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ORIGINAL ARTICLE

Risk Factors for Anastomotic Leakage Following Intersphincteric Resection for Very Low Rectal Adenocarcinoma

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Abstract
Background The aim of this study was to perform a retrospective analysis of the risk factors for anastomotic leakage following intersphincteric resection (ISR) for very low rectal cancer.
Methods Between 1993 and 2007, 120 patients with T1–T3 rectal adenocarcinomas located 1 to 5 cm (median 3 cm) from the anal verge underwent ISR without radiotherapy. Univariate and multivariate analyses of 47 prospectively recorded parameters were conducted.
Results All patients had total mesorectal excision after complete bowel preparation. Of them, 103 underwent partial resection, and 17 underwent complete resection of the internal sphincter. Some 108 patients had a defunctioning stoma. Morbidity and mortality rates were 33% and 0.8%, respectively. Fifteen patients (13%) developed clinical leakage, and six (5%) had severe leakage causing relaparotomy, permanent stoma, or death. Univariate analysis of risk factors for clinical leakage revealed tumor annularity, intraoperative blood transfusion, and pulmonary disease to be significant. Multivariate analysis showed transfusion (hazard ratio, 6.5 [95% confidence interval, 1.4 to 30]; p=0.018) and pulmonary disease (6.3 [1.6 to 26]; p=0.009) to be independently significant. Moreover, transfusion (71 [3.0 to 1000]; p=0.008), colonic J-pouch (32 [1.8 to 500]; p=0.018), and pulmonary disease (32 [1.1 to 1000]; p=0.044) were independently associated with severe leakage.
Conclusions This study suggests intraoperative blood transfusion and pulmonary disease as independent risk factors for clinical and severe leakage following ISR and colonic J-pouch as that for severe leakage. By considering these factors, we may be able to stratify high-risk patients and prepare countermeasures.

Keywords Rectal cancer · Surgery · Intersphincteric resection · Anastomotic leakage · Risk factor

Introduction

Although abdominoperineal resection is standard surgery for patients with massively invasive rectal adenocarcinomas located within 5 cm from the anal verge,[1] intersphincteric resection (ISR) has recently been considered as an alternative option to avoid permanent colostomy for selected patients.[2–4] ISR is defined as a procedure obtaining sufficient margins by removing part or whole of the internal sphincter and restoring bowel continuity for patients with rectal cancers involving or neighboring the anal canal.

Careful performance of ISR has been reported to allow satisfactory results both in the short and long term.[4–11] Furthermore, reported rates of anastomotic leakage follow-

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ing ISR have been as comparatively low as 5% to 16% in experienced hands.[7–11] However, anastomotic leakage after rectal cancer surgery can result in reoperation, morbidity, mortality, permanent stoma, prolonged hospitalization, anal stenosis, and anal dysfunction and may be associated with a higher local recurrence rate.[12,13] To reduce such complications, clarification of the risk factors for anastomotic leakage should help in identifying high-risk patients and planning countermeasures. The aim of this study was, therefore, to perform a retrospective exploratory analysis of risk factors for anastomotic leakage following ISR for very low rectal adenocarcinomas.

Patients and Methods

Between October 1993 and February 2007, 122 patients with T1 to T3 rectal adenocarcinomas located within 5 cm from the anal verge underwent ISR at the National Cancer Center Hospital, Tokyo. All of the T1 tumors were accompanied by massive submucosal invasion. Selection criteria for ISR were as follows: (1) sufficient medical fitness; (2) normal sphincter function; (3) distance between the tumor and the anorectal junction (upper edge of the surgical anal canal) less than 2 cm; (4) no involvement of the external sphincter; and (5) no signs of disseminated disease. Preoperatively, the patients were assessed with chest and abdominal computed tomography (CT), digital anorectal examination, and radiological studies, including endorectal ultrasonography, thin-section helical CT, or high-resolution magnetic resonance imaging.

Univariate and multivariate analyses of 47 prospectively recorded clinicopathologic variables were conducted for the 120 consecutive patients who did not receive neoadjuvant radiotherapy. Data from the remaining two given radiotherapy were excluded from the present analysis. Approval by the institutional review board was not required for the observational study. All patients gave informed consent for usage of their data for analysis.

