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Risk Factors for Esophagojejunal Anastomotic Leakage in Gastric Cancer Patients after Total Gastrectomy

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Background: Leakage at the esophagojejunal anastomosis site is an important postoperative complication of total gastrectomy. We analyzed our surgical cases to determine the risk factors for esophagojejunal anastomotic leakage.
Methods: This study included 309 patients who underwent total gastrectomy and esophagojejunal anastomosis. The onset of esophagojejunal anastomotic leakage according to age, gender, performance status, American Society of Anesthesiologists classification, body mass index, presence or absence of diabetes, invasion depth, lymph node metastasis, histological type, presence or absence of esophageal infiltration, operative duration, amount of blood loss, experience of blood transfusion, procedural approach, and the prognostic nutritional index was analyzed.
Results: Univariate analyses revealed a significant difference in the rate of esophagojejunal anastomotic leakage due to advanced age, male gender, the presence of diabetes, the presence of esophageal infiltration, and blood loss ≥1,100 g. In the multivariate analysis, which included factors identified in the univariate analyses, advanced age, male gender, the presence of diabetes, and blood loss ≥1,100 g were identified as independent risk factors for esophagojejunal anastomotic leakage.
Conclusions: Advanced age (≥68 years), male gender, diabetes, and massive blood loss are risk factors for esophagojejunal anastomotic leakage. (J Nippon Med Sch 2023; 90: 64–68)

Key words: gastric cancer, total gastrectomy, anastomotic leakage

Introduction

In recent years, the number of patients with upper-third gastric cancer and cancer of the esophagogastric junction has increased. Leakage at the site of the esophagojejunal anastomosis after total gastrectomy has declined as a result of advances in surgical devices and techniques; however, leakage still occurs. Anastomotic leakage occurs in 4.4%-15.1% of total gastrectomy cases[1]. Patients may die when major leakages occur. We analyzed our surgical cases with the aim of identifying risk factors for esophagojejunal anastomotic leakage.

Patients and Methods

Patients

This study included 309 patients who underwent total gastrectomy and esophagojejunal anastomosis for gastric cancer (patients with carcinomas of the esophagogastric junction were not included in this study) between February 1996 and March 2016. We used a circular stapler for esophagojejunostomy. The onset of esophagojejunal anastomotic leakage of Grade II or above, as per the Clavien-Dindo classification[2], was analyzed according to the patient background, including age, gender, performance status (PS), American Society of Anesthesiologists (ASA) classification, body mass index (BMI), and the presence of diabetes; tumor factors, including invasion depth,

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Table 1 Patients background

		All cases n = 309
Age		65.2±10.8
Sex	Male	222
	Female	87
PS	0	259
	1	47
	2	3
ASA	1	215
	2	75
	3	19
BMI		21.6±2.9
Diabetes	presence	44
	absence	265
Depth	T1	73
	T2	128
	T3	96
	T4	12
Lymph node metastasis	N0	130
	N1	71
	N2	78
	N3	30
Pathological type	differentiated	138
	undifferentiated	171
Esophageal invasion	presence	8
	absence	301
Operation time (min)		287.2±82.7
Bleeding volume (g)		718.9±612.1
Blood transfusion	presence	81
	absence	228
Procedure	Laparoscopy	16
	Open	293
PNI		46.1±9.9

lymph node metastasis, histological type, and the presence of esophageal infiltration; surgical factors, including operative duration, amount of blood loss, experience of blood transfusion, and procedural approach; and the prognostic nutritional index (PNI = 10 × serum albumin level [g/dL] + 0.005 × total lymphocyte count [mm^{-3}]) using preoperative blood test data. We used gastrointestinal angiography to diagnose anastomotic leakage. The TNM of gastric cancer was classified according to the 15th edition of the Japanese Gastric Cancer Association TNM classification system.

The mean patient age was 65.2 years, and the study cohort included 222 men and 87 women. The mean BMI was 21.6. Diabetes was present in 44 patients (14.2%). The histology was differentiated type in 138 patients and undifferentiated type in 171 patients. Esophageal infiltration was present in eight patients (2.6%). The mean operative duration was 287 min, and the mean blood loss volume was 718 g. The procedural approach was laparoscopy in 16 patients and laparotomy in 293 patients. PNI was 46.1 (**Table 1**).

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committees of Hasuda hospital (Approval No. 202205-01).

