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Prognostic factors for survival among gastric cancer patients receiving neoadjuvant chemotherapy: A cross sectional study from Turkey

Neoadjuvan kemoterapi alan mide kanseri hastalarında surviye etkili prognostik faktörler: Türkiye'den kesitsel bir çalışma

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Abstract

Aim: Gastric cancer is usually diagnosed once it has reached the advanced stage and is one of the leading causes of cancer-related deaths. We investigated the prognostic factors for survival among gastric cancer patients undergoing neoadjuvant chemotherapy to prolong overall survival.

Methods: A retrospective review was made of patients who underwent surgery for gastric cancer between November 2006 and September 2019. Clinicopathological characteristics were assessed in 46 patients receiving neoadjuvant chemotherapy and 194 patients not receiving neoadjuvant therapy. A Cox regression analysis was used to assess the prognostic factors for survival among the patients receiving neoadjuvant chemotherapy.

Results: The patients receiving neoadjuvant chemotherapy accounted for 19.2% of the total. The tumors in these patients were located primarily in the upper and middle portions (73.9%), to a statistically significant degree (P=0.001). There was no statistical difference in survival between the two groups, although a high number of positive lymph nodes was identified among the patients receiving neoadjuvant chemotherapy as the most significant prognostic factor for survival (P<0.01).

Conclusion: After neoadjuvant chemotherapy, multiple positive lymph nodes are the most important prognostic factor for survival; postoperative chemotherapy protocol can be changed or other methods can be applied together with chemotherapy.

Keywords: Gastric cancer, Neoadjuvant therapy, Prognostic factors, Overall survival

Öz

Amaç: Mide kanseri ileri evrede karşımıza çıkar ve kansere bağlı ölümler arasında en üst sıralarda yer almaktadır. Overall sürviyi uzatmak için neoadjuvan kemoterapi alan mide kanseri hastalarında surviye etkili prognostik faktörleri araştırmayı amaçladık.

Yöntemler: Kasım 2006 - Eylül 2019 tarihleri arasında mide kanseri nedeniyle ameliyat edilen hastalar retrospektif olarak incelendi. Neoadjuvan kemoterapi alan 46 hasta ile neoadjuvan kemoterapi almayan 194 hasta klinikopatolojik özelliklerine değerlendirildi. Neoadjuvan kemoterapi alan hastaların surviye etki eden prognostik faktörleri Cox regresyon analizi ile değerlendirildi.

Bulgular: Neoadjuvan kemoterapi alan hastalar tüm hastaların %19.2'sini oluşturmaktaydı. Bu hastaların tümör yerleşim yeri genellikle üst ve orta yerleşimliydi (%73,9) ve istatistiksel bir farklılık mevcuttu (P=0,001). İki grup arasında sürvi bakımından istatistiksel bir farklılık yoktu. Ancak neoadjuvan kemoterapi alan hastaların pozitif lenf nodu sayısının fazla olması surviye etkili en önemli prognostik faktör olarak bulundu (P<0,01).

Sonuç: Neoadjuvan kemoterapi sonrası pozitif lenf nodu sayısının yüksek olması sürvi bakımından en önemli prognostik faktör olup, cerrahi sonrası kemoterapi protokolü değiştirilebilinir veya kemoterapi ile beraber başka yöntemler uygulanabilinir.

Anahtar kelimeler: Mide kanseri, Neoadjuvan kemoterapi, Prognostik faktörler, Genel sürvi

