Cumhuriyet Tıp Derg 2012; 34: 173-182
Cumhuriyet Med J 2012; 34: 173-182

Original research-Orijinal araştırma *http://dx.doi.org/10.7197/1305-0028.1191*

Prognostic factors that affect the survival of gastric cancer

Mide kanserinde sağkalımı etkileyen prognostik faktörler

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Abstract

Aims. The purpose of this study is to review the factors that affect the survival and clinicopathological characteristics of gastric cancer cases monitored and treated at our centre. **Method.** 112 gastric cancer patients who admitted to the Radiation Oncology Department of Cumhuriyet University Medical Faculty Research and Application Hospital between 2006 and 2010 were included in the study. The demographic, clinical, and histopathology data of the patients were obtained from the patient files and the hospital records. **Results.** This study analysed data of 112 patients of whom 90 (80%) were men, and 22 (20%) were women. The factors that determined survival were stage of the cancer, T and N stages, high grade, performance status, presence of anemia and hypoalbuminemia, presence of metastasis, extravascular invasion, weight loss, metastatic lymph node ratio (>50%) and a high level of serum CEA and CA19-9. The stage, performance status, anemia at the time of diagnosis were determined as independent prognostic factors that affect survival after performing multivariate analysis. **Conclusion.** Many studies have defined numerous prognostic factors for gastric cancer. In concordance with the literature, this study sets forth that the most important factors in terms of prognosis are the stage, the performance status, and the presence of anemia at diagnosis the time of diagnosis.

Keywords: Gastric cancer, prognosis, anemia, stage, performance status

Özet

Amaç. Bu çalışmanın amacı, kliniğimizde takip ve tedavi edilen mide kanserli vakaların sağkalımını etkileyen faktörleri ve klinikopatolojik özellikleri gözden geçirmektir. **Yöntem.** 2006-2010 yılları arasında Cumhuriyet Üniversitesi Tıp Fakültesi Araştırma ve Uygulama Hastanesi Radyasyon Onkolojisi Bölümüne başvuran 112 mide kanserli hasta bu çalışmaya dahil edildi. Hastaların demografik, klinik ve histopatolojik verileri hasta dosyaları ve hastane kayıtlarından elde edildi. **Bulgular.** Bu çalışmada, 90'ı (%80) erkek ve 22'si (%20) kadın 112 hastanın verisi analiz edildi. Kanserin evresi, T ve N evresi, yüksek grade, performans durumu, anemi ve hipoalbuminemi varlığı, metastaz varlığı, ekstravasküler invazyon, kilo kaybı, metastatik lenf nodu oranı (>%50), yüksek CEA ve CA19-9 seviyesi sağkalımı belirleyen faktörlerdi. Çok değişkenli analizde, evre, performans durumu, tanı anında aneminin olması sağkalımı bağımsız olarak etkileyen prognostik faktörlerdi. **Sonuç.** Mide kanseri için birçok prognostik faktör tanımlamıştır. Bu çalışmada literatürle uyumlu olarak, evre, performans durumu ve tanıda aneminin varlığı en önemli prognostik faktörlerdi.

Anahtar sözcükler: Gastrik kanser, prognoz, anemi, evre, performans durumu

Geliş tarihi/Received: November 23, 2011; **Kabul tarihi/Accepted:** May 03, 2012