Statistical Analysis

All statistical analyses were performed using the JMP statistical software program (Cary, NC, USA). Continuous variables were expressed as mean ± SD. Two-tailed Student's *t*-tests and Mann-Whitney *U*-tests were used to compare continuous variables. Chi-squared tests were used for comparisons among groups. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multivariate Logistic regression models. The cut-off values for age, BMI, operative duration, amount of blood loss, and PNI were determined using receiver operating

Table 2 Each patients background

		Leakage cases n = 23	Non-Leak cases n=286	p value
Age		70.3±7.7	64.8±10.9	0.0205
Sex	Male	22	200	0.0022
	Female	1	86	
PS	0	19	240	0.7622
	1	4	43	
	2	0	3	
ASA	1	12	203	0.1878
	2	9	66	
	3	2	17	
BMI		22.1±2.8	21.6±2.9	0.3743
Diabetes	presence	8	36	0.0094
	absence	15	250	
Depth	T1	6	67	0.9905
	T2	9	119	
	T3	7	89	
	T4	1	11	
Lymph node metastasis	N0	9	121	0.6738
	N1	7	64	
	N2	4	74	
	N3	3	27	
Pathological type	differentiated	13	125	0.2359
	undifferentiated	10	161	
Esophageal invasion	presence	3	5	0.0138
	absence	20	281	
Operation time (min)		302±67	286±84	0.1705
Bleeding volume (g)		853±525	708±618	0.0889
Blood transfusion	presence	6	75	0.9885
	absence	17	211	
Procedure	Laparoscopy	2	14	0.4652
	Open	21	272	
PNI		46.3±8.2	47.4±6.5	0.5244

curve (ROC) for anastomotic leakage. P values of <0.05 were considered statistically significant.

Results

Among the 309 patients, anastomotic leakage of Grade II or above was observed in 23 patients (7.4%). Grade III was observed in 2 patients (0.6%), and Grade IV in 2 (0.6%). The group with anastomotic leakage was defined as the L group, and the group without anastomotic leakage was defined as the N group. In intergroup comparisons, no significant differences were detected in PS, ASA classification, BMI, invasion depth, lymph node metastasis, histological type, operative duration, amount of blood loss, experience of blood transfusion, procedural approach, or PNI. Patients in the L group (70.3 years) were significantly older than patients in the N group (64.8 years) (p = 0.0205). The L group included 22 men and 1 woman, whereas the N group included 200 men and 86 women; the ratio of males to females was significantly higher in the L group (p = 0.0022). The prevalence of diabetes was significantly higher in the L group (34.8%) compared with the prevalence in the N group (12.6%) (p = 0.0094). Esophageal invasion occurred at a significantly higher rate in the L group (13%) compared with the rate in the N group (1.7%) (p = 0.0138) (**Table 2**).

Based on the ROC curve analyses for anastomotic leakage, the respective cut-off values were 68 years of age, BMI of 22.2, operative duration of 264 min, 1,100 g of blood loss, and a PNI of 41.4. Based on these cut-off values, univariate analyses revealed significant differences in advanced age (≥68 years) (p = 0.0075), male gender (p = 0.0292), the presence of diabetes (p = 0.0056), esophageal invasion (p = 0.0054), and blood loss of ≥1,100 g (p = 0.0006). In the multivariate analysis including these factors, advanced age (≥68 years) (ORs = 4.98, 95% CI: 1.65-

Table 3 Uni- and multivariate analyses of clinical characteristics as factors related to anastomotic leakage

Variable	Univariate			Multivariate		
	ORs	95%CI	p value	ORs	95%CI	p value
Age (≥68/<68)	3.7	1.42-9.66	0.0075	4.98	1.65-15.05	0.0044
Sex (male/female)	9.46	1.26-71.3	0.0292	8.64	1.07-70.05	0.0434
PS (PS12/PS0)	1.09	0.36-3.36	0.8757			
ASA (ASA23/ASA1)	2.24	0.95-5.28	0.0648			
BMI (≥22.2/<22.2)	1.86	0.79-4.38	0.1578			
Diabetes mellitus (presence/absence)	3.7	1.47-9.35	0.0056	5.18	1.77-15.13	0.0027
Depth (T34/T12)	0.99	0.40-2.41	0.975			
Lymph node metastasis (presence/absence)	1.15	0.48-2.76	0.7458			
Pathological type (undifferentiated/differentiated)	0.46	0.17-1.22	0.1199			
Esophageal invasion (presence/absence)	8.43	1.88-37.83	0.0054	3.17	0.37-27.11	0.293
Operation time (≥264 min/<264 min)	2.34	0.89-6.17	0.0842			
Bleeding volume (≥1,100 g/<1,100 g)	4.84	1.96-11.93	0.0006	3.96	1.46-10.74	0.0069
Blood transfusion (presence/absence)	0.99	0.38-2.61	0.9885			
Procedure (Laparoscopy/Open)	1.85	0.39-8.69	0.4355			
PNI (<41.4/≥41.4)	1.99	0.58-6.85	0.2776			

