery, and patients were permitted to take liquid food on day 4. Blood and abdominal X-ray examinations were performed on days 1, 3, 5, and 7 after surgery.

Statistical analysis. The Mann-Whitney U test and Fisher's exact test were used to analyze continuous and categorical variables, respectively. Multivariate logistic regression analysis was conducted to identify factors related to AL at $P<0.05$. Covariates for multivariate analysis that were statistically significant on univariate analysis ($P<0.05$) were included in the multivariate model. All statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria), and a P-value < 0.05 was considered statistically significant.

Results

Patient characteristics and surgical outcomes. In total, 162 patients (89 men and 73 women) who underwent anterior resection with anastomosis using a double-stapling technique were divided into the side-to-end or end-to-end anastomosis groups between January 2012 and December 2019. Side-to-end anastomosis was performed in 63 patients (31 men and 32 women); end-to-end anastomosis was performed in 99 patients (58 men and 41 women). The characteristics of the patients and tumors are shown in Table I. The side-to-end anastomosis group tended to more frequently exhibit tumor locations in the lower rectum, compared to the end-to-end anastomosis group (end-to-end anastomosis group: RS/upper rectum (n=93), lower rectum (n=6), side-to-end anastomosis group: RS/upper rectum (n=49), lower rectum (n=14), $P<0.01$). No significant differences were observed in other characteristics between the two groups.

Table I. Patient characteristics.

Characteristics	Overall	End-to-end anastomosis	Side-to-end anastomosis	P-value
Patients, n	162	99	63	
Age, years, median (IQR)	63 (55-71)	64 (55-71)	62 (56-71)	0.74
Sex, male/female, n	89/73	58/41	31/32	0.26
BMI, kg/m^2, median (IQR)	22.1 (20.3-24.5)	22.5 (20.5-24.4)	21.9 (20.3-23.9)	0.32
Smoking, n	47	30	17	0.72
Cardiovascular disease, n	34	33	21	1.00
Lung disease, n	18	10	8	0.62
Liver disease, n	3	1	2	0.56
Renal disease, n	3	2	1	1.00
Diabetes mellitus, n	27	16	11	0.83
Preoperative chemoradiation therapy, n	3	0	3	0.06
Albumin, g/dl, median (IQR)	4.3 (4.1-4.6)	4.4 (4.1-4.6)	4.3 (4.0-4.5)	0.40
Location				<0.01
RS/upper rectum, n	142	93	49	
Lower rectum, n	20	6	14	
Tumor size, mm, median (IQR)	40 (25-55)	38 (25-55)	41 (26-53)	0.62
pStage[a], n				0.19
I	56	31	25	
II	31	24	7	
III	61	35	26	
IV	14	9	5	

[a]pStage was diagnosed using the Eighth edition tumor-node-metastasis staging system of the American Joint Committee on Cancer and Union for International Cancer Control; IQR, interquartile range; BMI, body mass index; RS, rectosigmoid.

