Journal of Surgery and Medicine
e-ISSN: 2602-2079

Predicting survival in gastric cancer: A prospective cohort study with 102 patients

Mide kanserinde sağkalımı tahmin etmek: 102 hasta ile prospektif kohort çalışma

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Abstract

Aim: Gastric cancer is one of the most aggressive tumors of the gastrointestinal tract. Course of disease can be different in every case. The aim of this study was to evaluate prognosis of gastric cancer patients and factors affecting survival.
Methods: Observational cohort study was planned. Primary gastric cancer patients enrolled into study. Patients with rare tumors were excluded. Patients were divided in 4 groups; Group 1: patients suitable for surgery and underwent surgical resection, Group 2: patients that were discovered unresectable during operation, Group 3: patients that were radiological inoperable, Group 4: patients who refused the surgery. We analyzed survival among groups, and evaluated effecting factors.
Results: 102 patients were included in the study. Sixty-six patients underwent surgical resection (group 1). Five patients were diagnosed as inoperable during surgery (group 2). Six-teen patients were determined as inoperable by radiologic evaluation (group 3). Fifteen patients (group 4) were evaluated as operable; however they refused surgery. No differences were detected among groups in comparison of gender with p of 0.250 (table 1). However, age distribution was different between groups with p of 0.043 because group 4 is formed by older patients with mean age of 71.0 (10.0). Survival analysis showed that patients in group 1 (14.0 (5.1) months) had better survival than other groups (P=0.011). Male patients showed better survival than female patients (14 (1.9) vs 6 (1.8) months, P=0.002).
Conclusion: Although course of gastric cancer differs in every patient, proper surgery at certain stages seems to be a feasible treatment option with acceptable survival rates.
Keywords: Gastric cancer, Survival, Course of disease

Öz

Amaç: Gastrik kanser, gastrointestinal sistemin en agresif tümörlerinden biridir. Her durumda hastalık seyri farklı olabilir. Bu çalışmanın amacı, mide kanseri hastalarının prognozunu ve sağkalımı etkileyen faktörleri değerlendirmektir.
Yöntemler: Gözlemsel kohort çalışması planlandı. Primer mide kanseri hastaları çalışmaya alındı. Nadir tümörleri olan hastalar çalışma dışı bırakıldı. Hastalar 4 gruba ayrıldı; Grup 1: Cerrahiye uygun ve cerrahi rezeksiyon yapılan hastalar, Grup 2: Operasyon sırasında rezeke edilemeyen tespit edilen hastalar, Grup 3: Radyolojik olarak çalışmayan hastalar, Grup 4: Cerrahiyi redden hastalar. Gruplar arasında sağkalımı analiz ettik ve etkili faktörleri değerlendirdik.
Bulgular: Çalışmaya 102 hasta alındı. Altmış altı hastaya cerrahi rezeksiyon yapıldı (grup 1). Beş hastaya ameliyat sırasında çalışmazlık tanısı kondu (grup 2). Altı genç hasta radyolojik değerlendirme ile inoperabl olarak belirlendi (grup 3). On beş hasta (grup 4) uygun olarak değerlendirildi; ancak ameliyatı reddetti. Cinsiyete göre gruplar arasında fark bulunmadı (P=0,250) (Tablo 1). Bununla birlikte, yaş dağılımı, P=0.043 olan gruplar arasında farklıydı çünkü grup 4, yaş ortalaması 71.0 (10,0) olan yaşlı hastalar tarafından oluşturulmuştur. Sağkalım analizi, grup 1'deki hastaların (14.0 (5,1) ay) diğer gruplardan daha iyi sağkalım gösterdiğini gösterdi (P=0,011). Erkek hastalar kadınlara göre daha iyi sağkalım gösterdi (14 (1,9) vs 6 (1,8) ay, P=0,002).
Sonuç: Her ne kadar mide kanseri seyri farklı olsa da, belirli evrelerde uygun cerrahi işlem, kabul edilebilir sağkalım oranları ile uygulanabilir bir tedavi seçeneği gibi görünmektedir.
Anahtar kelimeler: Mide kanseri, Sağkalım, Hastalığın seyri

Introduction

Gastric cancer is one of the most aggressive tumors of the gastrointestinal tract. While 5-year-survival of early gastric cancer is approximately 90%, it varies between 15-20% at advanced stage [1]. In Turkey, annual incidence of gastric cancer is 9.6/100,000 in men and 5.7/100,000 in women. Therefore, we expect to encounter 130,000 new cases each year. Gastric cancer's death rate is the second highest in male and third in female population [2]. Male incidence is higher than female and male/female ratio is 2/1. While it's rarely encountered before 40, its incidence gets higher with age and reaches its highest rate in around 60 years of age [3].

