



## Original Research

# Analysis of the Factors Affecting Survival in the Patients who Underwent Curative-Intent Gastrectomy due to Gastric Adenocarcinoma

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### Abstract

**Objectives:** Gastric cancer is the fifth most common cancer and the third most common cause of cancer-related deaths in the world. In this study, we aimed to evaluate the impact of clinicopathological factors on overall survival in the patients who underwent curative-intent gastrectomy due to gastric adenocarcinoma.

**Methods:** The medical records of 644 patients who underwent gastrectomy between January 2007 and January 2017 in our clinic were retrospectively reviewed. Among these patients, 359 patients were included in this study. The impact of several prognostic factors on survival was investigated.

**Results:** The mean age was 59.2±11.6 (29-83). Male/female ratio was 2.12. The median follow-up time was 19 months (CI=10.1-31.1). Median overall survival was 23±2.3 months (CI=18.3-27.6). Splenectomy, R1 (microscopically incomplete) resection, and advanced stage were independent risk factors for poor prognosis.

**Conclusion:** R1 resection, splenectomy, and advanced TNM stage were associated with poor prognosis in gastric cancer. Splenectomy should be avoided in the absence of direct invasion of the tumour or metastasis of lymph nodes on splenic hilum to prevent postoperative infectious complication-related mortality.

**Keywords:** Curative-intent gastrectomy; gastric adenocarcinoma; overall survival; prognostic factor; splenectomy.

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Although the incidence has decreased over the last 30 years, gastric cancer (GC) is still the fifth most common cancer and the third most common cause of cancer-related deaths in the world.<sup>[1]</sup> Five-year overall survival (OS) rate is approximately 90-100% in the cases diagnosed at an early stage, whereas this rate decreases to 15-25% at an advanced stage. Japan and East Asia (18-25/100.000)

have a higher incidence of GC compared to Europe and North America (8-10/100.000).<sup>[2]</sup> In the United States (US), the incidence is gradually decreasing, and it is considered as 15<sup>th</sup> most common cancer. It was estimated that 27.600 patients would be diagnosed with GC in the US in 2020. Five-year OS rate was estimated to be around 32%, so it was predicted that 11.010 US citizens would die due to

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GC in 2020.<sup>[3]</sup> In Turkey, it is the fifth most common cancer with an incidence of 14.3 per 100.000 among all cancers in men, while it is the sixth most common with an incidence of 6.5 per 100,000 in women.<sup>[4]</sup> In 2015, the mortality rate of the GC in Turkey was 5.5 per 100.000 in men and 2.9 per 100.000 in women.<sup>[5]</sup>

The curative treatment of the GC can be achieved by surgery. However, the extent of the lymph node dissection, the extent of gastric resection and resection of the adjacent organs, and their effects on complications and OS are still controversial.<sup>[6]</sup>

Factors affecting the prognosis of GC were investigated in the literature and the effects of different prognostic factors on OS were reported. In this study, we aimed to evaluate the effects of clinicopathological factors on OS in the patients who underwent curative-intent gastrectomy due to gastric adenocarcinoma.

## Methods

The files of a consecutive series of 644 patients who underwent gastrectomy between January 2007 and January 2017 were analyzed retrospectively. Eligibility criteria included histologically confirmed primary gastric adenocarcinoma and absence of distant metastasis. The exclusion criteria were as follows: 1) emergent surgery; 2) palliative surgery; 3) perioperative mortality; 4) incomplete patient records or follow-up.

Among these patients, 359 (55.7%) patients enrolled in this study. Preoperative gastroscopy and contrast-enhanced thoracoabdominal computed tomography (CT) were performed for all patients in this study. After the positron emission tomography-CT (PET-CT) unit was founded in our institute in December 2014, patients were evaluated with preoperative PET-CT (CTI, Knoxville, TN, USA) to decide the requirement of neoadjuvant chemotherapy. Locally advanced tumours (clinically  $\geq$ Stage IIA) were decided according to CT and/or PET-CT reports, and those patients were referred to the medical oncology department for neoadjuvant chemotherapy. Patients who accepted receiving chemotherapy underwent surgery after completion of neoadjuvant therapy. Patients who denied or left neoadjuvant therapy underwent surgical intervention directly. All patients underwent open surgery. The standard surgical procedure was gastrectomy, including lymph node dissection. The surgical procedure was selected according to the location and diameter of the tumour. To obtain negative surgical margins, resection of adjacent organs was added to the main procedure, if necessary. Cases that underwent histopathologically confirmed R0 (no cancer cells microscopically at the tumour site) or R1 (microscopically residual cancer cells at the resection margin) were ac-

cepted as a curative-intent gastrectomy.