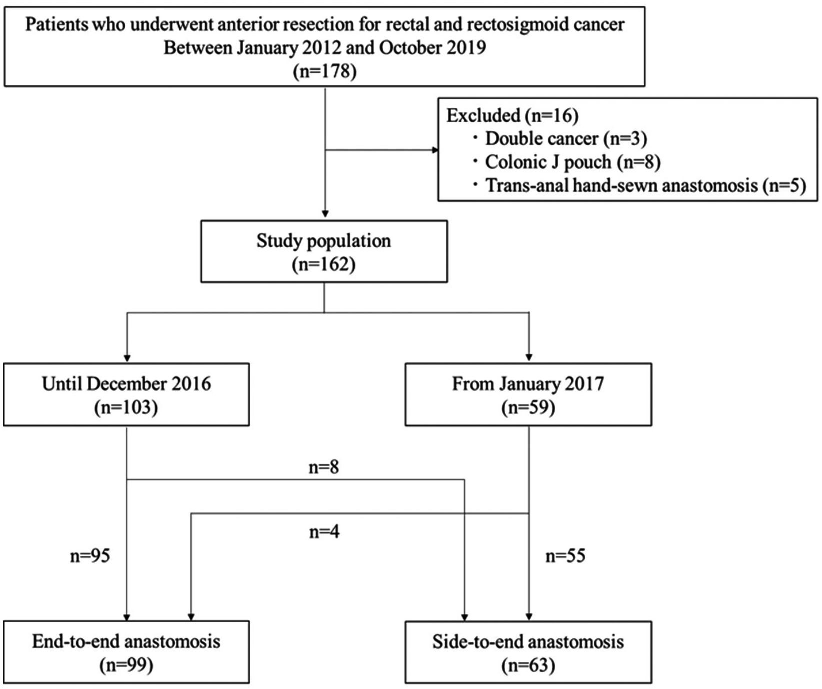

Figure 1. Flow chart of participant inclusion criteria in the present study.

Surgical outcomes are shown in Table II. No significant differences were observed in the approach (open or laparoscopy), surgical type (high or low anterior resection), lymphadenectomy grade, stoma diversion, lateral lymph

Table II. Surgical outcomes.

Surgical outcomes	Overall (n=162)	End-to-end anastomosis (n=99)	Side-to-end anastomosis (n=63)	P-value
Open/laparoscopy, n	12/150	8/91	4/59	0.77
Operation, n				0.09
HAR	52	37	15	
LAR	110	62	48	
D-number, n				0.38
3	114	67	47	
1 or 2	48	32	16	
Diverting stoma, n	18	7	11	0.07
Simultaneous resection, n	21	16	5	0.16
Lateral lymph node dissection, n	14	7	7	0.40
Operation time, min, median (IQR)	254 (208-346)	236 (200-298)	305 (236-395)	<0.01
Bleeding volume, ml, median (IQR)	10 (10-23)	10 (8-20)	11 (10-29)	0.03
Trans-anal tube, n	148	91	57	0.78
ICG-FA, n	114	54	60	<0.01
Additional resection after ICG-FA, n	11	7	4	1
Anastomotic leakage, n	21	18	3	0.02
Ileus, n	4	3	1	1.00
Surgical site infection,	3	2	1	1.00
Hospital days, median (IQR)	12 (10-16)	12 (10-18)	12 (11-16)	0.73
Mortality, n	0	0	0	N/A

IQR, interquartile range; HAR, high anterior resection; LAR, low anterior resection; D-number, lymph node dissection degree; ICG-FA, indocyanine green fluorescence angiography; N/A, not applicable.

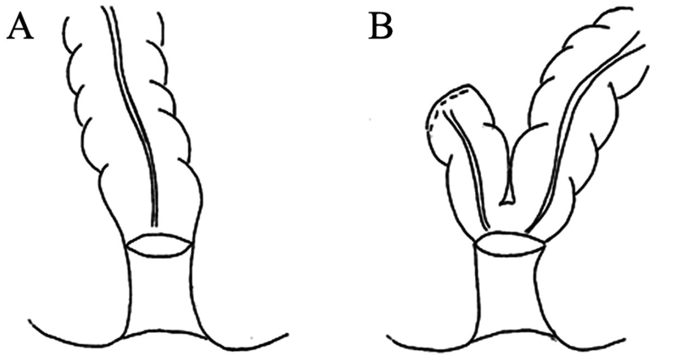

Figure 2. Illustration of anastomosis types. (A) End-to-end anastomosis and (B) side-to-end anastomosis.

node dissection, or trans-anal tube placement. The mean operating time was significantly longer in the side-to-end anastomosis group than in the end-to-end anastomosis group (236 vs. 305 min, P<0.01). Blood loss was also significantly greater in the side-to-end anastomosis group than in the end-to-end anastomosis group (10 vs. 11 ml, P=0.03). The rate of ICG-FA performance was higher in the side-to-end anastomosis group than in the end-to-end anastomosis group. Notably, no significant difference was observed in terms of additional colon resection after ICG-FA. The AL rate was significantly lower in the side-to-end anastomosis group than in the end-to-end anastomosis group (4.8 vs. 18.2%, P=0.02). Finally, no significant differences were observed between the groups in the incidence rates of other complications, nor in the number of postoperative hospital days.

