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Original Article

Risk factors for leakage after total gastrectomy

Orcun Yalav, Ugur Topal

Cukurova University, Faculty of Medicine, Department of General Surgery, Adana, Turkey

Abstract

Aim: Although many studies report risk factors for anastomotic leakage after gastrectomy for gastric cancer (GC), there are conflicting results in the literature. In this study, we aimed to identify the risk factors associated with anastomotic leakage after gastrectomy.
Material and Methods: Patients who underwent total gastrectomy for gastric cancer in a single center between September 2015 and September 2018 were evaluated retrospectively. The relationship between anastomotic leakage and clinical variables, tumor characteristics and intraoperative characteristics of 18 parameters were analyzed. The relationship between anastomotic leakage and survival was evaluated.
Results: A total of 102 patients were included in the study. Anastomotic leakage rate was 9.81% (10/102). A significant relationship was not determined between anastomotic leakage and age >60 (p:0.232), diabetes mellitus (p:0.334), ASA score >3 (p:0.587), albumin <3.5 gr/dl (p:0.253), neoadjuvant chemotherapy (p:0.582), TNM stage (p:0.650), total dissected lymph nodes (p:0.582), operation technique (p:0.163), intraoperative blood loss >300 (p:0.582), and operation duration >300 min (p:0.176). Multivariate regression analysis, showed female sex (p: 0.05), body mass index (BMI) >30 (p:0.024) and tumor localization (p:0.005) are independent risk factors for anastomotic leakage. There was a significant difference in mean survival between patients with and without anastomotic leakage (13.9 vs 34.9 months, p: 0.006).
Conclusion: Anastomotic leakage was associated with female sex, obesity, and tumor location. We also found that anastomotic leakage adversely affects long-term survival. Detecting risk factors after gastrectomy guides us in the management of patients at the risk for anastomotic leakage.

Keywords: Gastrectomy; complication; anastomotic leak

INTRODUCTION

Gastric cancer is the fourth most common cancer worldwide and the second most common cause of cancer-related deaths worldwide after lung cancer (1). Looking at the statistics of Turkey in 2015, the incidence of gastric cancer in males was 14.2/100,000 while it was 6.3/100,000 in females; and it was 2nd in men and 4th in women according to the frequency of cancer-related deaths (2). Surgical resection is generally considered the first treatment option, although treatment strategies for gastric cancer depend on the oncological stage (3). Curative resection is still the most effective treatment for GC. Anastomotic leak is the most feared postoperative complication associated with gastrectomy. This complication does not only have immediate clinical outcomes and increased postoperative mortality. Some studies have reported that postoperative complications such as anastomotic leakage may lead to poor prognosis and reduced survival in patients with GC (4).

Although advances in surgical techniques, better anatomical knowledge, increased awareness of risk factors and treatment options have contributed greatly to reducing the incidence and mortality of anastomotic leakage, they are still seen at rates ranging from 2.1% to 14.6% (5). Esophagojejunal anastomosis leakage following total gastrectomy is always associated with a high postoperative mortality and its incidence can be up to 60% (4).

In this study, we aimed to define the rates of anastomotic leakage after total gastrectomy, and to discuss the preoperative and intraoperative risk factors in our clinic accompanied by the literature.

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Corresponding Author: Ugur Topal, Cukurova University, Faculty of Medicine, Department of General Surgery, Adana, Turkey
E-mail: sutopal2005@hotmail.com

MATERIAL and METHODS

Patients

The patients who were diagnosed as gastric adenocarcinoma as a result of histopathological examination of the endoscopic biopsy specimen and who underwent total gastrectomy between September 2015 and September 2018 in the general surgery clinic of Çukurova University Faculty of medicine were included in the study. Patients without malignancy, non-adenocarcinoma malignancy, and who did not undergo D2 dissection were excluded. A total of 34 patients were excluded A common database was created by examining patient files and hospital information system records. Using this database, patient information was evaluated retrospectively.

