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[Original Article]

Higher modified Glasgow Prognostic Score and multiple stapler firings for rectal transection are risk factors for anastomotic leakage after low anterior resection in rectal cancer

Wataru Sakamoto, Shinji Ohki, Tomohiro Kikuchi, Hirokazu Okayama, Shotaro Fujita, Hisahito Endo, Motonobu Saito, Zenichiro Saze, Tomoyuki Momma and Koji Kono

Department of Gastrointestinal Tract Surgery, Fukushima Medical University

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Abstract

Objective : Anastomotic leakage (AL) is one of the most devastating complications of rectal cancer surgery. Not only does AL result in reduced quality of life, extended hospitalization and impaired defecatory function, it also has a high local recurrence rate. In this study, we investigated risk factors for AL as it may help to decrease its occurrence and improve patient outcomes.

Methods : This study was a retrospective, single-institution study of rectal cancer patients who underwent elective low anterior resection between April 2002 and February 2018 at Fukushima Medical University Hospital. Patients were divided into two groups according to the presence of AL. Patient-, tumor-, and surgery-related variables were examined using univariate and multivariate analyses.

Results : One hundred sixty-one patients, average age 63.5±11.5 years, were enrolled in the study. The overall AL rate was 6.8% (11/161). In the univariate analysis, modified Glasgow Prognostic Score (mGPS)=2 ($p=0.003$), use of multiple staplers (≥3 firings) for rectal transection ($p=0.001$) and intraoperative bleeding (≥250 g) were significantly associated with AL incidence. Multivariate analysis identified that mGPS = 2 (odds ratio [OR] : 19.6, 95% confidence interval [CI] : 2.96-125.00, $p=0.002$) and multiple firings (OR : 18.19, CI : 2.31-111.11, $p=0.002$) were independent risk factors for AL.

Conclusion : Higher mGPS score and multiple firings were independent risk factors for AL.

Key words : anastomotic leakage, low anterior resection, multiple stapler firings, modified Glasgow Prognostic Score, rectal cancer

Introduction

Anastomotic leakage (AL) is one of the most common and devastating complications of low anterior resection (LAR), a form of rectal cancer surgery. AL not only results in reduced quality of life and elongated hospital stay, but also adversely affects post-operative defecation and local recurrence[1-3]. Identifying risk factors for AL may reduce its incidence and improve patient outcomes. Many studies have reported risk factor analyses for AL after LAR or laparoscopic LAR (L-LAR), but the results have not been consistent[4-12]. In our hospital, we have employed L-LAR since 2005, and have expanded its applicability criteria gradually. Since 2014, we have been performing L-LAR for all rectal cancer cases except for T4b (UICC 7th). The aim of the current study was to identify the risk factors of LAR, including L-LAR, associated with AL as treatment evolved at our institution.

Corresponding author : Wataru Sakamoto E-mail : ws1024@fmu.ac.jp

Materials and Methods

Study population

Rectal cancer patients who had undergone LAR/L-LAR at Fukushima Medical University Hospital between April 2002 and February 2018 were enrolled in this study, regardless of whether preoperative treatments such as chemotherapy, irradiation, or chemoradiotherapy were performed. Rectal operations in which the anastomosis is located beyond the peritoneal reflection were regarded as LAR. Tumor location was determined by operative findings.

Analysis

Eleven patient- and tumor-related variables, and nine surgery-related variables were included in the analysis. The former included age (≥75, <75), sex, modified Glasgow prognostic score (mGPS 0+1 or 2, assigned on the first visit to our department. 0 : serum albumin ≥3.5 mg/dl and C reactive protein <0.5, 1 : either serum albumin ≥3.5 mg/dl or C reactive protein <0.5, 2 : serum albumin <3.5 mg/dl and C reactive protein ≥0.5), preoperative ileus, diabetes, preoperative bowel preparation (magnesium citrate [MG], polyethylene glycol [PEG], others), preoperative treatment (neoadjuvant chemotherapy and chemoradiotherapy), tumor location (RS [rectosigmoid], Ra [rectum above the peritoneal reflection] + Rb [rectum below the peritoneal reflection]), pathological stage (0+1, 2+3+4 ; UICC-TNM stage, 7th edition), pathological T stage (Tis-T2, T3+T4 ; UICC-TMN stage, 7th edition) and maximum tumor diameter (≥4 cm, <4 cm). The nine surgery-related variables were approach method (open, laparoscopic), inferior mesenteric ligation method (high ligation : IMA was ligated at its origin ; low ligation : left colic artery preserved), lateral lymph node dissection, number of curtilages of the linear stapler used for rectal transaction (3≤[multiple firings], 1+2), placement of trans-anal tube, diverting ileostomy, diameter of circular stapler (≥29 mm, <29 mm), operating time (≥300 min, <300 min), and intraoperative bleeding amount (≥250 g, <250 g). We created ROC curves to identify cut-off values for tumor size, operation time, and bleeding amount. As for age, ROC area under the curve was less than 0.5, therefore we set 75 years old as the cut-off because it corresponds to the start of latter-stage elderly healthcare in Japan's system of universal health insurance. The protocol for this study was approved (#29126) by the ethics committee of Fukushima Medical University, which is guided by local policy, national law, and the World Medical Association Declaration of Helsinki.