Furthermore, propensity score matching (PSM) was used to minimize the effects of potential confounders. The propensity score was calculated for each patient with variables (age, sex, BMI, smoking, preoperative chemoradiation therapy, location, tumor size, pStage, diverting stoma, ICG-FA, trans-anal tube) that were not equally distributed and were thought to be confounding factors between the two groups. In PSM, one-to-one matching between the groups was performed using the nearest neighbor matching method with a caliper width of 0.2. By PSM, 36 cases were selected in each group. Although not significantly different after PSM, the rate of AL still tended to be lower in the side-to-end anastomosis group than the end-to-end anastomosis group (5.6 vs. 19.4%, P=0.15) (Tables SI and SII).

Factors associated with anastomotic leakage. Based on these data, we investigated the factors associated with AL. The results of univariate and multivariate analyses of these factors are shown in Table III. Univariate analysis revealed that AL was significantly associated with a smoking habit, blood loss (>100 ml), anastomosis type (side-to-end anastomosis), and additional colon resection after ICG-FA. Importantly, performance of ICG-FA was not significantly associated with

Table III. Univariate and multivariate analyses of risk factors associated with anastomotic leakage.

	Univariate analysis			Multivariate analysis		
Characteristics	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age, >65 years	1.25	0.50-3.13	0.63			
Sex, male	2.26	0.98-6.17	0.11			
BMI, ≥25 kg/m^2	1.53	0.50-4.64	0.45			
Smoking	3.21	1.26-8.18	0.02	2.84	1.04-7.77	0.04
Cardiovascular disease	0.78	0.28-2.13	0.62			
Lung disease	2.13	0.63-7.24	0.22			
Liver disease	0.92	0.05-18.44	1.00			
Renal disease	0.92	0.05-18.44	1.00			
Diabetes mellitus	0.22	0.03-1.72	0.15			
Preoperative chemoradiation therapy	0.92	0.05-18.44	1.00			
Albumin, ≥4.0 mg/dl	1.34	0.27-6.60	0.72			
Location, lower rectum	1.84	0.55-6.15	0.32			
pStage, III-IV	1.65	0.65-4.17	0.29			
Surgical procedure, laparoscopy	0.41	0.10-1.65	0.21			
D-number, D3	0.91	0.60-1.37	0.65			
Diverting stoma	0.37	0.05-2.89	0.34			
Simultaneous resection	1.14	0.31-4.26	0.85			
Lateral lymph node dissection	1.97	0.50-7.74	0.33			
Operation time, ≥300 min	2.13	0.85-5.37	0.11			
Bleeding volume, ≥100 ml	3.94	1.30-11.90	0.02	3.43	0.99-12.00	0.05
Trans-anal tube	2.03	0.25-16.40	0.51			
ICG-FA	0.82	0.31-2.18	0.69			
Additional resection after ICG-FA	4.50	1.19-17.00	0.03	4.46	0.95-20.90	0.06
Tumor size, ≥40 mm	1.00		0.37			
Anastomosis, side-to-end anastomosis	0.23	0.06-0.80	0.02	0.22	0.06-0.82	0.02

BMI, body mass index; ICG-FA, indocyanine green fluorescence angiography

AL. Multivariate analysis showed that a smoking habit (odds ratio: 2.84, 95% confidence interval: 1.04-7.77; P=0.04) and anastomosis (side-to-end anastomosis, odds ratio: 0.22, 95% confidence interval: 0.06-0.82; P=0.02) were significantly associated with AL.

Discussion

We evaluated the surgical outcomes of trans-anal side-to-end anastomosis, and identified patient and operative factors associated with AL. The most important finding was that the AL rate was significantly lower in the side-to-end than end-to-end anastomosis group (4.8 vs. 18.2%, respectively, P=0.02). After PSM which was used to minimize the effects of potential confounders, the rate of AL tended to be lower in the side-to-end anastomosis group than the end-to-end anastomosis group. Furthermore, the AL differed significantly according to the method of anastomosis in both univariate and multivariate analyses. Finally, the tumors tended to be located lower down in the side-to-end anastomosis group than in the end-to-end anastomosis group. We suggest that side-to-end anastomosis using a double-stapling technique after anterior resection of rectal cancer may prevent AL. Our findings are important because few similar studies have been reported in the literature.