Study variables

Patient demographic characteristics were recorded with the following clinical, surgical and pathological characteristics: The patients with and without anastomosis leakage were compared in terms of demographic, clinicopathological and surgical factors. Compared factors were age, body mass index (BMI), American Society of Anesthesiologists (ASA) score, diabetes, presence of cardiovascular or pulmonary disease, preoperative blood tests, tumor location, neoadjuvant treatment, intraoperative blood loss, operation time, surgical approach (open, laparoscopic), histological grade, number of lymph nodes collected, number of metastatic lymph nodes, tumor diameter, TNM stage, and survival.

Definition of anastomotic leakage

Clinical signs of anastomotic leakage included abdominal pain, fever, pus or complicated discharge from the abdominal drain catheter, and peritonitis. Clinical suspicion of leakage was documented during reoperation or confirmed by a radiographic examination demonstrating contrast leakage from a viscus into a body cavity.

Surgical Technique

All patients were instructed and made to apply preoperative respiratory physiotherapy (triballs spirometry). In order to prevent thromboembolic complications, low molecular weight heparin (LMWH) was administered at 22:00 the night before surgery and varicose stockings were applied. Antibiotic prophylaxis of 1 g Cefazolin was induced before anesthesia induction and all operations were performed under general anesthesia. In the open technique, a midline or bilateral subcostal incision was preferred. All esophagojejunostomy anastomoses were performed with circular 26-29 mm diameter stapler. The jejenojejunal anastomosis was optionally performed as a linear incisor closure stapler or hand-sewn anastomosis. In laparoscopic technique, the patients were placed in supine position and arms were tied at the sides. The surgeon was on the right side of the patient and the resident was on the left side of the patient. 5 ports (5-12mm) were used. A pneumoperitoneum was created by entering under the umbilicus with a Veress needle and a 10 mm camera port was placed 3-4 cm laterally from the left supra-umbilical midline. 15 mm working port (for stapler) and right mid-clavicular 5 mm other working port from the right supra-umbilical region, and a second resident port on the left to the parallel of that was placed, with the other ports under direct vision. One more, preferably 5 mm, port for the liver retractor was entered from the right flank region. In both groups, D2 lymph node dissection for total gastrectomy as indicated in the Japanese gastric cancer guidelines, was performed. Omentectomy was performed in every patient, regardless of stage. The esophagojejunal anastomosis was performed using endoluminal stapler (OrVil ™, Covidien Japan, Tokyo, Japan) or laparoscopically with double-suture hand-sewn anastomosis. All openings in the bowel meso were closed with 3/0 non-absorbable sutures.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA). Descriptive statistical methods were used to evaluate the study data; mean, standard deviation, median, frequency, ratio, minimum, maximum. Pearson's Chi-square test was used for comparison of categorical variables, and logistic regression was used for multivariate evaluations. Kaplan-Meier analysis and Log Rank test were used for survival analysis. A p value of <0.05 was considered statistically significant

RESULTS

One hundred and two patients participated in our study. Patients were divided into two groups according to anastomotic leakage. Anastomotic leakage was detected in 10 patients. Leakage rate was 9.8% the leakage rate as 9.8%. Table 1 shows details of anastomotic leakage sites.

Table 1. Leakage site

Anastomotic leakage site	Number (%)
Esophagojejunostomy	6 (60)
Duodenal stump	4 (40)
Jejunojejunostomy	0 (0)
Total	10 (100.0)

There was no significant difference for anastomotic leakage in terms of being over 60 years of age (p:0.232), cardiovascular disease (p:0.494), diabetes mellitus (p:0.334), pulmonary disease (p:0.269), ASA score >3 (p:0.587), albumin level of 3.5 gr/dl (p:0.253), neoadjuvant chemotherapy (p:0.582), histological grade (p:0.798), TNM stage (p:0.650), number of total dissected lymph nodes (p:0.582) and metastatic lymph nodes (p:0.544), operation technique (p:0.163), intraoperative blood loss >300ml (p:0.582), operation duration >300 minutes (p:0.176) (Table 2).