Surgical methods

Patients usually received bowel preparation with MS or PEG, although sodium picosulfate hydrate was used in some patients, and some patients did not receive any preparation, depending on the bowel obstruction or operator's discretion. Total mesorectal excision (TME) or tumor-specific mesorectal excision (TSME) was performed depending on the tumor location. The rectum was transected using linear staplers or scissors after firing a purse string device. The choice of stapler varied depending on the time, operative approach and operator (Endocutter, Echelon, Powered Echelon, Curved Cutter : Ethicon Endo-Surgery, Cincinnati, OH, USA). Anastomosis was performed using a single or double stapling technique depending on the tumor location, rectal transaction method and operator's discretion. A circular stapler (CDH, Ethicon Endo-Surgery or EEA : Medtronic, Minneapolis, MN, USA) was used for anastomosis, and the size of the stapler was chosen depending on the diameter of the rectum or colon. The air-tightness of the anastomosis was not tested routinely. A diverting ileostomy was made at the operator's discretion. A pelvic drainage tube was inserted routinely through the posterior side of the anastomosis. In our hospital, a trans-anal drainage tube has been used since 2013 for LAR and L-LAR.

Definition of AL

AL was diagnosed by the following clinical findings : abdominal pain, fever, and pus or fecal discharge from the pelvic drainage tube. These clinical symptoms were confirmed by computed tomography, or water-soluble contrast enema. AL was classified into three grades : Grade A, requiring no active therapeutic intervention ; Grade B, requiring active therapeutic intervention other than surgery ; and Grade C, requiring re-operation[13]. We considered cases that fell into Grades B and C as AL in this study, and included them in the primary endpoint analysis.

Statistical analysis

All statistical analyses were performed using IBM SPSS statistics software, version 24 (IBM, Armonk, NY, USA). A chi-square test, Fisher's exact test, the Mann-Whitney U test, and Student's *t*-test were used for variable comparisons and analysis. A

P value of < 0.05 was considered statistically significant. To determine the factors associated with AL, multivariate logistic regression analysis was used and factors with *P* values of <0.05 in the univariate analyses were included in the model.

Results

Among 161 consecutive patients enrolled in this study, 99 (61.4%) were male and 62 (38.5%) were female. The average age was 63.5±11.5 years old (range 33-88). Their average BMI was 23.3±3.3 (range 16.6-39.7). Twenty-five patients (15.5%) had RS, 86 patients (53.4%) had Ra and 50 patients (31.1%) had Rb cancer. Preoperative interventions such as chemotherapy, radiotherapy, or chemoradiotherapy, were performed in 34 patients (21.1%).

The patients and their tumor characteristics are listed in Table 1. Among the 161 patients, AL oc-

Table 1. patient & tumor characteristics

		Anastomotic Leakage		*p* value
		negative	positive	
Age (years old)		63.7 (11.6)	61.6 (11.0)	0.569
BMI (kg/m^2)		23.4 (3.4)	22.62 (3.2)	0.492
Sex	Male	90	9	
	Female	60	2	0.151
Location	RS	25	0	
	Ra	77	9	
	Rb	48	2	0.12
Pathological Stage	0	5	0	
	I	40	2	
	II	31	4	
	III	54	3	
	IV	14	2	0.4
Pathological depth	Tis	7	0	
	T1	24	0	
	T2	30	2	
	T3	53	7	
	T4	19	2	0.388
Tumor size (cm)		3.8 (1.8)	4.8 (1.5)	0.076
Detection time (day)†		–	5.9 (3.4) (day 1-12)	
Grade‡	A	–	1	
	B	–	4	
	C	–	6	
Mortality		0	0	
Modified GPS	0	133	8	
	1	14	1	
	2	3	2	**0.011**
Serum albumin (g/dL)		4.1 (0.4)	3.9 (0.4)	0.116
CRP (mg/dL)		3.8 (1.8)	4.8 (1.5)	0.815

