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Original Article

Predictive factors associated mortality after gastrectomy

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Abstract

Aim: In this study, we aimed to identify the risk factors associated with postoperative mortality after gastrectomy.Surgical resection is the only potentially curative method for gastric cancer and is associated with severe morbidity and mortality.

Material and Methods: Patients who underwent gastrectomy for gastric cancer in a single center between September 2015 and September 2018 were evaluated retrospectively. The relationship between postoperative mortality and clinical variables of the patients, tumor characteristics and 10 variables related to intraoperative characteristics were analyzed.

Results: 133 patients were included in our study. Postoperative mortality occurred in 10 patients. Our postoperative mortality rate was 7.5%. Male sex (HR = 0.664, 95% CI =0.460–0.961, p=0.030), tumor localization (linitis plastica (HR = 3.594, 95% CI =1.375–9.390, p=0.009), tumor stage 3C (HR =1.713, 95% CI =0.906–3.239, p=0.0032) total gastrectomy (HR = 1.918 95% CI =1.042–3.532, p=0.036), conventional (open) surgery (HR = 2.807 95% CI =1.546–5.096, p= 0.001), operation duration >240 min (HR = 1.758, 95 % CI =1.064–2.906, p= 0.028), was independently associated with an increased risk of postoperative mortality. Age >60 (p=0.463), body mass index (p=0.414), ASA score >3 p=0.862, intraoperative blood loss >300 (p=0.083) and additional organ resection (p=0.649) were not independent risk factors for mortality.

Conclusion: Anastomotic leakage was associated with male sex, obesity, and tumor localization. Anastomotic leakage is related with poor survival. Determining the risk factors after gastrectomy guides us in the management of patients at risk for postoperative mortality.

Keywords: Gastrectomy; complication; postoperaritive mortality

INTRODUCTION

Gastric cancer ranks 5th among the most prevalent cancers worldwide and it are the 4th leading cause of cancer-related mortality (1). According to the 2015 statistics from Turkey, the incidence of gastric cancer is 14.2/100000 in males and 6.3/100000 in females; it is the 2nd and 4th leading cause of cancer-related death in males and in females, respectively (2).

Radical gastric resection remains as the most important step in the treatment of gastric cancers among multi-disciplinary therapeutic methods. Nevertheless, radical resections are associated with high morbidity and mortality rates. Although gastric surgery-related morbidity and mortality rates have decreased recently along with the use of minimal invasive techniques in gastric cancer surgery and with better perioperative care, overall morbidity and mortality rates remain high as 18-46% and 0.8-15%, respectively (3-6). Morbidity studies due to cancer-related gastric resections have focused on many factors such as age, albumin level, American Society of Anesthesiologists (ASA) score, type of gastric resection, additional organ resection and blood transfusion, but specific factors associated with postoperative mortality remained unclear (7-9).

In the present study, we aimed to determine the postoperative mortality rate in our clinic in the patients that underwent gastrectomy procedure for gastric cancer, as well as to identify related perioperative risk factors.

MATERIAL and METHODS

Patients that underwent gastric resection for gastric cancer between September 2015 and September 2018 in Cukurova University Faculty of Medicine (C.U.T.F), Department of General Surgery were enrolled into the study. Only the patients with primary gastric malignancy

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were included; other gastric surgery patients and palliative surgeries were excluded. After reviewing the patients' medical files and the hospital data system recordings, a common database was established. Patients' information in this database was retrospectively evaluated.

The patients eligible for the study were divided into two groups; without postoperative mortality (Group 1) and with postoperative mortality (Group 2). The groups were compared in terms of age (divided into <65 or >65 years), body mass index (BMI) (divided into <25, >25 <30 and >30), preoperative albumin level gr/dl (divided into <3.5,>3,5), preoperative hemoglobin concentration (gr/dl) (divided into <10 or >10), ASA score, comorbid conditions (diabetes, cardiovascular or pulmonary disease), tumor localization, neoadjuvant chemotherapy, intra-operative blood loss, duration of surgery, surgical method, type of gastric resection, histological type, number of dissected lymph nodes, number of metastatic lymph nodes, tumor diameter, TNM stage, and additional organ resection. Tumor staging for only adenocarcinoma patients was performed using tumor-node-metastasis (TNM) 2016 system. Postoperative mortality was defined as death occurring within 30 days after resection either during hospital stay or after hospital discharge.