All patients had follow-up at 6-month intervals after surgery until death or November 2017. The survival status of the patients was determined based on the data of the General Directorate of Population and Citizenship Affairs in November 2017.

OS of the patients was investigated according to prognostic parameters, including age, gender, blood group, presence of chronic diseases (Diabetes Mellitus/Hypertension/Chronic Obstructive Pulmonary Disease (COPD)/Congestive Heart Failure (CHF)/Coronary Artery Disease (CAD), smoking, asymptomatic hepatitis B carriage, preoperative hemoglobin value, type of gastrectomy, splenectomy status, resection margins, tumour location, tumour diameter, lymphovascular invasion, perineural invasion, Lauren classification (Mixt type was included in diffuse type),<sup>[7]</sup> differentiation degree, depth of tumour invasion (T stage), number of metastatic lymph nodes (N stage), Tumour/Node/Metastasis stage (TNM stage) and neoadjuvant chemotherapy. The stage was determined according to the 7<sup>th</sup> TNM staging system of the American Joint Committee on Cancer (AJCC)/Union of International Cancer Control (UICC).<sup>[8]</sup>

Written informed consent was obtained from the patient/relatives of patients whom participated in this study. Ethics committee approval was received for this study from the Ethics Committee of Izmir Kâtip Celebi University (Date 01.11.2017, decision number 249).

## Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Sciences version 20.0 (IBM Corp.; Armonk, NY, USA). The mean $\pm$ standard deviation and percentage and frequency values were used for the variables. The homogeneity of variances, which is a prerequisite for parametric tests, was checked by the Levene test. The assumption of normality was evaluated with the Shapiro-Wilk test. When the differences between the two groups were evaluated, Student's t-test was used if the parametric test met the prerequisites; otherwise Mann Whitney-U test was.

Survival analysis was investigated by the Kaplan-Meier method. The comparison of OS between categories of variables was evaluated by the Log Rank Mantel-Cox test. Binary Logistic Regression analysis was used to determine the correlation between independent variables and the dependent variable (Survival Status). The correlation between categorical variables was analyzed by Fisher's Exact test and Chi-Square test. When the expected frequencies was less than 20%, the Monte Carlo simulation method was applied for the inclusion of these frequencies in the analysis.  $P < 0.05$  was considered to be statistically significant.

## Results

### Clinicopathological Outcomes of the Patients

In this study, 359 patients enrolled. The mean age was  $59.2 \pm 11.6$  years (range, 29-83 years), and the median age was 60 years. The male to female ratio was 2.12. The median follow-up time was 19 months (CI=10.1-31.1). During the follow-up period, 129 (35.9%) cases were alive; however, 230 (64.1%) patients were dead. Median OS was  $23 \pm 2.3$  (CI=18.3-27.6) months.

Neoadjuvant chemotherapy was planned only for 86 (23.9%) patients but was administered adequately only for 23 (6.4%) patients, most of whom had applied after December 2014. Most of the patients (n=63) who were referred to the medical oncology department denied chemotherapy directly or after the adverse effects of the first session.

Splenectomy was applied for 47 (13.1%) patients. Direct involvement of the spleen was the reason for splenectomy in 43 (12%) patients, while four (1.1%) patients underwent splenectomy by accidental injury. Location of gastric tumours was the lower third of stomach in two patients, upper third in 21 patients, middle third in 20 patients and two-thirds of the stomach or more in four patients who underwent splenectomy. All patients in the splenectomy group underwent total gastrectomy. Forty (85.1%) out of 47 patients who underwent splenectomy died, while 190 (60.9%) out of 312 patients in the spleen-preserving group died during the follow-up period. In the splenectomy group, eight (20%) out of 40 patients died due to post-operative infectious complications, including pneumonia and deep surgical site infections, while 12 (6.3%) out of 190 patients died in the spleen-preserving group due to infectious complications. The difference between groups was statistically significant ( $p=0.011$ ). Other adjacent organ resections were performed in eight patients, including the distal pancreas in four, transverse colon in two, the abdominal wall in one and small intestine in one.

