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Original Article

Determinants of survival in gastric cancer: A single center experience

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Abstract

Aim: Gastric cancer is the second leading cause of cancer deaths worldwide. The effect of lymph node dissection and the extent of gastric resection on survival remains controversial, while improved survival has been reported with combined chemotherapy and radiotherapy. In this study, we aimed to present a single center experience.

Material and Methods: Patients undergoing gastric resection due to gastric cancer were retrospectively assessed in order to examine the determinants of survival in gastric adenocarcinoma. Gastric malignancies other than adenocarcinoma were excluded from the study. Result of preoperative diagnostic work up, operative data, histopathology of the surgical specimen, and postoperative follow up parameters were evaluated and recorded.

Results: Among a total of 139 patients operated due to gastric malignancy between January 2008 and January 2014 in our unit, 124 were diagnosed with an adenocarcinoma. The median duration of follow up was 6 months, during which 53 patients (42.7%) were found to have disease recurrence (10 local, and 43 systemic). A higher T stage was associated with shorter survival ($p<0.0001$), as was the N stage ($p<0.0001$). Parameters that emerged as having a statistical significance ($p<0.05$) in the univariate analysis, i.e. gender, tumor size, T stage, N stage, differentiation, and surgical margin status, were subjected to a multivariate analysis, where T stage, N stage, and proximal/distal surgical margin status maintained their significant association with the survival.

Conclusion: Several factors such as tumor stage, tumor diameter, histological type, and number of metastases emerged as having significant prognostic importance in patients with gastric cancer.

Keywords: Cancer; Gastric Cancer; Malignancy; survival.

INTRODUCTION

Gastric cancer is the fourth most common malignancy and second leading cause of cancer deaths worldwide, despite the observed decline in its incidence in the last decade. The male to female ratio is 1.85 (1), with more than half of the cases occurring in individuals ≥ 65 years of age, and 5% in those under 40 years of age (2). In Japan, patients are generally diagnosed at an earlier stage of the disease thanks to population surveillance efforts. Early stage gastric cancer is associated with a better prognosis than late stage disease, with a 5 year overall survival rate of up to 90% (3).

Curative treatment of gastric cancer is only possible with surgery (4). The effect of lymph node dissection and the extent of gastric resection on survival remains controversial, while improved survival has been reported with combined chemotherapy and radiotherapy (5).

MATERIAL and METHODS

Patients undergoing gastric resection due to gastric cancer between January 2008 and January 2014 at the General Surgery Unit of Fırat University Hospital were retrospectively assessed in order to examine the determinants of survival in gastric adenocarcinoma. Gastric malignancies other than adenocarcinoma were excluded from the study. Postoperative hospital mortality, i.e. non-cancer-related patients and early surgical deaths were excluded from this study. Result of preoperative diagnostic work up, operative data, histopathology of the surgical specimen, and postoperative follow up parameters were evaluated and recorded.

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The following parameters with a potential impact on survival were assessed: gender, age, carcinoembryonic antigen (CEA), ASA score, duration of surgery, tumor location, tumor size, macroscopic tumor type (Borrmann classification), histological type (WHO classification), tumor differentiation, number of lymph nodes removed and metastatic lymph nodes, status of the surgical margins, the distance of the tumor to the nearest surgical margin, and presence or absence of recurrence. Assessment of parameters such as the tumor location, tumor size, macroscopic type, histological type, differentiation, number of lymph nodes removed and metastatic lymph nodes, and status of the surgical margins as well as its distance to the tumor were based on histopathology report.

Statistical Analyses

The overall and disease-free survival rates were estimated using the demographic and clinical parameters, histopathological assessment date of the surgical samples, and follow-up data. The data were expressed as mean and standard deviation or median (range). A p value of less than 0.05 was considered significant. Parameters with a p value of <0.05 in the univariate analysis were subjected to a multivariate analysis.