Surgical Procedures

The day before surgery, bowel lavage with 2 L of polyethylene glycol was carried out, and all patients received parenteral antibiotic prophylaxis no more than 30 min before skin incision. The surgical procedures were as described previously[11] and basically similar to those originally documented by Schiessel et al.[4,7] The intersphincteric plane between the puborectalis and the internal sphincter was dissected cautiously as caudad as possible under direct vision, using long right-angle retractors and electrocautery. When the lower edge of the tumor was reached, the anal canal was closed just below the tumor and then irrigated with povidone iodine followed by saline. After retractors were applied to the anal canal, the anal canal mucosa and internal sphincter were circumferentially incised, and the intersphincteric plane was dissected cephalad. A resection margin of at least 1 cm was always attempted. If the rectum was not closed in the abdominal phase, it was closed using sutures during per-anal dissection. After removal of the rectum, the pelvic cavity and anal canal were washed, and then a coloanal anastomosis was made using 3-0 absorbable vertical mattress sutures. A pelvic drain was placed, and a defunctioning stoma was made.

Definition of Anastomotic Leakage

Clinical anastomotic leakage was defined as clinically apparent leakage including gas, pus, or fecal discharge from the pelvic drain or peritonitis. All anastomotic leakages were confirmed as extravasation of endoluminally administered water-soluble contrast material on radiography or computed tomography. An abscess around the anastomosis or a rectovaginal fistula was also considered as leakage. Radiological examination was performed by the surgeon and only when there was clinical suspicion of anastomotic leakage. Pouch fistula, pouch necrosis, and necrosis of neorectum were also regarded as evidence of a leakage. Severe leakage was defined as causing emergency relaparotomy, permanent stoma, or death.

Statistical Analysis

The chi-square test was used to compare proportions. The influence of each variable on the risk of clinical anastomotic leakage or severe leakage was calculated using the chi-square test. All variables associated with clinical leakage or severe leakage at $p<0.05$ were entered in a multivariate analysis using the multiple logistic regression model with the forward stepwise method (likelihood ratio). All statistical analyses were performed using SPSS for Windows, version 11.0J (SPSS-Japan Inc., Japan). A two-sided p value of less than 0.05 was considered significant.

Results

Of 39 patients (33%) who suffered complications, 30 were treated conservatively and nine received reoperations. Fifteen patients (13%) had clinical anastomotic leakage, and six underwent an emergency relaparotomy (Table 1). Five of those six had permanent stoma and one dying of

Table 1 Details of the Patients with Anastomotic Leakage

Severity	Reconstruction	Site of leakage	Treatment
Severe[a]	Colonic J-pouch (5)[a]	Pouch necrosis (2)[a] Anterior wall of pouch (1)	Pouch resection, colostomy and drainage (3)[a]
		Pouch anal anastomosis (1)	Ileostomy and drainage (1)
		Pouch-vaginal fistula (1)	Drainage and fistulectomy (1)
	Straight end to end (1)	Anovesical fistula (1)	Drain irrigation and fistulectomy (1)
Minor	Straight end to end (6)	Anastomosis (6)	Transanal drainage (3), Observation (2), Drain irrigation (1),
	Transverse coloplasty (3)	Anastomosis (3)	Drain irrigation (1), Transanal drainage (1), Observation (1)

Numbers in parentheses are numbers of patients

[a] One patient died

anastomotic leakage and sepsis (30-day mortality rate= 0.8%). Seven patients had permanent stoma due to complications (six patients) or local recurrence (one). Other complications included wound infection (nine patients), bowel obstruction (six), urinary tract infection (four), anal pain (two), cholecystitis (two), anastomotic stenosis (one), anal prolapse (one), peristomal hernia (one), and thrombocytopenia (one).

Of the 47 variables analyzed, 28 are summarized in Table 2. The remaining 19 variables were tumor size, pT, pN, pM, lateral pelvic lymph node metastasis, preoperative vital capacity, serum carcinoembryonic antigen, CA19-9, C-reactive protein, hemoglobin A1c levels, white blood cell count, hamatocrit, lymphocyte count, arterial blood oxygen tension, carbon dioxide tension, bicarbonate, base excess, liver disease, and drinking habit.

There were 92 male and 28 female patients with a median age of 57 years (range 26 to 75 years). Thirteen had pulmonary disease including chronic obstructive pulmonary disease in eight patients and restrictive respiratory disease in five. The median distance from the anal verge to the tumor was 3 cm (range 1 to 5 cm).

All patients underwent total mesorectal excision. In addition, 46 patients received extended lateral pelvic lymph node dissection. Sixty-seven patients underwent high ligation of the inferior mesenteric artery. A total of 103 patients underwent partial resection of the internal sphincter, and 17 underwent complete resection. A small part of the external sphincter was resected in six patients to obtain sufficient surgical margins. Combined resection of adjacent organs was performed for 12 patients. Two patients with solitary liver metastases and one with a solitary lung metastasis underwent complete resection of their metastases. Mobilization of the splenic flexure was performed for 35 patients. A colonic J-pouch was constructed for 24 patients, a transverse-coloplasty pouch for 38, and a straight anastomosis for 58. Some 108 patients had a defunctioning stoma which was closed 3 months after ISR. Median operating time was 339 min (range 200 to 590 min). Median blood loss was 462 mL (range 45 to 3,644 mL), and nine patients received intraoperative blood transfusions (Table 2).