Surgical Technique

All of the patients were trained about respiratory physiotherapy (tri balls incentive spirometer) and were made to practice prior to the surgical procedure. In order to prevent thrombo-embolic complications, low-molecular-weight heparin (LMWH) was administered one night before the surgery and compression stockings were put on in the morning of surgery. Antibiotic prophylaxis was provided using 1 gr Cefazolin before the induction of anesthesia. All of the surgical procedures were performed under general anesthesia.

Midline or bilateral subcostal incision was preferred in the conventional technique. Total omentectomy was included in all patients. The linear stapler was used for gastroenterostomy in patients who went to distal gastrectomy. The common enterotomy is closed in a single-layer fashion using a running suture. Side-to-side jejunojejunostomy is then performed at approximately 40 cm from the gastrojejunostomy with a hand-sewn technique or stapled anastomosis. A circular stapler 26 mm in diameter was preferred for esophagojejunostomy anastomosis for reconstruction after total gastrectomy.

In the laparoscopic technique, the patient was placed in supine position with the arms tied close to the body. The surgeon stood on the right side of the patient, while the assistant was on the left. Five ports were used. All of the transsections or resections were performed intracorporeally using endo-linear stapler technology. Omentectomy was performed in all patients either at the beginning or at the end of surgery. Esophagojejunal anastomosis was performed using endo-luminal stapler (OrVil™, Covidien Japan, Tokyo, Japan) or by laparoscopic hand-sewn technique with double-layer suturing. Any patency occurring in the intestinal meso was closed with 3/0 absorbable suture.

Lymph node dissection was conducted according to Japanese gastric cancer guidelines.

Statistical analysis

IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA) package program was used for the statistical analysis of data. Descriptive statistics of the study data were given as mean, standard deviation, median, frequency, ratio, minimum, and maximum. Comparison of categorical variables was done using Pearson's Chi-square test, whereas logistic regression was used for multi-variance evaluation. A p value <0.05 was considered statistically significant.

RESULTS

A total of 133 patients were enrolled into the study. Post-operative mortality occurred in 10 patients and mortality reasons were septic shock (due to anastomotic leakage) in 2 patients, pulmonary complications in 5 patients, cardiac complications in 2 patients and acute renal failure in 1 patient (Group 2). Postoperative mortality rate was 7.5%.

Thirty-five percent of the patients in Group 1 and 50% of the patients in Group 2 were >65 years old (p: 0.28). There was male predominance in the group with mortality, but no statistically significant difference was determined between the groups in terms of gender (p: 0.172). Body mass index was comparable between the groups (p: 0.86). The groups were similar in terms of the patients' comorbidity status (Cardiovascular disease p: 0.086; Diabetes mellitus p: 0.136; Pulmonary disease p: 0.380). ASA scores were similar between the groups, but 70% of the patients in Group 2 had an ASA score of >3 (p: 0194). No statistically significant difference was determined between the groups in terms of hemoglobin and albumin concentrations (p: 0.143 and p: 0.224, respectively). The number of patients receiving neoadjuvant chemotherapy was not different between the groups (p: 0.495).

No difference was determined between the groups in terms of tumor localization (p: 0.171). The most common tumor localization was the antrum in Group 1 (31.6%), and the corpus in Group 2 (40%). Adenocarcinoma was the most prevalent histological type in both groups (82.7% vs 90% p: 0.955). The number of dissected lymph nodes was significantly lower in the group with mortality (p: 0.021). The number of metastatic lymph nodes and tumor stage were comparable between the groups (p: 0.217 and p: 0.429, respectively). The most frequently encountered tumor stage was 3C according to the TNM classification.

The groups were similar in terms of surgical technique (open or laparoscopic), type of resection (subtotal or total gastrectomy), intraoperative blood loss, and additional organ resection. Demographic characteristics of the patients in each group are summarized in Table 1.

Table 1. Demographic and clinical characteristics of patients with postoperative mortality