Table 2. Demographic and clinical characteristics of patients

	Total (n: 102)	No leakage (n: 92)	Leakage (n: 10)	p
Age (year)				
<60	47 (46.1%)	44 (47.8%)	3 (30.0%)	0.232
≥60	55 (53.9%)	48 (52.2%)	7 (70.0%)	
Sex				
Male	67 (65.7%)	64 (69.6%)	3 (30.0%)	**0.018**
Female	35 (34.3%)	28 (30.4%)	7 (70.0%)	
Body mass index, (kg/m^2)				
<25	60 (60.0%)	56 (62.2%)	4 (40.0%)	**0.024**
≥25 and < 30	32 (32.0%)	29 (32.2%)	3 (30.0%)	
≥30	8 (8.0%)	5 (5.6%)	3 (30.0%)	
Cardiovascular disease				
No	76 (74.5%)	69 (75.0%)	7 (70.0%)	0.494
Yes	26 (25.5%)	23 (25.0%)	3 (30.0%)	
Diabetes mellitus				
No	90 (88.2%)	82 (89.1%)	8 (80.0%)	0.334
Yes	12 (11.8%)	10 (10.9%)	2 (20.0%)	
Pulmonary disease				
No	99 (97.1%)	90 (97.8%)	9 (90.0%)	0.269
Yes	3 (2.9%)	2 (2.2%)	1 (10.0%)	
ASA score				
<3	88 (86.3%)	79 (85.9%)	9 (90.0%)	0.587
≥3	14 (13.7%)	13 (14.1%)	1 (10.0%)	
Hemoglobin				
<10	32 (31.4%)	32 (34.8%)	0 (0.0%)	**0.019**
≥10	70 (68.6%)	60 (65.2%)	10 (100.0%)	

Hypoalbuminemia				
<3.5	56 (54.9%)	52 (56.5%)	4 (40.0%)	**0.253**
≥3.5	46 (45.1%)	40 (43.5%)	6 (60.0%)	
Neoadjuvant				
Yes	73 (71.6%)	66 (71.7%)	7 (70.0%)	0.582
No	29 (28.4%)	26 (28.3%)	3 (30.0%)	
Tumor location				
Antrum	37 ( )	34 (37.0%)	3 (30.0%)	**0.042**
Cardia	11 ( )	9 (9.8%)	2 (20.0%)	
Corpus	32 ( )	31 (33.7%)	1 (10.0%)	
Small curvature	13 ( )	12 (13.0%)	1 (10.0%)	
Linitis plastica	7 ( )	4 (4.3%)	3 (30.0%)	
EGJ	2 ( )	2 (2.2%)	0 (0.0%)	
Histological grade				
Poorly differentiated	42 (41.2%)	38 (41.3%)	4 (40.0%)	0.798
Undifferentiated	16 (15.7%)	14 (15.2%)	2 (20.0%)	
Well differentiated	23 (22.5%)	20 (21.7%)	3 (30.0%)	
Moderately differentiated	21 (20.6%)	20 (21.7%)	1 (10.0%)	
Total number of lymph nodes	31.15±14.08 (3-63)	30.90±13.68 (3-63)	33.50±18.08 (9-62)	0.582
Number of metastatic lymph nodes	7.77±10.48 (0-47)	7.56±10.11 (0-38)	9.70±13.92 (0-47)	0.544
TNM stage				
1A	14 (13.7%)	11 (12.0%)	3 (30.0%)	0.650
1B	6 (5.9%)	6 (6.5%)	0 (0.0%)	
2A	5 (4.9%)	5 (5.4%)	0 (0.0%)	
2B	24 (23.5%)	21 (22.8%)	3 (30.0%)	
3A	11 (10.9%)	10 (10.9%)	1 (10.0%)	
3B	8 (7.8%)	7 (7.6%)	1 (10.0%)	
3C	34 (33.3%)	32 (34.8%)	2 (20.0%)	
Surgical Technique				
Open	87 (85.3%)	80 (87.0%)	7 (70.0%)	0.163
Laparoscopic	15 (14.7%)	12 (13.0%)	3 (30.0%)	
Blood loss (ml)				
≤300	29 (28.4%)	26 (28.3%)	3 (30.0%)	0.582
>300	73 (71.6%)	66 (71.7%)	7 (70.0%)	
Duration of operation (min)				
≤300	94 (92.2%)	86 (93.5%)	8 (80.0%)	0.176
>300	8 (7.8%)	6 (6.5%)	2 (20.0%)	