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Introduction

Gastric cancer is the sixth most common type of cancer around the world, and is among the leading causes of cancer-related death [1]. More than 50% of all gastric cancer cases are diagnosed in the early stage in Asian countries like Japan and South Korea, whereas it is usually diagnosed only after reaching an advanced stage in Western countries, including the United States [2]. Stage at admission is the most important determinant of prognosis for gastric cancer [3]. Depending on the tumor, node and metastasis (TNM) system, the 5-year survival of early stage patients is above 90%, compared to a mean survival of 25% in stage III or stage IV patients, 60% of whom develop local recurrence or distant metastases [3]. The treatment approach to locally advanced gastric cancer varies from region to region around the world. The standard treatment for gastric cancer is perioperative chemotherapy or postoperative adjuvant chemotherapy in Western countries, including the United States, while in Asian countries, adjuvant chemotherapy after D2 gastrectomy is the standard treatment approach [4]. There have been several studies claiming that perioperative chemotherapy in gastric cancer results in decreased tumor diameter, leading to regression in tumor stage, increase in radical resection rates, no rise in postoperative complication rates and improvement in survival [5-7]. That said, there are also ongoing studies aimed at determining which perioperative regime should be applied, and for how long, as the prognostic factors for survival are still not exactly known in patients receiving neoadjuvant chemotherapy [7].

In the present study, we investigate the prognostic factors for survival among patients receiving neoadjuvant chemotherapy due to gastric cancer.

Materials and methods

This retrospective review included 320 patients operated due to gastric cancer in the Health Sciences University Kartal Koşuyolu High Specialty Educational and Research Hospital between November 2006 and September 2019. Patient details were accessed from clinical records and pathology reports. The assessment date for the survival analysis was accepted as August 31, 2020. D2 lymph node dissections were performed in line with the approach recommended by the Japanese Research Society for the Study of Gastric Cancer (JRSSG) [8], and the Tumor, Node, Metastasis (TNM) classification system of the American Joint of Committee on Cancer (AJCC), (8^{th} Edition, 2018) for staging within the study [9]. Of all, 15 patients with positive peritoneal cytology, 10 patients with liver metastasis during surgery, six patients with positive distal or proximal surgical margins, 15 patients who died within the first 90 days, and 28 patients with a depth of wall invasion into the mucosa or submucosa (T1) were excluded from the study. Consequently, the study was completed with 240 patients. Among diffuse-type patients, four were Borrmann classification type III (ulcero-infiltrative). Surgery-related complications were considered as those occurring within the first 30 days following surgery.

Statistical analysis

The normality of the numerical variables was analyzed with a Kolmogorov-Smirnov test, which revealed a non-normal distribution based on $P<0.05$, therefore, median (IQR) values were used. Categorical variables were expressed as numbers and percentages. The patients were divided into two groups based on whether they underwent adjuvant therapy. Chi-square test, a Fisher's exact test and a Mann-Whitney U test were used to determine any statistical differences between the groups within the categorical variables. The survival of the two groups was analyzed with a Kaplan-Meier test, while a log-rank test was used to identify any difference. The prognostic factors among the patients undergoing neoadjuvant chemotherapy were examined with univariate and multivariate analyses using a stepwise Cox regression analysis approach. Statistical analyses were conducted using the SPSS 26 soft version, and a *P*-value of <0.05 was considered statistically significant.

Results

Of the 240 patients included in the study, 19.2% (46 patients) were operated after undergoing neoadjuvant chemotherapy. The patients were divided into two groups, based on whether they received preoperative chemotherapy. The clinicopathological characteristics of the patients were compared between the two groups, and no statistical difference was found in terms of gender, age, tumor diameter, Lauren classification, total number of lymph nodes removed, metastatic lymph node status and stage, presence of vascular invasion, presence of perineural invasion, complication status or length of hospital stay. In contrast, a statistical difference was noted in tumor localization and type of surgery ($P=0.001$) (Table 1).

Table 1: Comparison of clinicopathological characteristics of patients by receipt of neoadjuvant therapy