In histopathological examination, mean tumour diameter was  $5.1 \pm 3.2$  cm (range, 0.1-16 cm). The mean number of removed lymph nodes was  $20.4 \pm 10.6$  (range, 1-60), and metastatic lymph nodes was  $6.5 \pm 8.4$  (range, 0-60). The descriptive characteristics of this study are detailed in Table 1.

### Univariate Survival Analysis of the Patients

The univariate analysis showed that age, blood group, CAD, smoking, type of gastrectomy, splenectomy, resection margins, location of tumour, tumour diameter, lymphovascular invasion, perineural invasion, Lauren classification, differentiation degree, T stage, N stage, and TNM stage were all significant predictors of OS (all  $p < 0.05$ ) (Table 1).

There was no statistically significant correlation between gender, diabetes mellitus, hypertension, COPD, CHF, hepatitis B carriage, preoperative hemoglobin, neoadjuvant chemotherapy and OS (all  $p > 0.05$ ).

There was no correlation between TNM stages and status of splenectomy in the study group ( $p=0.053$ ) (Table 2).

### Multivariate Logistic Regression Analysis of Independent Risk Factors

Logistic regression analysis using backward elimination method was applied for all prognostic factors considered at univariate analysis. In multivariate analysis, splenectomy (Fig.1), R1 resection (Fig. 2), and advanced TNM stage (Fig. 3) were independent risk factors (all  $p < 0.05$ , Table 3).

## Discussion

Radical gastrectomy is still the most effective treatment for GC. The median OS is 24 months in patients who underwent radical gastrectomy and the 5-year OS ratio was approximately 20-30%. In patients who underwent palliative surgery or did not receive treatment, the median OS was reported as 8 and 5.4 months, respectively.<sup>[9]</sup> Similarly, the median OS was 23 months in our study.

GC is mostly seen in older ages. As the average life expectancy increases, it is thought that the incidence of GC in advanced ages will increase compared to the younger ages.<sup>[10]</sup> In two different studies, including 2643 and 1464 patients, the rate of patients over 60 years of age was reported to be 49.6% and 47.6%, respectively.<sup>[11,12]</sup> The median age was 58.<sup>[12,13]</sup> Similar to the literature, in our series, mean age at the time of diagnosis was  $59.2 \pm 11.6$  (range, 29-83), and the median age was 60 years, and 48.2% of the patients were over 60 years of age. OS in patients over 60 years old has found significantly lower than in patients 60 years old and younger.<sup>[11-13]</sup> In addition, age has been shown to be an independent risk factor for poor prognosis.<sup>[11-14]</sup> In this study, the median OS in patients over 60 years old was found significantly lower ( $p=0.005$ ). In multivariate analysis, we determined that age was not an independent risk factor ( $p > 0.05$ ). This might be due to our dividing the patients into three groups (45 and 60-year thresholds) instead of two groups (60-year threshold) as many authors applied.

Males are twice more often affected than females. In the recent large series, the male/female ratio has been reported in the range of 1.7-2.3.<sup>[11-14]</sup> Many authors<sup>[12-14]</sup> reported that gender was not a prognostic factor. Some authors<sup>[11]</sup> found that female gender was a good prognostic factor, while others<sup>[15]</sup> declared it as a poor prognostic factor, especially in advanced tumours. In the present study, male/female ra-