Gastric cancer can be diagnosed in early stage in Japan due to their advanced methods of screening. It is diagnosed in later stages and harder to cure in Western Countries due to rare incidence and infrequent and insufficient screenings [1].

There are various studies over factors effecting prognosis. These include, sex, age, blood type and blood transfusion, body-mass-index, tumor localization, size, macroscopic type, histological grade, stage, metastatic lymph node count, tumor markers (CEA, Ca19-9), pre-operative hemoglobin and albumin levels, surgical procedure method, lymph node dissection (D1, D2, D3) and chemo/radiotherapy [1-3]. Studies showed that gastric cancer prognosis is affected in almost all cases by some factors while different results are seen for some others [2].

Main treatment of most gastric cancer is surgical resection and lymph node dissection. However, palliative surgery may be performed for some gastric cancer patients diagnosed at later stage with pre-operative radiological evaluation or discovered as unresectable during surgical exploration. Some patients receive only chemo/radiotherapy if they refuse the operation. However, there is limited information in literature concerning the end of the course of treatments. The aim of this study was to evaluate prognosis of gastric cancer patients and factors affecting survival.

Materials and methods

Observational cohort study was planned to evaluate primary gastric cancer patients who were diagnosed between 2009 and 2012, retrospectively using prospective database. Local ethics committee of our hospital approved the study that was prepared according to ethical standards of 1975 Helsinki Declaration's Human Experiment Committee which was revised in 2000 (www.wma.netle/policy/b3.htm).

Patients with rare tumors (i.e., gastrointestinal stromal tumor, lymphoma, and neuroendocrine tumor) were excluded. After investigating gastric cancer patients to evaluate operability with radiologic techniques (computed tomography, positron emission tomography), we informed the patients about surgery. Patients were divided in 4 groups; Group 1: patients suitable for surgery and underwent surgical resection, Group 2: patients that were discovered unresectable during operation, Group 3: patients that were radiological inoperable, Group 4: patients who refused the surgery.

After evaluating the patient as operable radiologically and having the consent for operation, total or subtotal gastrectomy was performed according to tumor's location. Standard lymph node dissection (D2) was performed. All patients were sent to medical oncology post-operatively (chemoradiotherapy).

Demographic data, i.e., age, gender, of the patients were recorded. Tumor location and TNM stage of group 1 patients were recorded. Tumors located in corpus and cardia were defined as "proximal" and "distal" if located in the remaining portion of the stomach. All patients were followed-up by telephone and routine examinations every three months in first two years, every six months following three years, and every one year after five years of diagnosis of the cancer. Patients who failed to comply follow-ups were not evaluated in survival analysis. Main outcome of our study is survival. Firstly, we analyzed survival among groups. Further analysis was performed for group 1 patients to evaluate the effect of tumor location and TNM stage on survival.

Statistical analysis

NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) were used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used to evaluate the study data. Mann Whitney U test was used in comparison of quantitative data with two groups, Kruskal Wallis test were used for three or more groups that aren't normally distributed. Fisher's Exact and Yates Continuity Correction test were used to compare qualitative data, Kaplan Meier Survival Analysis and Log Rank tests were used to evaluate survival. Median (standard error) was used to present the survival. Hazard ratio was calculated using Cox Regression Analysis to determine parameters affecting survival. Relevance was calculated as $P<0.05$ in the confidence interval of 95%.

Results

One-hundred and eleven patients with gastric cancer were evaluated in eligibility. Nine patients with rare tumors were excluded, and 102 patients were included in the study. Sixty-five were male, 37 were female (Male/Female ratio: 1.75). Mean age was 63.9 (12.3) years (ranging between 21 and 89). Flowchart of the study is shown in figure 1.
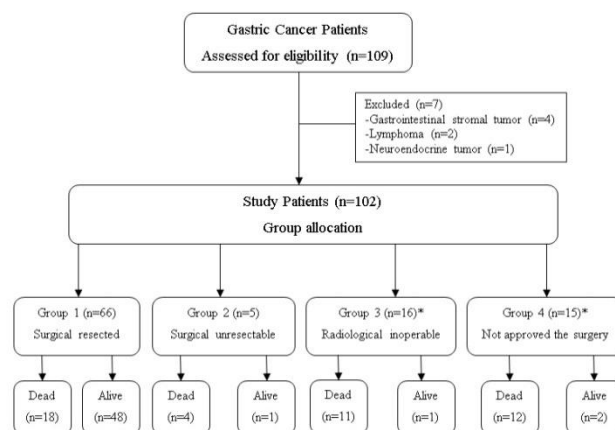

Figure 1: Flowchart of the study (* Five patients, four in group 3, one in group 4, left the follow-up, and their outcomes are unknown)

Sixty-six patients underwent surgical resection (group 1). Forty-two of these patients received total gastrectomy (proximal tumors) and 24 subtotal gastrectomy (distal tumors).