	Total (n: 133)	Mortality (-) (n: 123)	Mortality (+) (n: 10)	p
Age (year)				
<65	84 (63.2)	79 (64.2)	5 (50.0)	0.284
≥65	49 (36.8)	44 (35.8)	5 (50.0)	
Sex				
Male	81 (60.9)	73 (59.3)	8 (80.0)	0.172
Female	52 (39.1)	50 (40.7)	2 (20.0)	
Body mass index, (kg/m^2)				
<25	77 (59.2)	72 (60.0)	5 (50.0)	
≥25 and< 30	42 (32.3)	37 (30.8)	5 (50.0)	0.346
>30	11 (8.5)	11 (9.2)	0 (0.0)	
Cardiovascular disease				
Yes	35 (26.3)	30 (24.4)	5 (50.0)	0.086
No	98 (73.7)	93 (75.6)	5 (50.0)	
Diabetes				
Yes	18 (13.5)	15 (12.2)	3 (30.0)	0.136
No	115 (86.5)	108 (87.8)	7 (70.0)	
Pulmonary disease				
Yes	6 (4.5)	5 (4.1)	1 (10.0)	0.380
No	127 (95.5)	118 (95.9)	9 (90.0)	
ASA score				
<3	21 (15.8)	18 (14.6)	3 (30.0)	0.194
≥3	112 (84.2)	105 (85.4)	7 (70.0)	
Hemoglobin gr/dl				
<10	40 (30.1)	35 (28.5)	5 (50.0)	0.143
≥10	93 (69.9)	88 (71.5)	5 (50.0)	
Hypoalbuminemia gr/dl				
<3.5	58 (43.6)	52 (42.3)	6 (60.0)	0.224
≥3.5	75 (56.4)	71 (57.7)	4 (40.0)	
Neoadjuvant CT				
Yes	99 (74.4)	92 (74.8)	7 (70.0)	0.495
No	34 (25.6)	31 (25.2)	3 (30.0)	
Tumor location				
Antrum	42 (31.6)	40 (32.5)	2 (20.0)	
Bulb	2 (1,5)	2 (1,6)	0 (0,0)	
Greater Curvature	2 (1.5)	1 (0.8)	1 (10.0)	0.171
Fundus	3 (2.3)	3 (2.4)	0 (0.0)	
Cardia	13 (9.8)	12 (9.8)	1 (10.0)	
Corpus	40 (30.1)	36 (29.3)	4 (40.0)	

Lesser Curvature	15 (11.3)	15 (12.2)	0 (0.0)	0.171
Linitis plastica	7 (5.3)	5 (4.1)	2 (20.0)	
Multifocal	2 (1.5)	2 (1.6)	0 (0.0)	
EGJ	7 (5.3)	7 (5.7)	0 (0.0)	
Histological type				
Adenocarcinoma	110 (82.7)	101 (82.1)	9 (90.0)	0.955
Lymphoma	1 (0.8)	1 (0.8)	0 (0.0)	
Malignant melanoma	1 (0.8)	1 (0.8)	0 (0.0)	
Neuroendocrine	11 (8.3)	10 (8.1)	1 (10.0)	
Scc	2 (1.5)	2 (1.6)	0 (0.0)	
Stromal tumor	8 (6.0)	8 (6.5)	0 (0.0)	
Total number of dissected lymph nodes	27.15±15.04 (0-63)	28.00±14.91 (0-63)	16.60±13.01 (4-51)	**0.021**
Number of metastatic lymph nodes	6.54±9.69 (0-47)	6.25±9.54 (0-47)	10.2±11.23 (0-37)	0.217
TNM stage				
1A	14 (12.7)	14 (13.9)	0 (0.0)	0.429
1B	7 (6.4)	7 (6.9)	0 (0.0)	
2A	7 (6.4)	6 (5.9)	1 (11.1)	
2B	26 (23.6)	23 (22.8)	3 (33.3)	
3A	12 (10.9)	12 (11.9)	0 (0.0)	
3B	8 (7.3)	8 (7.9)	0 (0.0)	
3C	36 (32.7)	31 (30.7)	5 (55.6)	
Surgical technique				
Open	118 (88.7)	109 (88.6)	9 (90.0)	0.686
Laparoscopic	15 (11.3)	14 (11.4)	1 (10.0)	
Type of gastrectomy				
Subtotal	13 (9.8)	13 (10.6)	0 (0.0)	0.344
Total	120 (90.2)	110 (89.4)	10 (100.0)	
Blood loss (ml)				
≤250	47 (35.3)	46 (37.4)	1 (10.0)	0.075
>250	86 (64.7)	77 (62.6)	9 (90.0)	
Duration of surgery (min)				
≤240	113 (85.0)	104 (84.6)	1 (10.0)	0.538
>240	20 (15.0)	19 (15.4)	9 (90.0)	
Additional organ				
Yes	22 (16.5)	19 (15.4)	3 (30.0)	0.216
No	111 (83.5)	104 (84.6)	7 (70.0)	

ASA- American Society of Anesthesiologists score, CT –Chemotherapy, EGJ Esophagogastric junction
Scc- squamous cell carcinoma , TNM- tumor node metastasis

Table 2. Multivariate analysis for clinicopathological and operative variables that are associated with postoperative mortality