The median tumor diameter was 3.7 cm (range 1 to 12 cm). Pathologic findings are shown in Table 2. Resection margins were macroscopically negative in all patients but microscopically positive in four. The median number of lymph nodes removed at surgery was 29 (range 4 to 88), and 108 patients (90%) underwent dissection of 12 or more.

Univariate Analysis

Clinical anastomotic leakage was statistically significantly associated with tumor annularity, intraoperative blood transfusion, and pulmonary disease (Table 2). Severe leakage was significantly associated with tumor annularity, extended lateral pelvic lymph node dissection, a colonic J-pouch, intraoperative transfusion, preoperative serum total protein and albumin levels, the preoperative platelet count, and pulmonary disease (Table 2). Neither overall clinical leakage nor severe leakage showed significant association with the 19 variables not shown in Table 2.

Multivariate Analysis

In a multivariate analysis for clinical leakage, the significant variables in the univariate analysis were entered. Pulmonary disease (hazard ratio, 6.3 [95% confidence interval, 1.6 to 26]; $p=0.009$) and intraoperative transfusion (6.5 [1.4 to 30]; $p=0.018$) were found to be independently significant. The incidences of clinical leakage for patients with 0, 1, and 2 positive risk factors were estimated to be 8%, 28%, and 100%, respectively.

In a multivariate analysis for severe leakage, the eight significant variables in the univariate analysis were used.

Table 2 Univariate Analyses of 28 Clinicopathologic Variables Related to Clinical Anastomotic Leakage and Severe Leakage

	Number of patients	Clinical leak (%)	*p* Value	Severe leak (%)	*p* Value
Gender					
Male	92	12 (13)	1	5 (5)	1
Female	28	3 (11)		1 (4)	
Age					
<60 years	71	6 (8)	0.16	2 (3)	0.22
≥60 years	49	9 (18)		4 (8)	
Distance of the tumor from the anal verge					
<2.5 cm	21	1 (5)	0.47	0 (0)	0.59
≥2.5 cm	99	14 (14)		6 (6)	
Tumor annularity					
<3/4	101	10 (10)	0.033	3 (3)	0.033
≥3/4	16	5 (31)		3 (19)	
Unknown	3				
Histopathologic grade					
Well-differentiated	59	9 (15)	0.62	3 (5)	1
Moderately differentiated	53	6 (11)		3 (6)	
Poorly differentiated	8	0 (0)		0 (0)	
Pathological UICC TNM stage					
Stage I	50	7 (14)	0.91	1 (2)	0.23
Stage II	21	3 (14)		3 (14)	
Stage III	46	5 (11)		2 (4)	
Stage VI	3	0 (0)		0 (0)	
Microscopic resection margins					
Negative	116	15 (13)	1	6 (5)	1
Positive	4	0 (0)		0 (0)	
Internal sphincter resection					
Partial	103	15 (15)	0.13	6 (6)	0.59
Complete	17	0 (0)		0 (0)	
Combined resection					
No	108	15 (14)	0.36	6 (6)	1
Yes	12	0 (0)		0 (0)	
Extended lateral pelvic lymph node dissection					
No	74	8 (11)	0.57	1 (1)	0.03
Yes	46	7 (15)		5 (11)	
High ligation of the inferior mesenteric artery					
No	50	6 (12)	1	3 (3)	1
Yes	67	9 (13)		3 (4)	
Mobilization of the splenic flexure					
No	63	8 (13)	1	1 (2)	0.129
Yes	35	5 (14)		3 (9)	
Reconstruction					
Straight anastomosis	58	7 (12)	0.18	1 (2)	0.001
Transverse coloplasty	38	3 (8)		0 (0)	
Colonic J-pouch	24	5 (21)		5 (21)	
Defunctioning stoma					
No	14	1 (7)	1	0 (0)	1
Yes	106	14 (13)		6 (6)	
Anastomosis height from the anal verge					
<2.0 cm	57	5 (9)	0.28	1 (2)	0.21
≥2.0 cm	63	10 (16)		5 (8)	

Table 2 (continued)