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Introduction

Gastric cancer is an important health issue as it is diagnosed at an advanced stage, and it is aggressive even after curative surgery. Gastric cancer is responsible for approximately 934.000 new cases annually (8.6% of new cancer cases). Almost two thirds of cases occur in Eastern Europe, South America, and Asia [1]. Moreover, it is responsible for approximately 700.349 deaths worldwide annually and the case-fatality ratio of gastric cancer is higher in comparison to more common types of cancer (gastric cancer 0.75, Colon cancer 0.52, breast cancer 0.36, prostate cancer 0.33) [1]. The male/female ratio is approximately 1.5/1 [2]. Gastric cancer incidences change according to localization; cardia-originated tumors are five times higher in men [3]. Incidence of gastric cancer is observed more in black people, people with a low socio-economic background, and in developing countries [4]. Complete resection (R0) of the tumor can only be achieved with curative treatment for this illness; however, the extent of lymph node dissection is controversial (D1-D2 dissection) [5, 6]. A major problem in gastric cancer treatment is local recurrence. Local recurrence is observed in 50% of patients after surgery, and 52%-68% in autopsy series[7]. For patients that only undergo surgery the 5-year survival rate decreases by 50% for T2 patients, 45% for T3 patients, and 15% for T4 patients; for patients with lymph node involvement the survival rate decreases 20% for N1 patients, and 10% for N2 patients [7]. The most important prognostic factors are lymph node metastasis and the depth of the tumor. The prognosis of patients without lymph node involvement is better in comparison to patients that have lymph node involvement. Lymph node metastasis is positively correlated with the depth of the tumor. After curative surgery, serosal invasion and lymphovascular invasion are important prognostic factors for patients with negative lymph node involvement [8-12]. CEA and CA19-9 level increase by 30%-40% in primary stomach neoplasms; however, these high-level antigens generally occur in advanced stage [13, 14].

We aimed to determine the factors that affect the survival of our registered gastric cancer patients in the light of the current literature.

Material and method

The demographic, clinical, and histopathological data of gastric cancer patients registered at the Radiation Oncology Department of Cumhuriyet University Medical Faculty Research and Application Hospital between 2006 and 2010 were obtained from patient files and hospital records. The current state of patients that had not come to the follow-up visits in the last three months was obtained by calling them in order to form their survival analysis. The patient's performance status was evaluated according to the ECOG (Eastern Cooperative Oncology Group) scoring system at the time of their registration. Patients with a haemoglobin level below 12 g/dL for anemia and albumin level below 3.2 g/dL for hypoalbuminemia, and a weight loss exceeding 10% of their weight monthly were included in this study. The stage of patients was determined according to the 2002 UICC/AJCC TNM classification. Patients without sufficient data were eliminated from the study. The Chi-Square test, the Mann-Whitney U test, and Kaplan-Meier analysis were used for analyses. Multivariate analysis (Cox regression analysis) was used to assess the independent factors that have an effect on survival. P values ≤ 0.05 were considered as statistically significant throughout the study.

The Ethical Committee of Cumhuriyet University Faculty of Medicine approved this study in concordance with the declaration of Helsinki.

Results

This study analysed data belonging to 112 patients; 90 (80%) men, and 22 (20%) women. The median age of the patients was 62 (min-max=31-85). The median age for both genders was similar (Men=60, Women=58; p=0.284). Twenty-five (22%) patients had a history of cancer in the family, 52 (46%) had a history of smoking, and 31 (28%) had a disease that caused co-morbidity such as diabetes mellitus and hypertension. The