RESULTS

Among a total of 139 patients operated due to gastric malignancy between January 2008 and January 2014 in our unit, 124 were diagnosed with an adenocarcinoma. Table 1 shows the demographic and clinical data of the patients.

Table 2 depicts the perioperative parameters and histopathological results of the surgical samples. The median duration of follow up was 6 months, during which 53 patients (42.7%) were found to have disease recurrence (10 local, and 43 systemic). The results of univariate Kaplan-Meier survival analysis is shown in Table 3.

Table 1. Demographics and clinical information

Age	64 (27-88)
Gender	
Female	41 (33%)
Male	83 (67%)
ASA Status	
I	3 (3%)
II	39 (31%)
III	39 (31%)
IV	43 (35%)
Tumor localization	
Cardia	20(16%)
Corpus	34 (28%)
Antrum	66 (53%)
Diffuse infiltrating	4 (3%)

Table 2. Perioperative parameters, and results of histopathological examination

Surgical procedure	
Total	54 (44%)
Subtotal	70 (56%)
Operation time (minutes)	180 (130-260)
Largest diameter of the tumor (cm)	5.9 ± 0.3
Differentiation	
Well	17 (14%)
Moderate	55 (44%)
Poor	52 (42%)
Number of lymph nodes dissected	22 (0-109)
Number of metastatic lymph nodes	4 (0-71)
Metastatic lymph node/Total lymph node	0.31 ± 0.03
Resection margin status	
Positive	16 (13%)
Negative	108 (87%)
Distance between the tumor and resection margin	1.5 (0-9)
T Stage	
T1	16 (13%)
T2	22 (18%)
T3	62 (50%)
T4	24 (19%)
N Stage	
N0	37 (30%)
N1	24 (19%)
N2	26 (21%)
N3	37 (30%)

Table 3. Univariate Kaplan Meier overall survival based on prognostic parameters

	Median survival (months)	P
Age		
≤60	23	0.08
>60	14	
Gender		
Female	12	0.2
Male	23	
Tumor localization		
Cardia	21	
Corpus	23	0.3
Antrum	20	
Diffuse infiltrating	2	
Tumor size (cm)		
<4 cm	53	0.01*
≥4 cm	16	
CEA (ng/ml)		
≤4	21	0.2
>4	14	
T Stage		
T1	53	
T2	nr	<0.0001*
T3	13	
T4	7	
N Stage		
N0	nr	
N1	18	<0.0001*
N2	13	
N3	10	
Differentiation		
Well	nr	
Moderate	19	0.0007*
Poor	8	
Number of lymph node dissected		
<15		0.3
≥15		
Resection margin status		
Positive	7	0.002*
Negative	20	
Distance between the tumor and resection margin (cm)		0.007*
≤2 cm	14	
>2 cm	51	

(nr: non-reached)

Females were found to have significantly shorter survival than males (Figure 1).

A higher T stage was associated with shorter survival (p<0.0001), as was the N stage (p<0.0001) (Figure 1). Figure 1, 2). According to N stage overall survival was as shown in Figure 2.