Measurements		Univariate	Multivariate	
		P	HR (95% - CI)	p
Age group	<60	0.465	1.000	0.463
	≥60		1.150 (0.792-1.669)	
	Male	**0.028**	1.000	**0.030**
	female		0.664 (0.460-0.961)	
	<25		1.000	0.377
	≥25 and< 30	0.414	1.069 (0.714-1.599)	0.747
	≥30		1.586 (0.831-3.028)	0.162
ASA score	<3	0.863	1.000	0.862
	≥3		1.046 (0.632-1.729)	
Blood loss	≤300	0.079	1.000	0.083
	>300		1.395 (0.957-2.032)	
Tumor localization	Antrum	0.338	1.000	0.281
	Bulb		0.438 (0.104-1.842)	0.260
	Greater curvature		0.563 (0.077-4.117)	0.571
	Fundus		1.046 (0.322-3.400)	0.940
	Cardia		1.232 (0.642-2.363)	0.530
	Corpus		1.359 (0.858-2.151)	0.191
	Lesser curvature		0.947 (0.521-1.723)	0.859
	Diffuse (Linitis plastica)		3.594 (1.375-9.390)	**0.009**
	Multifocal		0.789 (0.190-3.280)	0.744
	EGJ		1.378 (0.613-3.096)	0.438
TNM stage	1A	**0.032**	1.000	**0.031**
	1B		1.100 (0.447-2.758)	0.822
	2A		0.490 (0.186-1.286)	0.147
	2B		0.719 (0.362-1.428)	0.346
	3A		0.975 (0.448-2.122)	0.949
	3B		0.769 (0.299-1.980)	0.587
	3C		1.713 (0.906-3.239)	0.097
Type of surgery	Laparoscopic	**0.002**	1.000	**0.001**
	Conventional		2.807 (1.546-5.096)	
Duration of surgery	≤240min	**0.038**	1.000	**0.028**
	>240min		1.758 (1.064-2.906)	
Type of gastrectomy	Subtotal	**0.023**	1.000	**0.036**
	Total		1.918 (1.042-3.532)	

ASA- American Society of Anesthesiologists score, CT –Chemotherapy , EGJ Esophagogastric junction
Scc- squamous cell carcinoma , TNM- tumor node metastasis

In the multivariate regression analysis, male gender (p: 0.028), advanced tumor stage [HR 1.713 (95% - CI 0.906-3.239, p: 0.032)], open surgery [HR 2.807 (95% CI 1.546-5.096, p: 0.001)], surgery duration >240 min [HR 1.758 (95% CI 1.064-2.906 p: 0.028)] and total gastric resection [HR 1.918 (95% - CI 1.042-3.532, p:0.036)] were found to be the independent risk factors for developing mortality.

Table 2 lists the odds ratio, 95% confidence interval and P-value for the variables that achieved statistical significance after including into the multivariate logistic regression model.

DISCUSSION

Today, gastric cancer is one of the cancers that require multidisciplinary treatment and that are difficult to manage. Lymphatic dissection together with gastrectomy remains to be the critical step in this multidisciplinary management. Nevertheless, gastric cancer surgery is a complex procedure with high morbidity and mortality rates. In two multicenter large studies performed recently, gastrectomy-related mortality rates were reported to be 4.2% and 4.7%, respectively (7,10). Identifying high-risk patients for postoperative mortality has particular importance in terms of taking perioperative measures. In the present study, postoperative mortality rate was 7.5%.

Many studies have been designed for morbidity and mortality rates after gastric cancer surgery, and some patient-related or surgery-related factors such as age, performance score, weight loss, ASA score, medical comorbidity, hypoalbuminemia, anemia, metastatic disease, multi-visceral organ resection, surgeon, and low-volume hospital have been defined as the independent risk factors for morbidity and mortality after gastric cancer surgery (7,10-15). Nevertheless, identification of local morbidity and mortality rates and related factors by the physicians and institutions dealing with cancer surgery and taking necessary measures would make positive contribution to the patients' quality of life and survival.

Focusing on the postoperative mortality studies, where the advance age has been stated as the risk factor for many cancer surgeries, heterogeneous distribution of the age groups attracts attention (7,15,16). In the present study, the patients were grouped according to the age limit of 65 years, but we determined no relationship between age and postoperative mortality. Although, in the same studies, the gender was not found as a risk factor associated with postoperative mortality, the present study determined male gender as an independent risk factor.