performance status of patients were assessed at registration; 60 (54%) patients were identified as ECOG0, 38 (34%) patients were identified as ECOG1, and 14 (12%) patients were identified as being above ECOG1Fifty seven (51%) patients had a haemoglobin level below 12g/dL, and 37 (34%) patients had an albumin level below 3.2 g/dL. A high preoperative CEA level was observed in 25 (29%) patients, and a high preoperative CA19-9 level was observed in 22 (25%) patients. Regarding tumor site, 21 (19%) tumors were localized in the proximal part of the stomach (gastroesophageal junction, fundus and cardia) and 91 (81%) tumors were localized in the distal part of the stomach (corpus, antrum and plyrous). Forthy nine (45%) patients were diagnosed in the early stage, whereas 63 (55%) patients were diagnosed in the advanced stage. According to the histopathological diagnosis, the most frequent type of pathology was adenocarcinoma; observed in 107 (95%) patients. The majority of patients were Grade III; 41 (47%) patients. Perineural and vascular invasion was not identified in pathology reports of patients diagnosed in the advanced stage who unable to undergo curative surgery. Perineural invasion was seen in 46 (60%) of patients in which perineural and lymphovascular invasion was detected, while lymphovascular invasion was seen in 52 (67%) patients. Advanced staged patients generally underwent only biopsy; 24 (%22) patients, 48 (43%) patients underwent a total gastrectomy, 39 (35%) underwent a subtotal gastrectomy. The lymph node dissection type of patients that underwent surgery at other centres could not be completely identified because they admitted to our clinic after surgery was performed at another health center, and they lacked surgical epicrisis. But most patients had undergone adequate lymph node dissection. The median tumor size was 5cm, the median number of examined lymph nodes was 19, and the median number of involved lymph nodes was 5. Six (5%) patients had been treated only with surgery 20 (18%) patients with surgery + chemotherapy, 62 (55%) patients with surgery + chemoradiotherapy, 17 (15%) advanced stage patients with chemotherapy, 2 (2%) patients only with radiotherapy, and 5 (5%) patients with palliative treatment. Table 1 illustrates the demographic characteristics of the patients. Twenty eight (68%) advanced stage patients had a Grade III, 37 (67%) patients had anemia, 26 (56%) patients had perineural invasion, 27 (52%) patients had lymphovascular invasion, 18 (75%) patients had a high CEA level, 18 (82%) had a high CA19-9 level, 27 (82%) had extravascular invasion, 23 (85%) patients had metastatic lymph nodes ratio (>50%), and 35 (68%) patients had a performance status above ECOG 0. All of these characteristics were statistically significant in the advanced stage. Table 2 illustrates p values of characteristics in the early and advanced stages. The median follow-up was 18 months (1-64 months); the median survival for all stages was 28 months, and 2-year survival was 53%. A median survival time could not be obtained for Stage I and Stage II patients; the 2-year survival was 90% for Stage I patients, and 76% for Stage II patients. The median survival was 22.2 months for Stage III patients, and 12.4 months for Stage IV patients; the 2-year survival was 37% for Stage III patients, and 20% for Stage IV patients. According to the univariate analysis, stage, T and N stages, metastatic lymph node ratio (involved lymph node/examined lymph node), weight loss, performance status, anemia, hypoalbuminemia, grade, CEA, CA19-9, extravascular invasion, metastasis at time of the diagnosis, and metastasis developed during follow-up were determined as factors that have an effect on survival. Perineural and lymphovascular invasion, tumor size and site have no statistical significant by univariate analysis. Table 3 illustrates factors that have an effect on survival. According to the multivariate analysis, early and advanced stage, the patient's performance status, and anemia at the time of the diagnosis were determined as independent prognostic factors that have an effect on survival. Table 4 illustrates multivariate analysis results. Local recurrence was seen in 3 (3%) patients, while distant metastasis developed in 17 (18%) patients. Distant metastasis was seen in the liver of 13 (76%) patients; the lungs, bones, the supra region of neck and the intraabdominal were the other regions where metastasis developed.

Table 1. Demographic characteristics of gastric cancer patients.

		n	%
Gender	Male	22	20
	Female	90	80
Family Cancer history	Yes	25	22
Smoking	Yes	52	46
Co-morbidity	Yes	31	28
ECOG PS	0	60	54
	1	38	34
	>1	14	12
Anemia	Hgb<12 g/dL	57	51
Hypoalbuminemia	Alb<3.2 g/dL	37	34
CEA	High	25	29
CA19-9	High	22	25
Histopathology	Adenocarcinoma	88	78
	Signet ring cells	19	17
	Neuroendocrine	4	4
	Sarcomatoid carcinoma	1	1
Tumor site	Gastroesophageal junction	2	2
	Fundus, cardia	19	17
	Corpus	53	47
	Antrum, pylorus	38	34
Surgery Type	Subtotal gastrectomy	39	35
	Total gastrectomy	48	43
	Biopsy	24	22
Stage	I	12	11
	II	37	34
	III	44	40
	IV	19	15
Grade	I	14	16
	II	32	37
	III	41	47
Perineural Invasion	+	46	60
Lymphovascular Invasion	+	52	67
Tumor size	Median size: 5 (1-15 cm)		
Number of examined lymph nodes	Median number of examined lymph nodes : 19 (2-41)		
Number of involved lymph nodes	Median number of involved lymph nodes: 5 (0-30)		
Treatment	Surgery	88	79
	Chemotherapy	101	90
	Radiotherapy	64	57