ORs: Odds ratios, CI: confidence interval

15.02, p = 0.0044), male gender (ORs = 8.64, 95% CI: 1.07-70.05, p = 0.0434), the presence of diabetes (ORs = 5.18, 95% CI: 1.77-15.13, p = 0.0027), and blood loss of ≥ 1,100 g (ORs = 3.96, 95% CI: 1.46-10.74, p = 0.0069) were identified as independent risk factors for postoperative esophagojejunal anastomotic leakage (**Table 3**).

Discussion

The mortality rate of gastric cancer has declined in recent years; however, gastric cancer is still the primary cause of cancer-related deaths[3–5]. In 2018, gastric cancer was the second and fourth most common cause of death among men and women, respectively, in Japan[6]. Despite advances in chemotherapy and molecular targeted therapy[7,8], the most effective treatment for gastric cancer is still gastrectomy with adequate lymph node dissection. Gastrectomy with D2 lymph node dissection is the standard procedure in many countries, including Japan and Korea[9].

Risk factors and predictive factors for complications following gastrectomy have been described in several reports[10]. In particular, postoperative anastomotic leakage is a major postoperative complication, with a reported incidence of 4.4%-15.1% after total gastrectomy[1]. However, many instances of anastomotic leakage are minor and can be cured with conservative treatment by nil per os and high-calorie intravenous infusion. In instances of major leakage, some patients may die of septicemia and disseminated intravascular coagulation[11]. Anastomotic leakage is caused by various factors, including patient factors, local factors, and surgical factors[12].

Sex-based differences influence the incidence of postoperative complications[13]. Various theories regarding the mechanism by which sex-based differences occur have been proposed. However, hormones, such as estrogen and aldosterone, are acutely involved in the immune response, and we believe that differences in the immune response to invasion caused by surgery for gastric cancer affects the incidence of complications[14].

Blood loss is a risk factor for complications after open gastrectomy[15–19]. Furthermore, a recent complication prediction system called Surgical Apgar Score (SAS), which consists of intraoperative blood loss, lowest intraoperative mean arterial pressure, and lowest intraoperative heart rate, was proposed for several types of surgeries, including colorectal surgery, vascular surgery, and urology[20–23]. This surgical score reflects intraoperative hemodynamic stability and is influenced by the quality of surgery and anesthesia and the patient's pre- and intraoperative condition. In the field of gastric cancer, Miki et al. reported that modified SAS can be applied to gastrectomies and was associated with the complication rate in their study[24].

Elderly individuals have a high rate of preoperative comorbidity and postoperative complications, and many die of other illnesses. Therefore, minimally invasive surgery is recommended to minimize dissection in elderly individuals[25,26]. Furthermore, comorbidities include heart disease, respiratory disease, diabetes, renal failure, and malnutrition. In particular, poorly controlled diabetes delays wound healing and increases the risk of anastomotic leakage. Furthermore, diabetes increases the risk of infection; therefore, postoperative blood sugar should be carefully controlled[27]. The most basic countermeasure against anastomotic leakage is prevention. Comorbidities should be controlled as much as possible.

The major limitations to our study are its retrospective nature and the single institutional Japanese-based cohort. The optimal cut-off values for age, BMI, operation time, bleeding volume, and PNI may be different in other studies with different endpoints and different patient cohorts. Further prospective studies with a larger sample size are warranted to confirm the association between anastomotic leakage and age, sex, diabetes, and bleeding volume.

In conclusion, due care should be paid to prevent anastomotic leakage in the elderly, males, and patients with diabetes. We believe that it is imperative to keep blood loss at a minimum during surgery.

Conflict of Interest: All authors declare that they have no conflicts of interest.

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