The mechanism by which the anastomosis method affects the AL rate remains unclear. However, one possible explanation is poorer vascular perfusion at the distal end of the colon, as suggested in a previous randomized study (14). Adequate blood flow at the site of anastomosis is important for the prevention of AL (14-18). Blood flow at the anastomotic site of side-to-end anastomosis may be better than at the anastomotic site of end-to-end anastomosis. In principle, we perform ligation of the inferior mesenteric artery for D3 lymph node dissection. It has been reported that a left colic artery-sparing procedure provides better blood flow to the distal end of the colon but does not contribute to AL (22,23). Further studies are required to determine the impacts of inferior mesenteric artery ligation.

Smoking was a risk factor for AL in the present study. An association between smoking and AL has been reported previously, with reduced mucosal blood flow cited as a possible contributing factor (24-30). In this study, selection bias might have significantly impacted the results because smoking histories were not available. A smoking index would have been useful to discriminate between current and ex-smokers.

In the present study, operating time was significantly longer in the side-to-end anastomosis group than the end-to-end anastomosis group. There were several reasons for this difference. First, tumors were located more frequently at the lower rectum in the side-to-end anastomosis group. Second, ICG-FA tended to be performed in more patients in the side-to-end anastomosis group. As side-to-end anastomosis was introduced in January 2017 in our hospital, ICG-FA was not routinely performed prior to that time. Third, side-to-end anastomosis generally requires slightly longer than end-to-end anastomosis. However, the location of the tumor and performance of ICG-FA, rather than the type of anastomosis, may have led to the longer operating time. Notably, significantly more blood was lost in the side-to-end anastomosis group than in the end-to-end anastomosis group. Tumor location, rather than the type of anastomosis, may have been the main reason for the blood loss.

This study had some limitations. First, the criteria to determine side-to-end anastomosis or end-to-end anastomosis were partially subjective. Tension at the anastomosis site was determined by the surgeon, and it is sometimes difficult to determine whether high tension is present. An objective evaluation of tension at the anastomosis site and objective criteria for selection of anastomosis type are needed. Second, this was a small-scale, retrospective, single-center study and the number of cases of AL was small, so the results might have been subject to various biases, although biases were reduced by PSM. Third, smoking history data were not available and a detailed review was not conducted, which might have enabled the use of a smoking index and discrimination between current smokers and ex-smokers. Fourth, it has been reported that side-to-end anastomosis may be superior to end-to-end anastomosis in terms of postoperative bowel function; however, no comparison of functional outcome was performed between side-to-end anastomosis and end-to-end anastomosis in the present study (19, 20, 31-35). Fifth, data are not available about the intactness of the mesorectum and the CRM status of the resected specimens in the two groups. It is difficult to demonstrate the usefulness of a single factor for preventing AL, because AL is multifactorial. Prospective, randomized controlled, and multi-institutional studies are required to validate these findings.

In conclusion, side-to-end anastomosis with a double-stapling technique might be useful for prevention of AL, following AR. Further large-scale randomized controlled trials are required to validate the usefulness of side-to-end anastomosis for reducing the rate of AL in patients who undergo AR.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HK, TI, NN, AK, TT, SI, TO, AK, TH, JN, SM, MM, MT and OI conceived the study concept and design, and were involved in data interpretation. HK, TI, NN, AK, JN and SM were involved in data collection. TI and NN confirm the authenticity of all the raw data. HK, TI, SM and MT performed the data analysis. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the institutional review board of the International University of Health and Welfare Mita Hospital (Minato-ku, Japan; approval no. 5-19-41), and disclosed in the form of opt-out. The informed consent forms for treatment included consent for the use of patient data and materials for research purposes.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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