**Table 1.** Univariate analysis of overall survival according to demographic and clinicopathologic factors

	No. of Patients (n=359) (%)	Median overall survival (months)	95% CI	p
Age (years)				
≤45	48 (13.4)	37	28.1-45.8	0.005
46-60	138 (38.4)	26	19.8-32.1	
≥61	173 (48.2)	18	15.1-20.8	
Gender				
Female	115 (32)	24	17.6-30.3	0.773
Male	244 (68)	20	13.0-26.9	
Blood group				
A	160 (44.6)	18	15.1-20.8	0.01
Others	199 (55.4)	32	23.7-40.2	
Diabetes mellitus				
Yes	47 (13.1)	18	14.0-21.9	0.07
No	312 (86.9)	24	17.4-30.5	
Hypertension				
Yes	74 (20.6)	20	13.1-26.8	0.099
No	285 (79.4)	24	16.2-31.7	
COPD				
Yes	38 (10.6)	15	4.8-25.1	0.123
No	321 (89.4)	24	18.7-29.2	
CHF				
Yes	12 (3.3)	17	13.6-20.3	0.297
No	347 (96.7)	23	17.9-28.0	
CAD				
Yes	39 (10.9)	16	8.7-23.2	0.022
No	320 (89.1)	24	17.4-30.5	
Smoking				
Yes	151 (42.1)	17	15.0-18.9	<0.001
No	208 (57.9)	33	25.3-40.6	
Hepatitis B Carriage				
Yes	12 (3.3)	14	10.6-17.3	0.208
No	347 (96.7)	24	18.7-29.2	
Preoperative Hemoglobin				
<120 g/L	160 (44.6)	20	14.1-25.8	0.38
≥120 g/L	199 (55.4)	25	18.3-31.6	
Type of Gastrectomy				
Subtotal	177 (49.3)	37	26.6-47.3	<0.001
Total	182 (50.7)	18	15.9-20.0	
Splenectomy				
Yes	47 (13.1)	16	11.9-20.0	0.002
No	312 (86.9)	28	21.1-34.8	
Resection Margins				
R0	261 (72.7)	37	30.1-43.8	<0.001
R1	98 (27.3)	12	9.9-14.0	
Location of tumour				
Upper third	95 (26.5)	18	14.5-21.4	<0.001
Middle third	88 (24.5)	19	13.7-24.2	
Lower third	163 (45.4)	40	22.3-57.6	
Two-third or more	13 (3.6)	8	6.8-9.1	
Tumour diameter				
≤5 cm	223 (62.1)	27	19.3-34.6	0.047
>5 cm	136 (37.9)	18	14.4-21.5	
Lymphovascular invasion				
Yes	200 (55.7)	16	13.8-18.1	<0.001
No	159 (44.3)	44	26.3-61.6	

**Table 1. CONT.**

	No. of Patients (n=359) (%)	Median overall survival (months)	95% CI	p	
Perineural invasion					
Yes	189 (52.6)	17	15.1-18.8	<0.001	
No	170 (47.4)	41	27.0-54.9		
Lauren classification					
Diffuse	196 (54.6)	20	16.3-23.6	0.009	
Intestinal	163 (45.4)	32	21.7-42.2		
Differentiation degree					
Well differentiated	32 (8.9)	Reference		0.006	
Moderately differentiated	131 (36.5)	29	18.7-39.2		
Poorly differentiated/Undifferentiated	196 (54.6)	20	16.3-23.6		
T Stage					
T1a	23 (6.4)			<0.001	
T1b	33 (9.2)	61			
T2	27 (7.5)				
T3	55 (15.3)	30	18.3-41.6		
T4a	204 (56.8)	17	14.9-19.0		
T4b	17 (4.7)	10	6.6-13.3		
N Stage					
N0	93 (25.9)			<0.001	
N1	66 (18.4)	41	25.5-56.4		
N2	78 (21.7)	20	15.5-24.4		
N3a	77 (21.4)	14	11.8-16.1		
N3b	45 (12.5)	13	10.0-15.9		
TNM Stage					
Stage 1A	38 (10.6)			<0.001	
Stage 1B	21 (5.8)	61	33.4-88.5		
Stage 2A	34 (9.5)	36	4.4-67.5		
Stage 2B	47 (13.1)	34	13.3-54.6		
Stage 3A	41 (11.4)	20	6.7-33.2		
Stage 3B	65 (18.1)	22	13.4-30.5		
Stage 3C	113 (31.5)	13	10.9-15.0		
Neoadjuvant Chemotherapy					
Yes	23 (6.4)	23	18.3-27.6		0.146
No	336 (93.6)	21	16.3-25.6		

COPD: Chronic obstructive pulmonary disease; CHF: Congestive heart failure; CAD: Coronary artery disease.