	Number of patients	Clinical leak (%)	*p* Value	Severe leak (%)	*p* Value
Operating time					
<6 h	68	8 (12)	0.79	1 (1)	0.084
≥6 h	52	7 (13)		5 (10)	
Blood loss					
<500 mL	64	6 (9)	0.29	2 (3)	0.42
≥500 mL	56	9 (16)		4 (7)	
Intraoperative blood transfusion					
No	111	11 (10)	0.014	2 (2)	<0.001
Yes	9	4 (44)		4 (44)	
Preoperative body mass index					
<25	89	10 (11)	0.53	4 (4)	0.65
≥25	31	5 (16)		2 (6)	
Preoperative FEV_1 (%)					
<70%	8	3 (38)	0.061	2 (25)	0.051
≥70%	112	12 (11)		4 (4)	
Preoperative serum total protein level					
Normal (6.3–8.3 g/dL)	113	13 (12)	0.21	4 (4)	0.039
Abnormal	7	2 (29)		2 (29)	
Preoperative serum albumin level					
Normal (3.7–5.2 g/dL)	110	12 (11)	0.11	3 (3)	0.007
Abnormal	10	3 (30)		3 (30)	
Preoperative blood hemoglobin level					
Normal (11.3–14.9 g/dL)	85	8 (9)	0.13	2 (2)	0.059
Abnormal	35	7 (29)		4 (11)	
Preoperative platelet count					
Normal (125,000–375,000/μL)	115	13 (11)	0.12	4 (3)	0.02
Abnormal	5	2 (40)		2 (40)	
Diabetes mellitus					
No	106	12 (11)	0.38	6 (7)	1
Yes	14	3 (21)		0 (0)	
Cardiovascular disease					
No	98	10 (10)	0.15	4 (4)	0.30
Yes	22	5 (23)		2 (9)	
Pulmonary disease					
No	107	10 (9)	0.011	3 (3)	0.017
Yes	13	5 (38)		3 (23)	
Smoking habit					
No	79	11 (14)	0.58	6 (8)	0.094
Yes	41	4 (10)		0 (0)	

The remaining 19 variables not shown here did not demonstrate any significant association

FEV_1 forced expiratory volume in the first second of expiration

Intraoperative transfusion (hazard ratio, 71 [95% confidence interval, 3.0 to 1,000]; $p=0.008$), a colonic J-pouch (32 [1.8 to 500]; $p=0.018$), and pulmonary disease (32 [1.1 to 1,000]; $p=0.044$) were independently associated with adverse outcomes. The incidences of severe leakage for patients with 0, 1, 2, and 3 positive risk factors were estimated to be 0%, 6%, 67%, and 100%, respectively.

Discussion

In this study, the incidences of clinical anastomotic leakage and mortality after ISR were 13% and 0.8%, respectively. These are comparable to the respective incidences of 5% to 16% and 0 to 0.8% in recent ISR series.[7–11] Since these figures are even comparable to the 2.8% to 19.2% and 0%

to 2.5% observed with anterior resection,[14–26] appropriately administered ISR can be regarded as safe in terms of leakage and mortality. However, such figures should be interpreted cautiously because incidences of anastomotic leakage depend on the definition, patient selection, and treatment details. Patient factors like gender,[15,16,18,22,25] age,[25] American Society of Anesthesiology score,[25] heart disease,[26] malnutrition,[17] weight loss,[17] obesity,[15] smoking habit,[26] and alcohol abuse[17] have been reported to independently influence the incidences of leakage after anterior resection, and so have treatment factors such as neoadjuvant chemoradiotherapy,[18,22] bowel preparation,[19] timing of surgery,[25] surgeon caseload,[25] anastomotic level, [14,15,18,19,22] intraoperative contamination,[17,18] pelvic drainage,[21] defunctioning stoma,[16,20,21,24] operation time,[17] and blood transfusion.[17,19]

To our knowledge, there have only been few studies addressing risk factors for anastomotic leakage following ISR. Rullier et al.[15] investigated 272 anterior resections for rectal cancer, in which 131 anastomoses were situated 5 cm or less from the anal verge. Multivariate analysis of their overall population showed that male sex and the level of anastomosis were independent factors for leakage. In a second analysis of 131 very low anastomoses, obesity was an independent factor. The authors concluded that a protective stoma is suitable after anastomoses situated at or less than 5 cm from the anal verge, particularly for men and obese patients.

In the present study, all of the patients had undergone complete bowel preparation, elective surgery by high-volume colorectal specialists, and pelvic drainage, all of which have been reported to be independently beneficial for reducing leakage.[19,21,25] Most had a defunctioning stoma as well.[16,20,21,24] None had received neoadjuvant chemoradiotherapy considered to be an independent risk factor for leakage.[18,22] Therefore, these already known significant factors could not be evaluated in this study. Our multivariate analysis revealed intraoperative blood transfusion and pulmonary disease to be independently associated with overall clinical leakage and severe leakage, and a colonic J-pouch was associated with severe leakage. These results suggest that under the circumstances prevailing in our institution, we can stratify high-risk patients by using these factors and prepare countermeasures against them.