Additional operations were performed in six patients (three splenectomy, one distal pancreatectomy, one cholecystectomy and resection of liver segment 5, one nephrectomy). Average dissected lymph node count was 34.3 (10-65) and mean lymph node metastasis count was 10.9 (range 0-60). Five patients were diagnosed as inoperable during surgery (group 2) and only one of them received palliative gastro-enterostomy.

Post-operative complications occurred in 18 (25.4%) patients (11 surgical site infection, three pulmonary infection, two anastomosis leakage, one renal failure, one sub-phrenic abscess, one pulmonary emboli, one evisceration). Three patients (4.2%) died within the first month after operation, and accepted as surgical mortality.

Six-teen patients were determined as inoperable by radiologic evaluation (group 3). Fifteen patients (group 4) were evaluated as operable; however they didn't give consent for surgery and received only oncological treatment (chemo/radiotherapy). All patients operated or not, were directed to the medical oncology department for further treatment (chemo/radiotherapy).

No differences were detected among groups in comparison of gender with P of 0.250 (table 1). However, age distribution was different between groups with P of 0.043 because group 4 is formed by older patients with mean age of 71.0 (10.0).

Table 1: Demographics of study patients

		Group 1 (n=66)	Group 2 (n=5)	Group 3 (n=16)	Group 4 (n=15)	P-value
Age, Mean (SD)		63.2 (12.2)	66.8 (6.7)	59.0 (13.3)	71.0 (10.0)	[1] 0.043*
Gender,	Male	40 (60.6)	5 (100)	9 (56.3)	11 (73.3)	[2] 0.250
n (%)	Female	26 (39.4)	0 (0)	7 (43.8)	4 (26.7)	

SD: Standard deviation, [1] Anova test, [2] Chi-square test, *$P<0.05$

Survival analysis

Five patients abandoned the follow-up therefore 97 patients were evaluated in survival analysis. Median survival of all patients was 10.0 (1.5) months (range 0 - 79).

Survival analysis showed that patients in group 1 (14.0 (5.1) months) had better survival than other groups ($P=0.011$, table 2, figure 2). Male patients showed better survival than female patients (14 (1.9) vs. 6 (1.8) months, $P=0.002$, table 3, figure 3).

Table 2: Kaplan Meier survival analysis of groups

	Estimate (month)	Std. Error	95% Confidence Interval Lower Bound	Upper Bound	P-value (Log Rank)
Group 1	14.000	5.078	4.048	23.952	0.011
Group 2	5.000	2.191	0.706	9.294	
Group 3	4.000	0.569	2.884	5.116	
Group 4	6.000	0.617	4.790	7.210	
Overall	10.000	1.513	7.034	12.966	

Group 1: Resected surgically, Group 2: Surgically unresectable, Group 3: Radiological inoperable, Group 4: Not approved the surgery
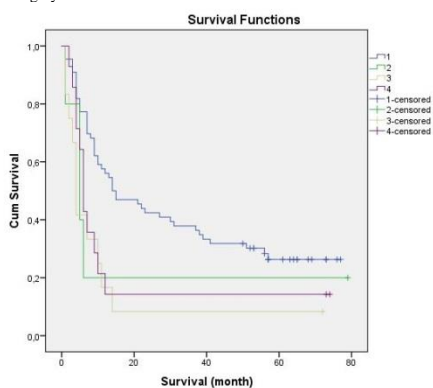

Figure 2: Survival analysis between groups (Group 1: Resected surgically, Group 2: Surgically unresectable, Group 3: Radiologically inoperable, Group 4: Not approved the surgery)

Further analysis was performed for group 1 patients as a subgroup analysis. No differences were detected in respect to location of the tumor ($P=0.884$, table 4, figure 4). Advanced TNM stages showed less survival ($P<0.001$, table 5, figure 5).