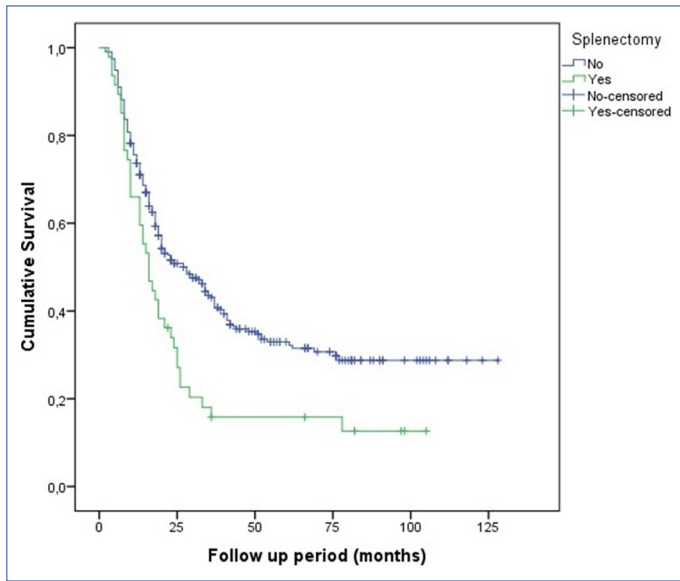
**Table 2.** Splenectomy status of the patients according to TNM stages

TNM Stage	Splenectomy		P
	Yes, n (%)	No, n (%)	
Stage 1A	2 (5.3)	36 (94.7)	0.053
Stage 1B	1 (4.8)	20 (95.2)	
Stage 2A	2 (5.9)	32 (94.1)	
Stage 2B	6 (12.8)	41 (87.2)	
Stage 3A	6 (14.6)	35 (85.4)	
Stage 3B	6 (9.2)	59 (90.8)	
Stage 3C	24 (21.2)	89 (78.8)	
Total	47 (13.1)	312 (86.9)	

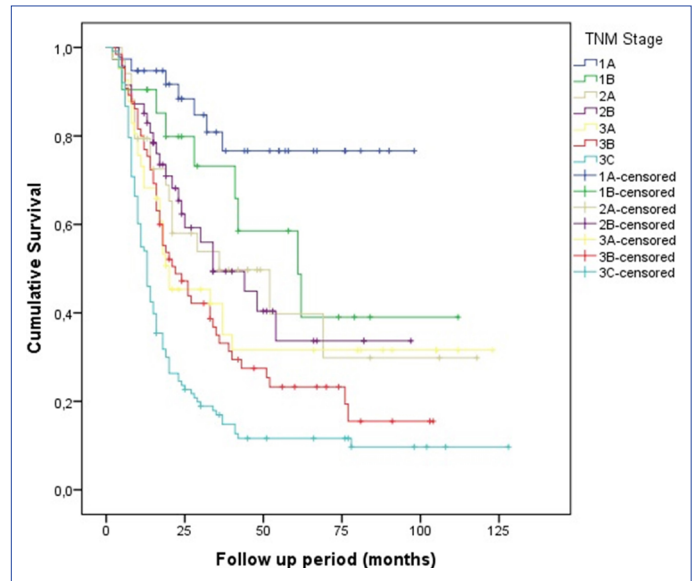
tio was 2.12 and, we did not find a significant relationship between OS and gender.

In a study investigating the effects of blood group on prognosis, blood group A was a poor prognostic factor.<sup>[16]</sup> Median OS in patients with blood group A was 18 months and blood group A was associated with reduced OS in our study (p=0.01).

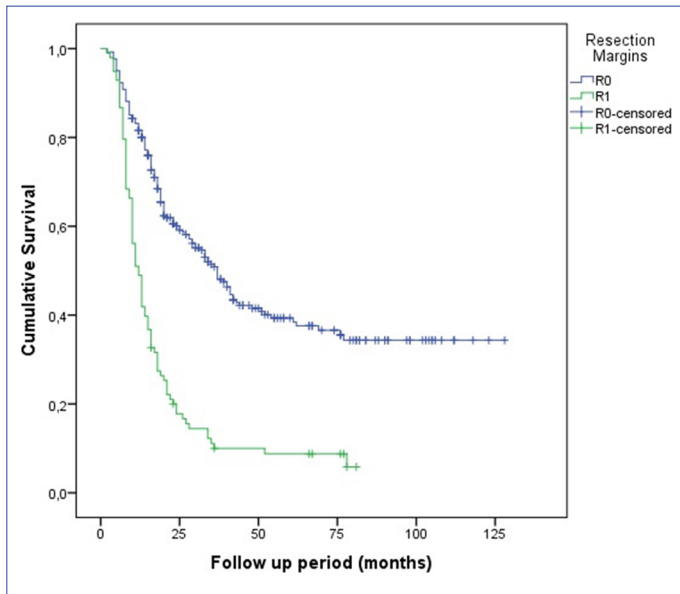
There is a limited number of studies about the effects of comorbid diseases on OS in GC patients. In a study involving patients under 65 years of age, no correlation was found between OS and chronic diseases, including diabetes mellitus, hypertension, COPD and CAD.<sup>[17]</sup> In another study published in 2014, the rates of diabetes mellitus and hypertension were