In a multicenter cohort study evaluating 955 esophageal and gastric cancer surgeries, comorbid conditions of the patients were investigated, and it was emphasized that patients with comorbidity are associated with higher morbidity and mortality rates (17). Although the literature comprises similar outcomes, the present study failed to show a relationship between comorbidity and postoperative mortality.

Tumor localization is one of the most important factors in determining the extent of gastric resection. In a case with advanced-stage gastric cancer involving proximal aspect of the stomach or located in the lesser curvature-corpus junction of the stomach, total gastrectomy should be the procedure to be preferred as it meets the oncological principles. However, complications are more prevalent in the patients undergoing total gastrectomy vs. subtotal gastrectomy with anastomosis leakage being the leading (18). In a study, 2580 gastric cancer patients (999 with total gastrectomy; 1581 with subtotal gastrectomy) were evaluated in terms of postoperative morbidity and mortality following radical curative gastric resection. Mortality rates were statistically significantly higher in the total gastrectomy group (p: 0.015) (8). In the present study as well, multivariate analysis revealed higher postoperative mortality rates in the patients with tumors located in the cardia in particular and with diffuse involvement (linitis plastica). Total gastrectomy was preferred more frequently increasing the postoperative mortality rate by 1.9 fold.

Disease stage is the other factor associated with postoperative mortality following gastric cancer surgery. Postoperative mortality rate is higher in the cases with advanced-stage gastric cancer (18). Stratilatovas E. et al. evaluated 10-year outcomes of 1676 patients that underwent total and subtotal gastrectomy procedures; they determined tumor stage (OR 1.97, 95 % CI 1.39-2.77, $p < 0.05$) as an independent factor increasing the mortality rate (19). In the present study, we determined similar results with the literature in terms of the relationship between tumor stage and the risk of developing postoperative mortality. The risk of postoperative mortality was found to be increased by 1.7 fold particularly in stage-3C patients.

In the recent years minimal invasive surgery has begun to be implemented in many fields because of the advantages it has brought along. In gastric surgery, however, the situation is a little bit different. Although minimal invasive surgery takes place in the guidelines for early-stage gastric cancer cases, it remains unclear for advanced-stage gastric cancer patients. Nevertheless, positive outcomes from experienced centers reporting preliminary results on this topic encourage the surgeons to perform laparoscopic surgery more frequently (20). Among our patients that developed mortality, only one was in the laparoscopic surgery group. Mortality rate was higher in the conventional surgery group.

In gastric cancer surgery, performing en block resection would be a more appropriate oncological approach if tumor is extending out of the serosa and invading the visceral organs. Nevertheless, visceral organ resections due to iatrogenic injuries or to any other reason increase the morbidity and mortality rates.

In the Dutch trial, total pancreaticosplenectomy procedure has been implemented as a standard procedure during gastrectomy (21). The updated Japanese Rules of Gastric Resection 2011 defends pancreas- and spleen-preserving

techniques during D2 lymphadenectomy (22).

In the present series, there were 22 patients that underwent additional organ resection due to tumor invasion; only 3 of these patients developed mortality, and additional organ resection was not found as a mortality-enhancing factor.

Exposure to anesthesia due to prolonged surgery duration is a significant risk factor for postoperative morbidity and mortality; however, none of the earlier studies has reported clear information about optimum surgery duration. Kodera Y. et al. and Martin A. et al demonstrated that surgery duration of >297min and >200 min, respectively is associated with postoperative mortality (23,9). In the present study, surgery duration of > 240 min was found to be an independent risk factor for postoperative mortality.

As was mentioned above, most of the studies evaluating morbidity and mortality following gastric cancer surgery have specified the influencing factors as patient-related and surgery-related such as age, gender, number of comorbid conditions, diet, number of dissected lymph nodes, extent of gastric resection, type of reconstruction, surgery duration, estimated blood loss, presence of combined resection, and volume of the hospital and the surgeon (24,25). Whereas some of these factors are unchangeable, some can be changed and postoperative morbidity and mortality can be minimized. One of the most important limitations of the present study is the retrospective study design resulting in the surgical procedures' having not been performed by the same surgical team. The second is the low patient volume due to the present study's being a single-center study. Nevertheless, we think that the present study would be a loadstar to determine the morbidity and mortality rates in our institution and to identify related factors and accordingly to take necessary measures.

CONCLUSION

In conclusion, understanding the risk factors for potential morbidity and mortality following gastric cancer surgery, determining the changeable ones among these factors, and taking necessary measures are important for the prevention of postoperative mortality.

Competing interests: The authors declare that they have no competing interest.

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