Although the exact mechanism whereby anastomotic leakage may be related to blood transfusion is unclear, it is known that allogeneic blood transfusion induces immunosuppression and predisposes to postoperative infection.[27] Allogeneic leukocytes have a critical role in the induction of transfusion-induced immunosuppression.[27] Tang et al.[27] reported that intra- or postoperative blood transfusion was an independent risk factor for overall surgical site infection, incisional infection, and organ/space infection with and without clinical anastomotic leakage in a prospective study of 2,809 consecutive patients undergoing elective colorectal resection. Therefore, susceptibility to infection induced by transfusion may promote development of anastomotic leakage.

To avoid intraoperative transfusion, it is preferable to treat anemia before surgery using oral and parenteral iron therapy. Transfusion should be reserved for patients with cardiovascular instability and continued and excessive blood loss. Furthermore, it should be given before the operation because deleterious effects appear to be more likely with intra- or postoperative transfusion.[27] Operative blood loss should be minimized by cautious procedures. If excessive blood loss is expected, autologous blood transfusion should be considered, especially in the presence of other risk factors.

In line with previous reports on intestinal anastomotic leakage, we found an independent association with pulmonary disease. Jonsson et al.[28] measured oxygen tension and collagen deposition in subcutaneous wounds in 33 postoperative patients and found that this and the resultant tensile strength are limited by perfusion and tissue oxygen tension. Hopf et al.[29] measured subcutaneous wound oxygen tension in 130 surgical patients and observed that this factor is a strong predictor of infection. Millan et al.[23] determined intramucosal pH at colorectal anastomoses, which reflects blood supply and oxygenation of the mucosa, and found that it can accurately predict the risk of anastomotic leakage. Smoking is a major cause of chronic obstructive pulmonary disease and is known as an independent risk factor for anastomotic leakage after anterior resection.[26] Therefore, although the exact pathophysiology remains to be clarified, it is reasonable to speculate that pulmonary disease predisposes to anastomotic hypoxia which in turn hinders wound healing, aggravates infection, and promotes anastomotic dehiscence.

Because of their chronic and irreversible nature, the chronic obstructive pulmonary disease and restrictive respiratory diseases seen in our series are difficult to treat. However, intensive respiratory management including continuous pulse oximetry monitoring, supplemental oxygen, appropriate analgesia, bronchoscopy when needed, and early mobilization, similar to the management applied after esophageal cancer surgery,[30] may prevent the respiratory complications and hypoxemia which can lead to anastomotic leakage.

Although the incidence of leakage with a colonic J-pouch was reported to be significantly lower than with straight coloanal anastomosis[31] and transverse coloplasty[32] in anterior resection, we paradoxically found a J-pouch to be an independent risk factor for severe leakage in our ISR series. Of the five patients who underwent J-pouch construction and suffered severe leakage, four were male, four received an intraoperative transfusion, and two had

pulmonary disease. Therefore, it appears that a colonic J-pouch reconstruction after ISR may confer extra risk on males with intraoperative transfusion and/or pulmonary disease. Since males have a longer anal canal than females, the presence of a bulky J-pouch and anastomosis may increase the sphincteric squeeze pressure and worsen anastomotic blood and oxygen supply, thereby predisposing to leakage. Thus, in the presence of other risk factors, countermeasures including a switch to other reconstruction methods may need to be considered.

There are limitations to the present study. First, the study design is retrospective, and this may cause biases. Especially, because all or nearly all patients had complete bowel preparation, elective surgery by high-volume colorectal specialists, pelvic drainage, and defunctioning stoma and did not have neoadjuvant chemoradiotherapy, the significance of these factors could not be evaluated in this study. Second, because the numbers of events were limited particularly for severe leakage, many other risk factors which were significant in the previous studies on leakage after anterior resection were not significant in this study. Thus, further confirmation with a larger number of patients would be preferable.

In conclusion, the present retrospective exploratory study suggests that intraoperative blood transfusion and pulmonary disease are independently significant risk factors for overall and severe anastomotic leakage after ISR, and a colonic J-pouch was associated with severe leakage. By taking account of these factors, we may be able to stratify high-risk patients and prepare countermeasures. However, because numbers of patients and events in this study were limited, further investigation and validation are warranted with larger datasets or in future prospective trials.

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