**Figure 1.** Survival curves of the patients according to splenectomy ( $p=0.002$ ; Kaplan-Meier method).



**Figure 3.** Survival curves of the patients according to the TNM stage ( $p<0.001$ ; Kaplan-Meier method).



**Figure 2.** Survival curves of the patients according to resection margins ( $p<0.001$ ; Kaplan-Meier method).

18% and 56%, respectively, and only CAD had been reported as a poor prognostic factor.<sup>[18]</sup> In the present study, CAD was a poor prognostic factor in univariate analysis ( $p=0.022$ ).

The carcinogenic effect of smoking was clearly demonstrated. Smoking has been considered to be a poor prognostic factor for GC patients.<sup>[19,20]</sup> Smoking has also been shown to be an independent risk factor.<sup>[19]</sup> In contrast, in a study in China, it was reported that smoking did not impact OS.<sup>[21]</sup> The rate of cigarette smokers was 42.1%. There was a significant difference in OS between smokers and non-smokers in univariate analysis ( $p<0.001$ ).

A limited number of articles investigated the effects of hepatitis B carriage on OS in GC. The incidence of hepatitis B carriage was reported 1.4%, and the effects on OS has not been shown before.<sup>[17]</sup> In this study, the rate of patients with hepatitis B was 3.3% ( $n=12$ ). Similarly, we did not find a significant relationship between OS and hepatitis B carriage.

Although preoperative anemia had been reported to reduce median OS, it was not considered to be an independent risk factor.<sup>[21,22]</sup> In this study, no significant correlation was obtained between OS and preoperative hemoglobin. This may be explained by our exclusion criterion of severe-

**Table 3.** Multivariate analysis of parameters predicting overall survival

	B	S.E.	p	Hazard ratio	95% CI
<b>Splenectomy</b>					
Yes	0.799	0.483	0.006	2.223	0.863-5.726
No	-	-	-	1.00	
<b>Resection Margins</b>					
R0	-	-	-	1.00	-
R1	1.261	0.405	0.002	3.529	1.595-7.805
<b>TNM stage</b>					
TNM stage 1A	-	-	-	1.00	
TNM stage 1B	1.167	0.615	0.058	3.213	0.962-10.732
TNM stage 2A	1.471	0.545	0.007	4.353	1.496-12.666
TNM stage 2B	1.222	0.519	0.019	3.395	1.227-9.389
TNM stage 3A	1.856	0.537	0.001	6.401	2.235-18.328
TNM stage 3B	2.227	0.520	<0.001	9.752	3.519-27.025
TNM stage 3C	2.845	0.526	<0.001	17.207	6.137-48.247

ly anemic patients who underwent urgent surgery due to tumour bleeding and were predicted a high mortality rate. Gastrectomy type and resection width are determined according to tumour location and tumour size. While total gastrectomy is more preferred in proximal or large-sized tumours, subtotal gastrectomy can be performed in distal and small-sized tumours. Proximal gastrectomy is another option in proximal tumours. As a result of widespread minimally invasive surgery and an increase in surgical options, the rate of total gastrectomy was reported in the range of 9-30% in some series.<sup>[11,23-25]</sup> Rate of total gastrectomy was 50.7% in our patient group, which was higher compared to literature. This higher rate might be due to our patients were predominantly in an advanced stage and had large-sized tumours. The type of gastrectomy (total/subtotal) had been reported to impact OS<sup>[11,23,24]</sup> and it was shown to be an independent risk factor by some authors.<sup>[23]</sup> By contrast, Tang et al.<sup>[25]</sup> declared no effect on prognosis in patients with mucinous carcinoma. In our study, total gastrectomy was associated with reduced OS of the patients in univariate analysis; however, this relation was not proven by multivariate analysis ( $p < 0.001$ ,  $p > 0.05$ , respectively).