Discussion

Even though numerous studies have successfully indentified prognostic factors for gastric carcinoma, treatment is still not at the desired level due to the aggressive progress of the tumor. Studies in literature have shown two important prognostic factors as the degree of penetration of the tumor through the gastric wall and the presence of lymph node involvement. Gunji et al. [15] demonstrated that gastric cancer patients with four and more positive lymph nodes were likely to suffer recurrence and had a shorter survival. Okajima [16] indicated that the anatomic distribution of a metastatic lymph node had prognostic importance. Marchet et al. [17] conducted D1, D2, and D3 dissections on 1853 gastric cancer patients; they identified that the metastatic lymph node ratio was the most important prognostic factor, regardless of the dissection type and number of metastatic lymph nodes.

Table 2. Characteristics of early and advanced stage patients.

		Stage I-II n (%)	Stage III-IV n (%)	p
Grade	I	9 (64)	5 (36)	0.004
	II	22 (69)	10 (31)	
	III	13 (32)	28 (68)	
Anemia	No	31 (56)	24 (44)	0.01
	Yes	18 (33)	37 (67)	
Perineural Invasion	No	21 (70)	9 (30)	0.02
	Yes	20 (44)	26 (56)	
Extracapsular Invasion	No	33 (77)	10 (23)	<0.001
	Yes	6 (18)	27 (82)	
Hypoalbuminemia	No	35 (48)	38 (52)	0.167
	Yes	13 (36)	23 (64)	
Lymphovascular Invasion	No	16 (67)	8 (33)	0.209
	Yes	25 (48)	27 (52)	
CEA	Normal	31 (51)	30 (49)	0.026
	High	6 (25)	18 (75)	
CA19-9	Normal	33 (51)	32 (49)	0.006
	High	4 (18)	18 (82)	
ECOG PS	ECOG0	33 (56)	26 (44)	0.008
	ECOG>0	16 (32)	35 (68)	
Lymph node ratio	<%50	44 (72)	17 (28)	<0.001
	≥%50	4 (15)	23 (85)	
Localization	Proximal	10 (48)	11 (52)	0.603
	Distal	40 (44)	51(56)	

Researchers divided patients into two groups based on their examined number of lymph nodes; Group 1 consisted of 1421 patients with more than 15 lymph nodes and group II consisted of 432 patients with 15 or less lymph nodes. In conclusion of univariate analysis, age (>70), tumor site, surgery type, grade, T stage, the anatomical location and number of the metatstatic lymph nodes were deemed important prognostic factors in Group I, while important prognostic factors in Group II were gender, age, tumor site, surgery type, T stage, and the anatomical location and number of the metastatic lymph nodes. According to 2002 UICC/AJCC TNM classifications, the appropriate amount of lymph nodes to be removed during gastric cancer staging is 15 and more lymph nodes [18]. In this study, the median number of examined lymph nodes was 19 (2-41). The two-year survival rate was 86% for N0 patients, 73% for N1 (1-6 involved lymph nodes), 45% for N2 (7-15) patients, 35% for N3 (16 and over) patients, and 6% for Nx patients; in conclusion of univariate analysis the nodal stage had an effect on survival. The two-year survival rate for Nx patients is low as Nx patients are generally in Stage IV. Additionally, prognosis of patients with extravascular invasion in metastatic lymph nodes affected more adversely. In their study, conducted on 1654 patients that had undergone a curative gastrectomy, Siewert et al. [8] identified that metastatic lymph nodes ratio (<%20 and >%20) and the presence of residual disease were two important independent prognostic factors during their 10-year analysis. They determined that the development of postoperative complications, N stage, depth of wall invasion, presence of distant metastasis, tumor size were associated with prognosis. Numerous studies have proven that metastatic lymph nodes ratio is an important prognostic factor; these studies also investigate the prognostic importance of different ratios [8, 17]. In our study, we accepted this ratio as 50%. A lymph node ratio above and below 50% had an effect on survival according to univariate analysis. The two-year survival for patients with a lymph node ratio below 50% was 77%, and the two-year survival for patients with a lymph node ratio above 50% was 34%.