Age, BMI, tumor size, serum Albumin, CRP were described in average (standard deviation).
† : the day of anastomotic leakage developed described in post operative day. ‡ : Grade A : Anastomotic leakage (AL) which was not required therapeutic intervention, Grade B : AL which was required active intervention other than surgery, Grade C : AL which was required re-operation.
BMI : body mass index, GPS : Glasgow prognostic score

curred in 11 patients (6.8%), nine (81.8%) of whom were male and two (18.1%) were female. AL-Grade C occurred in six cases, all of which had a diverting ileostomy. AL-Grade B occurred in five cases, all of which were cured using conservative therapy. The average time point at which AL was confirmed was postoperative day 6 (range 1-12). There were no deaths related to AL.

Patients were divided into two groups : those without AL ($n=150$) and those with AL ($n=11$). By univariate analysis, AL was significantly associated with preoperative mGPS=2 ($p=0.003$), operative bleeding >250 ml ($p=0.001$) and multiple firings ($p=0.001$, Tables 2 & 3). No significant associations were found with the other variables (Tables 2 & 3).

In the multivariate analysis including factors with a p value of ≤0.05 in the univariate analysis, preoperative mGPS=2 and multiple firings were significantly correlated with AL (respectively : odds ratio [OR] 19.61, 95% confidence interval [CI] 2.96-125.00, $p=0.02$; and OR 18.19, CI 2.31-111.11,

Table 2. Univariate analysis of patient/tumor-related factors

		Anastmotic Leakage		
Variables		negative	positive	*P* value
age	<75	126	9	
	≧75	24	2	0.849
sex	Male	90	9	
	Female	60	2	0.151
BMI	<25	51	3	
	≧25	99	8	0.649
mGPS	0 + 1	147	9	
	2	3	2	**0.003**
Serum albmin	<3.5	6	3	
(g/dL)	≧3.5	143	8	**0.006**
CRP	≧0.5	12	2	
(mg/dL)	<0.5	138	9	0.263
ileus	Yes	7	2	
	No	143	9	0.060
diabetes	Yes	7	2	
	No	143	9	0.060
preparation	MC	125	8	
	PEG	18	2	
	Others	3	1	0.292
presurgical treatment	Yes	32	2	
	No	118	8	0.805
location	RS	25	0	
	Ra+Rb	125	11	0.141
pathological Stage	0+I	45	2	
	II+III+IV	99	9	0.363
pathological depth	Tis−T2	61	2	
	T3+T4	72	9	0.075
tumor size	<4 cm	73	3	
	≧4 cm	76	8	0.164

BMI : body mass index, CRP : C-reactive protein, RS : rectosigmoid, Ra : rectum above peritoneal reflection, Rb : rectum below peritoneal reflection, MC : magnecium citrate, PEG : polyethylene glycole
P value of <0.05 was considered statistically significant.

Table 3. Univariate analysis of surgery-related factors

		Anastmotic Leakage		
Variables		negative	positive	*P* value
operation methods	open	84	8	
	laparoscopic	66	3	0.279
Ligation of IMA	high ligation†	128	8	
	low ligation‡	22	3	0.265
Lateral lymph node dissection	Yes	29	3	
	No	121	8	0.524
multiple firing§	Yes	6	3	
	No	140	8	**0.001**
placement of transanal tube	Yes	27	3	
	No	123	8	0.446
diverting ileostomy	Yes	34	3	
	No	116	8	0.726
Diameter of circular stapler	≦29	101	6	
	>29	43	5	0.281
Operating time	<300	97	6	
	≧300	52	5	0.481
Intraoperative bleeding	<250	87	5	
	≧250	44	6	**0.001**

P value of < 0.05 was considered statistically significant.
IMA : inferior mesenteric artery
† : IMA was ligated at its root. ‡ : IMA was ligated at superior rectal artery. (left colic artery was preserved.) § : multiple firings : number of linear stapler-curtilages used for rectal transaction is three and over.