The splenectomy requirement during gastrectomy is controversial. Although it is thought to be useful in the dissection of more lymph nodes and to provide negative surgical margins, especially in tumours invading the greater curvature, splenectomy has been shown to increase perioperative bleeding and morbidity.<sup>[26]</sup> In the absence of tumour invasion or prominent metastatic lymph node, it was recommended to avoid splenectomy.<sup>[27]</sup> No correlation was reported between splenectomy and OS of patients before 2017.<sup>[26,27]</sup> On the other hand, Jeong et al.<sup>[28]</sup> advocated that splenectomy was associated with poor prognosis and an independent risk factor in patients who underwent total gastrectomy due to stage III proximal GC. In the present study, splenectomy was performed in 47 patients (13.1%). In the univariate analysis, splenectomy was associated with reduced OS (16 months and 28 months, respectively) ( $p = 0.002$ ). Also, splenectomy was an independent risk factor in multivariate analysis ( $p = 0.006$ ). A recent systematic review and meta-analysis reported that splenectomy was associated with increased postoperative infectious complications and overall morbidity.<sup>[29]</sup> Consistent with that meta-analysis, we found a significantly increased mortality rate due to postoperative infectious complications, such as pneumonia in patients who underwent splenectomy.

The importance of negative surgical margins in tumour surgery is incontrovertible. R0 resection should be achieved for

longer disease-free survival and OS because R1 resection, where microscopic residual tissue remains, is associated with local recurrence and hence poor prognosis. There is no accepted standard approach for the evaluation of the surgical margin. Institutional traditions or surgeon's preferences become prominent to determine the margin status. Surgeons often visually evaluate the resection margins intraoperatively to decide whether the resection is adequate or not. Although current literature suggests routine intraoperative frozen section analysis (FSA) for the margins due to high accuracy, sensitivity, and specificity, a recent study has advocated that FSA of the surgical margins was not essential in many gastric adenocarcinoma cases to obtain an R0 resection.<sup>[30]</sup> R1 resection was reported to significantly reduced OS compared to R0 resection and to be an independent risk factor.<sup>[23,31]</sup> Similarly, our additional analysis showed that OS in the R1 resection group was significantly lower than in the R0 resection group ( $p < 0.001$ ). Furthermore, multivariate analysis revealed positive resection margins to be an independent prognostic factor ( $p = 0.002$ ). Higher rates of positive surgical margins in our series, compared to studies<sup>[23,31]</sup> conducted in the Far East, might be due to patients' had advanced tumours and not routinely application of intraoperative FSA for surgical margins in all patients.

Currently, the most common location for GC is the lower third part of the stomach. In recent years, the proportion of proximal tumours increased, especially in Western countries, suggesting that there may be different reasons for etiology.<sup>[32]</sup> OS in distal GC was reported to be significantly longer compared to proximal GC. OS in middle third tumours is between proximal and distal tumours. Tumour location was not considered to be an independent risk factor for mortality.<sup>[11,12,17]</sup> In our study group, the lower third of the stomach was the most common location. Similarly, tumour location was found to impact OS in univariate analysis; however, this relation was not proven by multivariate analysis ( $p < 0.001$ ,  $p > 0.05$ , respectively).

Tumour diameter plays a role in understanding the level of disease and predicting prognosis in almost all cancers. There are some studies supporting that larger tumour diameter shortens OS.<sup>[12,17,24,25,27]</sup> In recent articles, tumour diameter has been reported to be an independent risk factor.<sup>[12,17,25,27]</sup> In the present study, it was stated that the increase in diameter had a significant negative effect on OS ( $p = 0.047$ ), consistent with the literature. However, tumour diameter was found not to be an independent risk factor ( $p > 0.05$ ).

Lymphovascular and perineural invasion are parameters showing the aggressiveness of the tumour in histopathological examination. They both have been accepted to be poor prognostic factors due to a significantly reduced

OS.<sup>[12,23,24,27]</sup> Liu et al.<sup>[12]</sup> reported that both parameters were independent risk factors. Both parameters were positive in most of the patients, and they were poor prognostic factors (both,  $p < 0.001$ ), consistent with the previous literature.