Table 3. Prognostic factors that affect survival according to univariate analysis.

Univariate Analysis		2 year survival (%)	p
Stage	I	90	<0.001
	II	76	
	III	37	
	IV	20	
Grade	I	84	0.009
	II	66	
	III	49	
Perineural Invasion	No	65	0.489
	Yes	60	
Lymphovascular Invasion	No	76	0.079
	Yes	55	
Tumor size	<5 cm	67	0.187
	>5 cm	57	
Lymph node stage	0	86	<0.001
	I	73	
	II	45	
	III	35	
Metastasis at Diagnosis	No	57	0.019
	Yes	25	
Anemia	No	74	0.001
	Yes	31	
Hypoalbuminemia	No	67	<0.001
	Yes	26	
Performance status	ECOG0	72	<0.001
	ECOG>0	34	
CEA	Normal	63	<0.001
	High	31	
CA19-9	Normal	61	<0.001
	High	29	
T stage	I	83	<0.001
	II	87	
	III	60	
	IV	26	
Weight Loss	No	61	0.009
	Yes	38	
Lymph node ratio	<%50	77	<0.001
	>%50	34	
Tumor site	Proximal	64	0.497
	Distal	50	
Metastasis	No	59	0.002
	Yes	20	
Extravascular Invasion	No	73	0.014
	Yes	52	
Age	<65	60	0.029
	>65	40	

Table 4. Independent prognostic factors for multivariate analysis.

Multivariate Analysis		Exp(B)	%95 confidence interval	p
Stage	I-II and III-IV	2,75	1,18-6,44	0,019
Performance status	ECOG0 ECOG>0	2,92	1,34-6,36	0,007
Anemia at Diagnosis	No Yes	2,06	1,02-4,16	0,043