Table 3: Survival analysis of genders

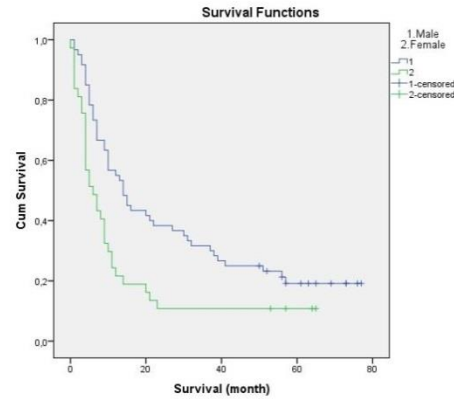| Gender	n (%)	Median Estimate (month)	Std. Error	95% Confidence Interval Lower Bound	Upper Bound	P-value (Log Rank)
Male	65 (63.7)	14.000	1.935	10.207	17.793	0.002
Female	37 (36.3)	6.000	1.824	2.425	9.575	
Overall	102 (100)	10.000	1.228	7.593	12.407	

Figure 3: Survival analysis according to genders

Table 4: Survival analysis of tumor locations in group 1

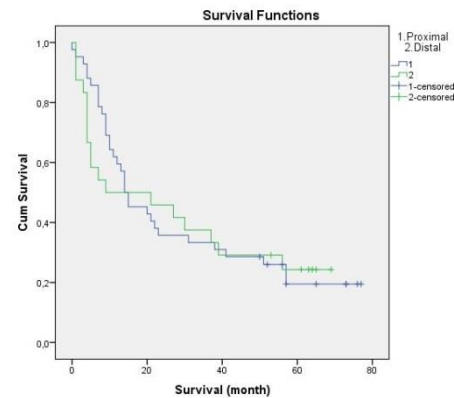| Location	n (%)	Median Estimate	Std. Error	95% Confidence Interval Lower Bound	Upper Bound	P-value (Log Rank)
Proximal	42 (63.7)	14.000	3.780	6.590	21.410	0.884
Distal	24 (36.3)	9.000	13.472	0.000	35.405	
Overall	66 (100)	14.000	4.062	6.038	21.962	

Figure 4: Survival analysis of tumor locations in group 1

Table 5: Survival analysis according to TNM stages in group 1

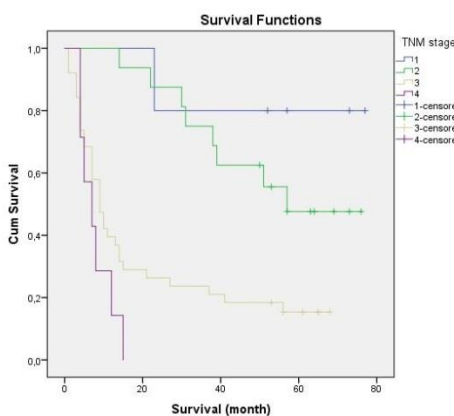| TNM stage	n (%)	Median Estimate (month)	Std. Error	95% Confidence Interval Lower Bound	Upper Bound	P-value (Log Rank)
Stage 1	5 (7.8)	.	.	.	.	<0.001
Stage 2	16 (23.4)	57.000	.	.	.	
Stage 3	38 (57.9)	9.000	1.539	5.984	12.016	
Stage 4	7 (10.9)	7.000	2.619	1.868	12.132	
Overall	66 (100)	14.000	5.078	4.048	23.952	

Figure 5: Survival analysis according to TNM stages in group 1

Discussion

In this study, we found that the patients with gastric cancer who were unresectable detected during operation, radiological inoperable detected preoperatively and refused the operation, has showed lesser survival than the patients who were suitable for surgery and underwent surgical resection.

Gastric cancer is still a significant cause of death among cancers even though its incidence reduced and resectability rate got higher since the second half of the 20th century in western countries. Prognosis is still poor despite the fact that post-operative mortality rate lowered from 14% to %6 in western countries. Poor survival time is mostly related to late diagnosis and local/regional recurrence (4). Excluding Japan, early gastric cancers' 5-year-survival-time is 25-40%. Male incidence is 1.8-2 times higher than female. Incidence gets higher with age and mostly seen in the 6th and 7th decades. Various retrospective multivariate analyses indicate that age is an irrelevant factor for prognosis [4-6]. In our study, we observed that most gastric cancer patients are diagnosed in an advanced stage and surgically resected patients' mortality rate is 3%, and male incidence is 1.75 times higher and 66.6% of the patients are the 6th and 7th decades of age, just as in literature.