Many classification systems have been proposed in the histological classification of GC, but none of them has fully reflected the phenotypic and genotypic features of tumours. The classifications accepted today were suggested by Lauren<sup>[7]</sup> and the World Health Organization (WHO).<sup>[6]</sup> The diffuse type of the Lauren classification and poorly-cohesive type of the WHO classification both have been advocated to be poor prognostic factors.<sup>[12,13,23,27]</sup> On the contrary, some authors<sup>[11,24,25]</sup> reported no difference in OS between the groups. The majority of our patients had diffuse-type tumours. We found a significant relationship between OS and Lauren subtypes ( $p = 0.009$ ). When histological grade was evaluated, prognosis has been declared to be significantly better in well-differentiated tumours.<sup>[14,17,31]</sup> We determined that the differentiation degree impacts the OS of the patients ( $p = 0.006$ ). These results were consistent with the previous studies.

The prognostic significance of the T stage was investigated and the advanced T stage was associated with poor prognosis.<sup>[11,17,24,25,27,31]</sup> Additionally, it was reported to be an independent risk factor.<sup>[17,25,27,31]</sup> In our study, the T stage showed a significant relationship with OS in univariate analysis; however, it was not found as an independent risk factor ( $p < 0.001$ ,  $p > 0.05$ , respectively). N stage depends on the number of removed metastatic lymph nodes regardless of the number of dissected lymph nodes. To determine a reliable N stage, removal of at least 15 lymph nodes was recommended.<sup>[8]</sup> Advanced N stage is considered to be a poor prognostic factor.<sup>[11,17,23-25,27,31]</sup> In addition, N was reported to be an independent risk factor.<sup>[17,25,27,31]</sup> In our patient group, an adequate number of lymph nodes ( $\geq 15$  nodes) were removed in 256 (71.3%) patients, and a significant difference in OS was observed between subgroups of the N stage ( $p < 0.001$ ). However, multivariate analysis revealed that the N stage was not an independent risk factor.

The TNM staging system is used to predict prognosis and determine optimal treatment, as in other malignancies. Its impact on prognosis is non-controversial. Almost all of the previous studies reported that OS in the advanced stage decreased significantly.<sup>[11-13,25]</sup> It remains the most accepted criterion as an independent risk factor.<sup>[11-13,25]</sup> In our study, the TNM stage had a significant impact on OS and stood out as an independent risk factor (both,  $p < 0.001$ ).

Neoadjuvant chemotherapy is considered to be the first-line treatment for patients with  $\geq$  Stage IB resectable GC. Multicentric randomized trials demonstrated that neoadju-

vant chemotherapy improves disease-free and overall survival in GC.<sup>[33]</sup> In the present study, we found no correlation between neoadjuvant chemotherapy and OS. This result may be due to an inadequate number of locally advanced GC patients who underwent neoadjuvant therapy or insufficient radiological evaluation of the patients. On the other hand, some patients who were a candidate for neoadjuvant therapy denied therapy or left incomplete due to the adverse effects of chemotherapy or their stereotypes. Before evaluating by PET-CT scan, only CT evaluation was considered to be insufficient in most cases to evaluate the presence of locally advanced disease.

This study has several limitations that should be pointed out. Firstly, this is a retrospective study. Additionally, surgical interventions were performed by multiple surgeons in a single tertiary institution setting. Also, intraoperative FSA for surgical margins was not routinely performed for the whole study group, and this study did not address information about adjuvant therapies. Finally, the number of patients and the follow-up period are inadequate to draw strong conclusions. Multicenter randomized clinical trials with a larger sample size should be conducted to prevent statistical prejudices and validate our results.

## Conclusion

R1 resection, splenectomy, and advanced TNM stage were independent risk factors for poor prognosis. All of these prognostic factors except for splenectomy are considered to be independent risk factors for decades. Contrary to the literature, the present study is one of the rare studies describing the statistically significant negative impact of splenectomy on OS in a patient group who underwent curative-intent gastrectomy. We recommend avoiding splenectomy in the absence of direct invasion of the tumour or metastasis of lymph nodes on splenic hilum due to increased risk of postoperative infectious complication-related mortality.

## Disclosures

**Ethics Committee Approval:** Ethics committee approval was received for this study from Ethics Committee of Izmir Kâtip Celebi University (date 01.11.2017, decision number 249).

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

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