Dockerty [19] reported that the 5-year survival was 100% for tumor invasion just to the mucous membrane, 61% for tumors passing through the mucous membrane, 44% for tumors invading the entire stomach wall, and 15% for tumors with nodal distribution. The British Study Group analysed the tumor site, gross appearance of the tumor, the number of involved lymph nodes, depth of tumor invasion, the nodal stage, and the tumor grade, and concluded that depth of tumor invasion, lymph node involvement, and positive surgery borders were prognostic factors [20]. According to the univariate analysis of our patients, the increased depth of tumor invasion has an adverse effect on survival. The two-year survival rate was 83% in T1 tumor, 87% in T2 tumor, 60% in T3 tumor, and 26% in T4 tumor.Saito et al. [21] stated that the size of the tumor was related to lymphovascular invasion, lymph node metastasis, depth of wall invasion, and differentiation. According to the multivariate analysis, depth of wall invasion, lymph node metastasis, lymphovascular invasion, the size of the tumor were also defined as independent prognostic factors. In conclusion of analyses, prognosis for a tumor size <8cm was better than a tumor size >8cm. However, the adverse prognostic factor of the tumor size is controversial [22, 23]. Due to the fact that the median tumor size was 5cm, the statistical analysis of the tumor size in our study was done based on this value. When patients were analysed between ≤5cm and >5cm, the tumor size did not have an effect on survival. Whereas the two-year survival was 67% for a tumor size ≤5cm and 57% for a tumor size >5cm. However, T and N stages were factors that had an effect on survival according to the univariate analysis; the stages (I-II and III-IV) were independent prognostic factors according to the multivariate analysis. Prognosis was affected adversely by lymphatic, venous, and perineural invasion [24, 25]. Lee et al. [26] analysed 304 patients without lymph node involvement. They demonstrated that lymphovascular invasion and depth of wall invasion were independent prognostic factors for survival. In our study, prognosis was not significantly related to perineural and lymphovascular invasions, even though patients with perineural and lymphovascular invasions were generally in advanced stages. In general, high grade and diffuse-type carcinoma, seen in advanced stages, are adverse prognostic factors. Gross tumoral appearance as described by Borrmann has been shown to have prognostic significance in several large studies. These studies concluded that Borrmann type I and type II (polypoid and ulcerating) cancers seem to have a better prognosis than Borrmann type III and IV (infiltrating cancers and linitis plastica) cancers [27, 28]. But other studies did not confirm this result. While the location of the tumor carries independent prognostic importance, proximal tumors (cardia, gastroesophageal junction) are tumors that display more aggressive behaviour [24]. In our study, analysis was only conducted on proximal and distal localization due to the lack of linitis plastica cases. However, it was determined that tumor localization had no effect on the prognosis of our patients. We believe that this is due to the limited number of patients with proximal tumors. In addition, our study proves that high grade patients are usually in the advanced stages and have a worse prognosis, as stated in literature. Men have a worse prognosis than women, because their tumors are localized generally in cardia [29]. In our study, a statistically significant relationship was not identified between gender and prognosis. Kodera et al. [30] identified a %17 preoperative elevated CEA level and a %16 preoperative elevated CA19-9 level in 663 gastric cancer patients. According to the multivariate analysis of this study, the prognostic importance of CA19-9 was higher in comparison to the prognostic importance of CEA. In our study, 29% of patients had a high CEA level, and 25% of patients had a high CA19-9 level. A high preoperative CEA level had an adverse effect on the prognosis of patients, regardless of all other major prognostic factors being good [31-33]. According to the univariate analysis in our study, a high levels of CEA and CA19-9 had an adverse effect on prognosis. Investigations to date have demonstrated that inflammation-based factors such as elevated serum CRP levels (C-reactive protein), and hypoalbuminemia could be markers to predict malignant potential of the tumor or worse prognosis of patients with gastrointestinal tumors [34-36]. Anemia, high grade, a high level of CEA and CA19-9, perineural invasion, and a bad performance status were seen more in advanced stage

patients. According to the univariate analysis, anemia, hypoalbuminemia, performance status, and weight loss had an effect on prognosis. According to the multivariate analysis conducted on gastric cancer patients, Maehara et al. [37] identified 10 prognostic factors; depth of wall invasion, lymph node involvement, lymph node dissection, tumor size, liver metastasis, peritoneal dissemination, lymphatic invasion, and vascular invasion, lesions in the whole stomach, and lesions in the middle of the stomach were independent prognostic factors. According to the multivariate analysis conducted in our study, the independent prognostic factors were stage, anemia at the time of the diagnosis, and the performance status of the patients. Anemia at the time of the diagnosis made prognosis 2.06 times worse, the performance status made prognosis 2.92 times worse, and the stage made prognosis 2.75 times worse.

In concordance with the literature, our study proves that stage, performance status, and anemia at the time of the diagnosis are the most important prognostic factors that define survival. Identifying prognostic factors of gastric cancer before hand sheds light for clinicians when planning the process and treatment of the illness. We believe that conducting future multi-center studies will be a better approach to increase the number of cases analysed.

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