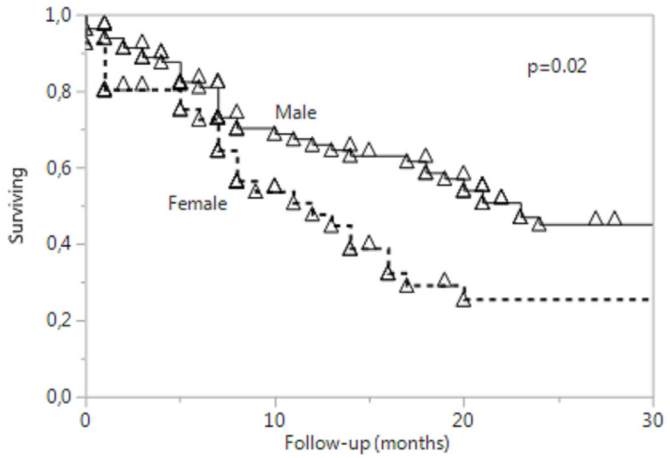

Figure 1. Kaplan Meier overall survival based on gender

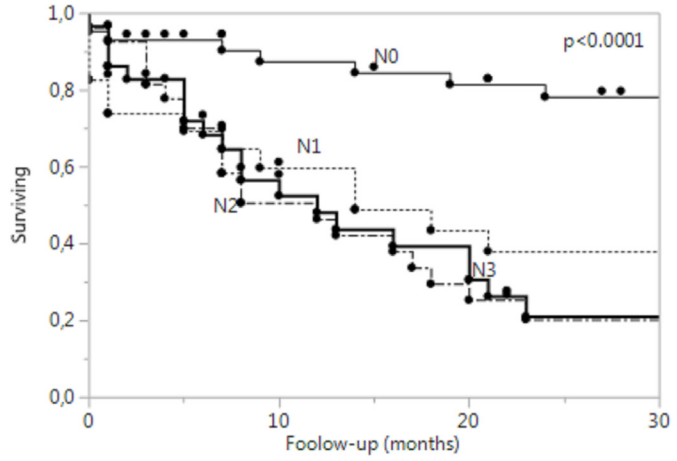

Figure 2. Kaplan Meier overall survival based on N stage

Kaplan-Meier survival analysis showed no significant association between the total number of lymph nodes and survival (number of lymph nodes ≥15 or <15) (p=0.3). However, tumor differentiation and survival had a significant association (p=0.007) (Figure 3). Tumor positivity at the surgical margin (p=0.002) (Figure 4).

Parameters that emerged as having a statistical significance (p<0.05) in the univariate analysis, i.e. gender, tumor size, T stage, N stage, differentiation, and surgical margin status, were subjected to a multivariate analysis, where T stage, N stage, and proximal/distal surgical margin status maintained their significant association with the survival (Table 4). The results of the univariate analysis for parameters with a potential effect on disease-free survival are shown in Table 5.

Also, among the parameters that had a statistical significance (p<0.05) in the univariate analysis, i.e. T stage, differentiation, number of metastatic lymph nodes, only T stage remained significant in terms of its effect on survival in the multi-variate analysis (Table 6).