Table 4. Result of Multivariate analysis

variables	OR	95% CI	*P* value
mGPS (2)	19.61	2.96-125.53	**0.02**
multiple stapler firing (≧3)	18.19	2.93-112.06	**0.02**
Intraoperative bleeding (≧250 ml)	3.04	0.66-13.99	0.153

Multiple logistic regression analysis
P value of <0.05 was considered statistically significant.
OR : odds ratio, CI : confidence interval mGPS : modified Glasgow prognostic score

p=0.02, Table 4).

Discussion

This was a single institution, retrospective observation study to determine risk factors of AL after low anterior resection. The observation period of the study spanned 16 years. Even as a single institution study, many surgeons were involved ; surgical devices, such as circular staplers, linear staplers, and ultrasonic scissors varied ; and even the main surgical approach changed from open to laparoscopic. Even so, multivariate analysis clearly showed that mGPS and multiple firings were risk factors for AL.

In general, the rate of AL occurrence following LAR has been reported to be between 3.6 and 15.3% worldwide[14]. Specifically, Matsubara *et al.* reported an AL incidence in Japan of 9.7% by analyzing our National Clinical Database[15]. Thus, it seems likely that our surgical quality for anastomosis, with AL=6.8% during LAR and L-LAR, is adequate. Previous studies reported risk factors for AL such as anastomosis level[4], tumor location[5-8,16], tumor size[9], multiple stapler firings[4,8,10,16], operation time[6,8], intraoperative blood loss[11,12], body mass index[7], male gender[8,14], and preoperative chemoradiotherapy[16].

In the present study, risk factors for AL were identified as intraoperative bleeding, mGPS=2, and multiple firings by univariate analysis, and as

mGPS=2 and multiple firings by multivariate analysis. The mGPS score is a representative inflammation-based score, combining indicators of decreased plasma albumin and elevated C-reactive protein (CRP). Many studies have revealed associations between elevated GPS/mGPS and poor prognosis in a number of malignancies, including colorectal cancer[17,18]. Recently, inflammatory markers, including GPS/mGPS, have also been characterized as risk factors for postoperative complications[19,20]. In the current study, we confirmed that mGPS=2 was a risk factor for AL. To our knowledge, this is the first report to identify high mGPS as risk factor for AL.

Elsewhere, multiple firings have been reported as a risk factor for AL[4,8,16], consistent with our analysis. Kawada *et al.* posited that an increased number of stapler firings could result in small defects between the staple lines, leading to AL[14]. The number of stapler firings for rectal transection is likely to be affected by several factors, including narrow pelvis, obesity, bleeding, and inadequate port placement. Although we evaluated intraoperative bleeding, BMI, and sex as risk factors in the present study, there were no significant associations between these factors and AL. In addition, in order to prevent multiple firings, Ito *et al.* emphasized the efficacy of additional medial-suprapubic ports for transection of the rectum[4], and Kuroyanagi *et al.* emphasized the efficacy of planned rectal transection by using two endostaplers and punching out the point at which they crossed using a circular stapler[21]. In addition, there is a possibility that the surgical approach (open or laparoscopic) may affect the risk of AL. However, in the present study, we found that laparoscopic surgery was not a significant risk factor for AL. Potentially, robotic surgery may reduce the risk of multiple firings by stabilizing the operative field and by using a well articulating endostapler for transection of the rectum ; however, to our knowledge, no study has yet been reported comparing the number of firings between robotic and endoscopic surgery.

Blood supply to the anastomosis is also thought to be an important factor for AL, and decreased blood flow is a risk factor[22,23]. Since it has been reported that real-time assessment of blood flow around an anastomosis with indocyanine green is acceptable[24], further study to objectively evaluate the blood flow is necessary.

This study has several limitations. First, the observation period of the study extended to 16 years, from 2002 to 2018. Within that period, we have introduced laparoscope-assisted surgery, anastomotic devices have evolved, and the members of our surgical team have changed several times, during which learning curves could have influenced outcomes. Even with these limitations, mGPS and multiple firings still emerged as risk factors of AL ; therefore, these two may persists as risks of LAR in the future. Second, the AL cohort was relatively number (n=11). This may be a reason why other risk factors that emerged in previous reports were not extracted in this study.

In conclusion, higher mGPS score and multiple stapler firings were independent risk factors for AL. It has been suggested that improvement of mGPS score by preoperative strategies such as nutrition support team intervention and infection control, as well as single or double use of staplers for rectal transection, may reduce the AL occurrence rate.

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Conflict of Interest Disclosure

The authors declare no conflicts of interest.

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