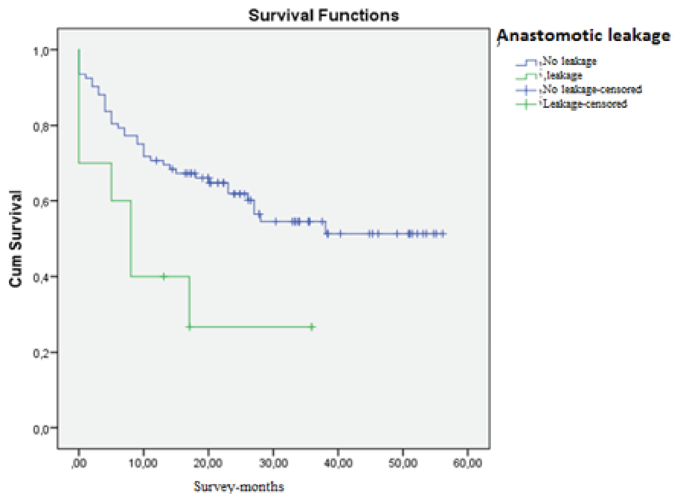

Figure 1. Kaplan-Meier curve presenting the overall survival rate

Multiple regression analysis revealed that sex (p=0.045), BMI >30 (p:0.024), tumor location (p:0.006) were independent risk factors for the occurrence of anastomotic leakage. Table 3 lists the odds ratios, 95% confidence intervals, and P-values for the variables that achieved statistical significance after being entered into the multivariate logistic regression model.

The presence of anastomotic leak significantly shortened the mean survival time (13.93 vs 34.92 months, p:0.016). It is shown in Table 4 and Figure1.

Table 4. Overall survival rate

Anastomotic leakage	Average (Mean+sd (Min-Max))	p
(-)	34.92+2.55 (29.90-39.93)	**0.016**
(+)	13.93+4.62 (4.87-22.99)	

Table 3. Multivariate analysis to identify clinicopathological and operative variables that are associated with leakage

Measurements		Univariate	Multivariate	
		P	HR (95% - CI)	p
Age group	<60	0.347	1.000	0.363
	≥ 60		1.888 (0.480 – 7.425)	
Sex	Male	**0.045**	1.000	0.057
	Female		3.731 (0.960-14.507)	
BMI	<25	0.115	1.000	0.069
	≥ 25 and < 30		1.443 (0.323-6.450)	0.631
	≥30		5.799 (1.261-26.680)	**0.024**
ASA Score	<3	0.899	1.000	0.901
	≥3		0.876 (0.111 – 6.945)	
Tumor localization	Antrum	0.088	1.000	0.050
	Cardia		2.739 (0.446-16.819)	0.276
	Corpus		0.513 (0.052-5.047)	0.567
	Small curvature		0.983 (0.102-9.450)	0.988
	Linitis plastica		10.3888 (1.939-55.648)	**0.006**
	EGJ		0.000 (0.000-0.000)	0.988
TNM stage	1A	0.698	1.000	0.988
	1B		0.000 (0.000-0.000)	0.992
	2A		0.000 (0.000-0.000)	0.992
	2B		0.621 (0.125-3.085)	0.561
	3A		0.492 (0.051-4.743)	0.539
	3B		0.716 (0.074-6.911)	0.772
	3C		0.439 (0.072-2.668)	0.371
Operation type	Conventional	0.208	1.000	0.177
	Laparoscopic		2.564 (0.653 - 10.067)	
Operation duration	≤300 min	0.190	1.000	0.141
	>300 min		3.283 (0.675 - 15.957)	
Blood loss	≤300 ml	0.961	1.000	0.961
	>300 ml		0.966 (0.249 – 3.751)	

DISCUSSION

Anastomotic leakage is a terrifying experience that not only threatens the patient's life, but also the surgeons make a great effort to manage the treatment. It is one of the most common complications after gastrectomy for gastric cancer (6).