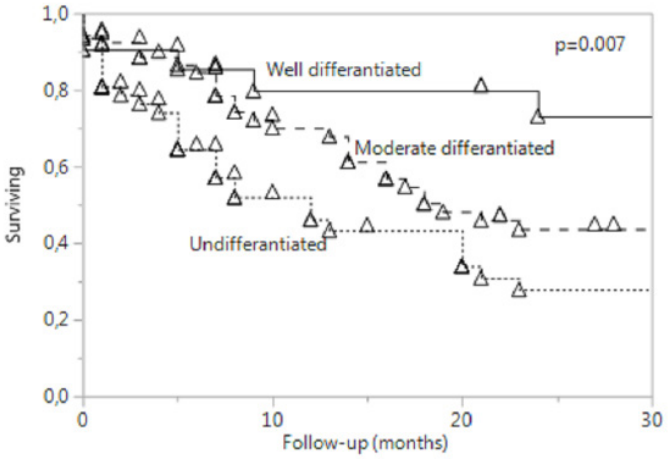

Figure 3. Kaplan-Meier overall survival based on tumor differentiation

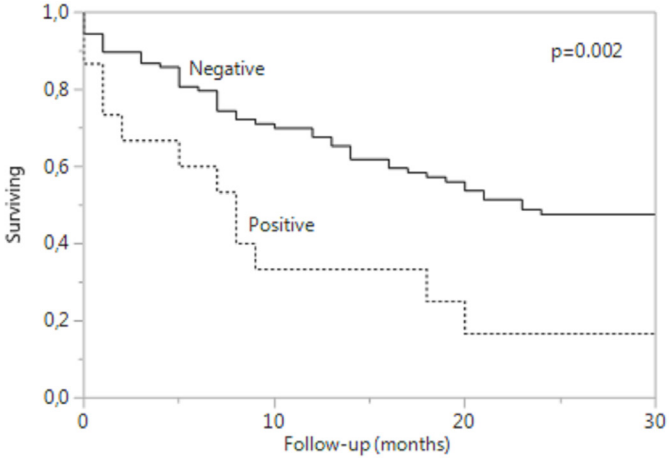

Figure 4. Kaplan-Meier overall survival based on resection margin status

Table 4. Multivariate analysis for overall survival using the Cox Proportional Hazards Model

Parameter	p
Gender	
Female vs Male	0.3
Tumor size (cm)	
<4 cm vs ≥4 cm	0.1
T	0.005*
N	0.02*
differentiation	0.2
Resection margin status	0.01*

Table 5. Univariate Kaplan Meier disease-free survival based on prognostic parameters

	Median survival (months)	P
Age		
≤60	14	0.08
>60	15	
Gender		
Female	13	0.5
Male	15	
Tumor localization		
Cardia	11	
Corpus	343	0.3
Antrum	14	
Diffuse infiltrating	nr	
Tumor size (cm)		
<4 cm	35	0.007
≥4 cm	13	
CEA (ng/ml)		
≤4	16	0.1
>4	8	
T Stage		
T1	35	
T2	nr	<0.0001*
T3	14	
T4	3	
N Stage		
N0	35	
N1	13	0.08
N2	14	
N3	13	
Differentiation		
Well	nr	
Moderate	14	0.0007*
Poor	13	
Number of lymph nodes		
<15	15	0.6
≥15	14	
Number of metastatic lymph nodes		
≤6	34	
6-15	11	0.02*
>15	2	
Resection margin status		
Positive	2	0.005*
Negative	16	
Distance between the tumor and resection margin (cm)		
≤2 cm	13	0.02
>2 cm	19	

(nr: non-reached)

Table 6. Multivariate analysis for disease-free survival using the Cox Proportional Hazards Model

Parameter	p
T	0.02*
differentiation	0.1
Number of metastatic lymph nodes	0.8

DISCUSSION

Although the incidence of gastric cancer has been decreasing in recent years, particularly in the developed cancers, gastric adenocarcinomas remain a leading cause of cancer deaths worldwide (1). The poor prognosis in this condition is frequently associated with local, regional, and systemic recurrence as well as with late diagnosis at advanced stage (6). One of the major prognostic factors in gastric cancer is the R0 resection status, which is associated with lower risk of regional recurrence and related deaths (7). On the other hand, other prognostic factors have also been reported, although a certain degree of inconsistency can be observed across different studies regarding prognostic significance of individual factors. The ratio of the number of metastatic lymph nodes to the number of lymph nodes removed has prognostic significance in gastric cancer. Since the demonstration of the fact that regional recurrence may influence survival in gastric cancer patients by Japanese researchers, the surgical approach has changed, placing more emphasis on lymph node dissection (4). Presence of metastatic lymph nodes as well as the depth of invasion is known to be the primary determinants of prognosis in gastric cancer (8). Lymph node metastasis represents an important factor in terms of recurrence and poor prognosis (9), with 10-year overall survival rates of 27% and 72% in node positive and negative patients, respectively (10). With regard to TNM staging system, the disease stage is the single most important determinant of prognosis in these patients (11).