Stage, lymph node metastasis and penetration through the gastric wall are significant for prognosis. Prognosis in early stage can be very good; however, 60% of the patients have already lost the chance to have surgery when diagnosed. Most of these patients are either in the 3rd or 4th stage [7]. Metastatic lymph node count and extent of serosa invasion negatively affect prognosis. Five-year-survival for stage IA is 90%, 80% for stage IB, 65% for stage II, 50% for stage IIIA, 30% for IIIB and 5% for stage IV, and operated stage I and IV patients' five-year-survival are found to be 88.2% and 3.7% respectively. These results were to be found relevant statistically in univariate and multivariate analyses [8]. In our study, we found tumor stage to be a significant factor for prognosis just as in literature. Mortality rate of our operated gastric cancer patients were found to be 0% for early stage, 18.2% for stage II, 67.8% for stage III and 100% for stage IV.

Lymph node metastasis is also an important prognostic factor. Huang et al.'s [9] retrospective analysis of 236 D2 resected patients with gastric cancer originating from cardia and fundus showed that adequate lymph node resection and low count of metastatic lymph nodes (lower than 30%) increase survival time. Know et al. [10] grouped patients according to their ratio of dissected lymph nodes to metastatic lymph nodes as 0%, 1-25%, 26-50 and higher than 50% and reported 5-year-survival as 83%, 66%, 30% and 23% respectively. In a multi-centric study, among retrospectively scanned 777 advanced stage gastric cancer patients' survival time, the most significant difference was found to be the threshold of 11 metastatic lymph node (chi-square value 42.88, HR:2,523, CI 95%, 1.913, 3.329 ($P<0.001$)-cox rational risk model). According to this conclusion, patients were divided into 2 groups, lymph node metastasis count 10 or below and above 10. Prognosis was found to be better in patients with lymph node metastasis count lower than 10 [11].

Stewart et al.'s [12] study with 1654 gastric cancer patients showed us lymph node involvement higher than 20% is the most important poor prognostic factor. It was stated that extended lymphadenectomy may increase the excised metastatic lymph node count and therefore prolong survival time. Metastatic lymph node count and stage is a very important prognostic factor.

Primary treatment of gastric cancer is surgery, and enough surgical resection margins are the most important prognostic factor [12]. Sixty-six patients have gone under resection and D2 lymph node dissection in our series. Average dissected lymph node count was 34.3 (10-65) and mean lymph node metastasis count was 10.9 (0-60). As we mentioned before, stage, lymph node metastasis and penetration through the gastric wall are significant factors for prognosis. Therefore, improvements in population screening for gastric cancer are of high importance to diagnose and treat in an early stage just like all cancer types. Screening programs like endoscopic procedures and tumor marker analysis's are found to be successful in diagnosis of gastric cancer in an early stage, especially in the Far East countries [13,14].

Adequate surgical resection is also an important prognostic factor for gastric cancer and most of cancer as stated in the literature [15-18]. This also means adequate lymph node dissection which makes it a surgical prognostic factor. We strongly believe that D2 lymph node dissection should be standardized for gastric tumors just as the Swedish studies made in meso-colic resection for rectum tumors.

In the United States, the reported overall 5-year relative survival rate of all people with stomach cancer is approximately 29%. The relative survival rate comes from comparison of the observed survival of stomach cancer to that expected for normal people. In our study, we found 5-year survival as 38.1% in all group. Since we did not studied to reveal relative survival, it is little higher from relative survival reported in the literature [15,19]. Further studies are needed to evaluate relative survival of all people with stomach cancer in our country.

Over the last 30 years, survival rate has improved gradually as new therapeutic modalities emerged. However the overall survival rate reported in the United States is poor due to most stomach cancers are diagnosed at an advanced stage. The stage of the cancer has been reported as the major factor on a patient's prognosis [19]. In our study, we demonstrated the same outcome as reported in literature.

The study has a number of possible limitations. The main limitation of this study is that the number of patients in study groups was small at some level. Future larger studies with definitive statistical results would be of interest. The other limitation was that stage of gastric cancer was not obvious in the patients who refused surgery. Although this study was conducted in one hospital in Turkey, the results may be generalizable to other areas.

Our findings suggest that patients should be more informed about the surgery to decrease refusal and late admissions with more advanced stage, and screening programs should be encouraged. With this study, comparing the study groups and judging a better course of disease may be little excessive interpretation of the statistical analysis. Several

questions remain to be resolved, and aforementioned data found in this study should be proven, in particular. Despite the limitations, this study demonstrates that surgery remains the most effective method in the treatment of gastric cancer.

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