Although significant improvements have been made in surgical instruments and postoperative management, anastomotic leaks continue to develop after gastrectomy. When anastomotic leakage develops, the quality of life of the patient decreases, the length of hospital stay increases and the cost of surgery are increased. Therefore, it is important to determine risk factors before surgery, and manage factors that can be controlled (7).

Risk factors previously reported for total gastrectomy include patient and tumor characteristics and intraoperative factors (3). Adequate blood supply and adequate tension in the anastomosis area are important for adequate recovery (8). Long operation time, increased intraoperative bleeding amount, anastomosis procedures, and surgeon inexperience (<30 cases annually) have all been reported as intraoperative risk factors (9-11). Tu et al. developed a nomogram to estimate the risk of individual anastomosis leakage in a retrospective cohort. Patient age ≥ 65 years, anemia (hemoglobin ≤ 8.0 g / dL) and malnutrition were independently associated with leakage risk (6). In a large, retrospective, cohort study using a Japanese web-based nationwide registry age, sex, ascites, hypertension, previous percutaneous coronary intervention, steroid administration, weight loss, poor ASA score, splenectomy, Brinkman index, body mass index, high aspartate aminotransferase and high white blood cell count were defined as risk factors for anastomotic leakage following total gastrectomy (12).

Kim SH et al. found that male sex was a risk factor for anastomotic leakage. In their study, men were 4.2 times more likely to develop anastomotic leakage than women (P = 0.001) (13). Similarly, M. C. Kim et al. found that men are more likely to have anastomotic leakage (14). However, some studies on anastomotic leakage after gastrectomy did not reveal a relationship between sex and anastomotic leakage (6,15). In our series, in contrast to the literature, the rate of anastomotic leakage was higher in the female sex, and being female increased the risk of anastomotic leakage by 3.7 times.

Obesity increases the risk of postoperative complications. Body mass index (BMI) is a standard criterion for obesity, but visceral fat area (VFA) may be more effective in predicting esophagogastric anastomotic leakage. The presence of a thick mesentery in patients with high VFA tends to produce excessive tension and pressure in the anastomosis site, which may cause anastomotic leakage (5,16,17). Malnutrition and anemia as well as obesity play a role in the development of anastomotic leaks (6). In our series, the risk of anastomotic leakage increased especially with a body mass index above 30.

Tumor localization may increase the risk of anastomotic leakage due to surgical technique. Especially esophagocardial junction tumors may have more anastomotic leakage (13). In our series, anastomotic leakage was more frequent in patients with linitis plastica. We attributed this increase to technical difficulty.

Although few studies in the literature have analyzed the effect of anastomotic leakage in patients with esophagogastric cancer, the results are difficult to interpret, as they usually contain both esophageal and gastric tumors with various types of resection. The results are generally contradictory, indicating that early morbidity has no effect on long-term or worse survival rates (18-20). In the series of M. Sierzega et al., overall median survival of patients with leakage was significantly lower than that for patients with uneventful healing of the anastomosis (4•1 (0•3 to 7•9) versus 23 (20•1 to 25•8) months; p < 0•001) (21). In our series, the mean survival was lower in the group with anastomotic leakage (13.93 vs 34 months, p: 0.016). We cannot justify this decrease in survival to anastomotic leakage alone; there were other factors that could affect survival in the groups, so it is difficult to interpret this result.

The most important limitation of our study was its retrospective nature and being a single center study. However, we believe that it contributes to the literature for this clinical entity, whose risk factors have been debated.

CONCLUSION

In conclusion, determination of risk factors for anastomotic leakage may be helpful in changing surgical techniques and preoperative management. Although the mechanism by which anastomotic leakage occurs is not fully understood, understanding the clinicopathological and operative factors that may increase the development of this complication is important for the prevention of this complication.

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Orçun Yalac ORCID: 0000-0001-9239-4163
Ugur Topal ORCID: 0000-0003-1305-2056

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