Accordingly, TNM stage had a significant effect on survival in our study. The median overall survival was 53 months in T1 patients vs. 7 months in T4 patients. Kim et al. (12) examined 9262 patients and classified patients on the basis of the ratio of metastatic lymph nodes to removed lymph nodes as those having a ratio of 0. 0.1, 0.3, 0.5, and >0.5, and found decreased survival with increasing ratio. Similarly Ding et al. reported a survival of 91.2%, 70.6%, and 12% in patients with a ratio of 0. 0.01 to 0.02, and >0.2, respectively. Our patients had an average metastatic to removed lymph node ratio of 0.31±0.03, similar to the previous reports. Histology of the tumor is also related with the prognosis, with the diffuse type having a worse prognosis than the intestinal type (14). Also proximal tumors are associated with a poor prognosis as compared to distal ones owing to their larger size, increasing frequency, deeper invasion, and more frequent lymph node metastasis (15). In our series the overall survival in tumors located in the cardia, corpus, and antrum, and in diffuse infiltrative tumors were 21, 23, 20, and 2 months, respectively. However the tumor site

did not have a significant effect on survival. Tumor size can be readily estimated both before and during surgery, and may represent a prognostic factor in these patients (16,17), although its importance remains controversial. For instance, in a study involving 679 patients with gastric cancer this parameter had statistical significance in the univariate analysis, while it lost its significance in the multivariate analysis (18). On the other hand, others have reported that tumor diameter has independent prognostic significance in gastric cancer (19). For example, Bilici A et al. reported that tumor diameter was an independent prognostic factor when a cut-off value of 8 cm was used (20). In our study, tumor size was classified as those having a diameter of ≥4 or <4 cm, with an overall survival of 16 months vs. 53 months in these two tumor categories, respectively, suggesting a significant impact of tumor size on overall survival. The disease-free survival for these two tumor categories were 13 vs. 35 months, respectively.

Again, inconsistent results have been reported in terms of the effect of age on prognosis in patients with gastric cancer (21,22). Several studies found an increased occurrence of the diffuse type in younger patients with a poor prognosis (23,24). Baba et al. (25) observed that patient age had a significant prognostic value in those who had no lymph node metastasis. In our study, the median survival in patients < 60 and ≥ 60 years of age was 14 and 23 months, and this finding was not statistically significant despite a 9-month difference. The disease free survival in these two groups were 15 and 14 months, respectively.

In a study by Saito et al. (26) involving 1985 patients, in a multi-variate analysis with Cox proportional Hazardz Model invasion, age, tumor size, tumor depth, lymph node metastasis, peritoneal metastasis, liver metastasis, and lymph or blood vessel invasion emerged as independent prognostic factors. Although our sample size was small, the multivariate analysis showed that T and N stage, as well as the proximal/distal surgical margin status had a significant impact on survival. In contrast with the abovementioned study, although age and tumor size had prognostic significance in the univariate analysis, they lost their significance in the multi-variate analysis.

In the study by Liang et al. (27) the univariate analysis showed that gender, tumor size, tumor histology, extranodal metastasis, surgical margin status, pT4, lymph node metastasis, M1 and gastrectomy had significant prognostic value, while multivariate analysis found that only the surgical margin status, pT4, lymph node metastasis, M1 and gender had independent prognostic value. The univariate analysis for disease-free survival in our study found that gender, tumor size, T and N stage, tumor differentiation, and proximal/distal surgical margins had a survival effect. In the multi-variate analysis T and N stage as well as the proximal/distal surgical margin status remained significant. Graziosi et al. (24) also found a correlation between survival and gender, age, tumor site, Lauren class, lymphovascular involvement, adjuvant treatment, neo-adjuvant treatment, HIPEC, and TNM stage in a univariate analysis, while lymphovascular involvement had independent prognostic significance in the multi-variate analysis. Our multi-variate analysis showed that T and N stage were significant factors for survival. Parameters with a statistical significance in the univariate analysis for disease-free survival were subjected to a multi-variate analysis, showing a significant result for the T stage.

CONCLUSION

Despite certain limitations of our study such as its retrospective nature, short follow-up duration, and small sample size, several factors such as tumor stage, tumor diameter, histological type, and number of metastases emerged as having significant prognostic importance in patients with gastric cancer.

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