		Neoadjuvant therapy				
		No		Yes		
		n	%	n	%	*P*-value
Gender	Male	133	68.6%	37	80.4%	0.111
	Female	61	31.4%	9	19.6%	
Location	Upper	41	21.1%	20	43.5%	0.001*
	Middle	48	24.7%	14	30.4%	
	Distal	105	54.1%	12	26.1%	
Type of Surgery	Subtotal	104	53.6%	12	26.1%	0.001*
	Total	90	46.4%	34	73.9%	
Lauren Classification	Intestinal type	59	30.4%	13	28.9%	0.841
	Diffuse type	135	69.6%	32	71.1%	
Depth of invasion	T1	0	0.0%	2	4.3%	0.040**
	T2	25	12.9%	4	8.7%	
	T3	90	46.4%	25	54.3%	
	T4	79	40.7%	15	32.6%	
N stage	N0	60	30.9%	10	21.7%	0.666
	N1	38	19.6%	8	17.4%	
	N2	32	16.5%	10	21.7%	
	N3a	39	20.1%	12	26.1%	
	N3b	25	12.9%	6	13.0%	
Stage	Stage I	15	7.7%	4	8.7%	0.659
	Stage II	73	37.6%	14	30.4%	
	Stage III	106	54.6%	28	60.9%	
Vascular invasion	Negative	71	36.6%	11	23.9%	0.103
	Positive	123	63.4%	35	76.1%	
Perineural invasion	Negative	53	27.3%	17	37.0%	0.196
	Positive	141	72.7%	29	63.0%	
Complications	No	144	74.2%	28	60.9%	0.071
	Yes	50	25.8%	18	39.1%	
		Median	IQR	Median	IQR	
Age		63	53–69	61	52–65	0.071
Tumor size (cm)		5.0	3.5–7.0	4.8	3.0–7.0	0.607
Total number of lymph nodes		24	17–32	26	19–35	0.289
Length of hospital stay (days)		9	8–14	10	8–18	0.253

*Chi-square $P<0.05$, **Likelihood ratio $P<0.05$

The tumor was proximally located in 43.5% and 21.1% of the patients receiving and not receiving neoadjuvant therapy, respectively. Accordingly, 73.9% of the patients receiving neoadjuvant therapy underwent a total gastrectomy, compared with 46.4% of those not receiving neoadjuvant therapy. There

was also a statistical difference in the depth of wall invasion by the tumor between the two groups (P=0.040). Although early stage (T1) patients were excluded from the study, the stage of tumor invasion depth was found to be T1 in two patients receiving neoadjuvant therapy.

There was no statistical difference in survival between the two groups (P=0.571) (Figure 1), with the mean survival of patients receiving neoadjuvant therapy being 56.305(7.545) months, compared to 71.695 (4.878) among those who did not receive neoadjuvant therapy (Table 2).

Table 2: Comparison of overall survival with the Kaplan-Meier method by neoadjuvant chemotherapy status

	Mean(SD)(months)	95% CI	*P*-value
No	71.695(4.878)	62.134-81.256	0.571
Yes	56.305(7.545)	41.516-71.094	
Overall	71.346(4.541)	62.446-80.245	

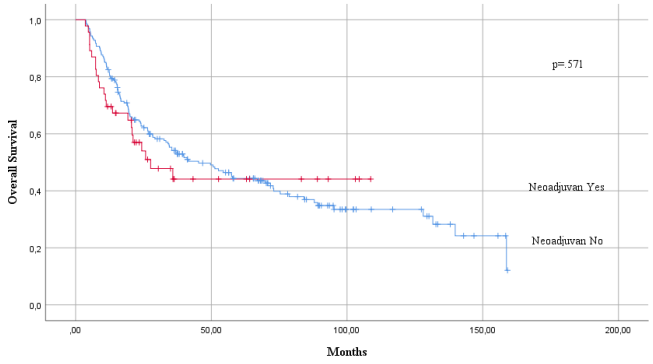

Figure 1: Comparison of survival of patients according to neoadjuvant chemotherapy status.

The prognostic factors for survival among patients receiving neoadjuvant therapy were examined via univariate and multivariate analyses using a stepwise Cox regression analysis. The univariate and multivariate analyses revealed no prognostic significance of gender, age, tumor localization, Lauren classifications, tumor diameter, depth of wall invasion, total number of lymph nodes removed, the presence of vascular invasion or perineural invasion. The N stage, on the other hand, was found to have significant prognostic value in both the univariate and multivariate analyses (P<0.001, P=0.001, respectively) (Table 3). An increased number of positive lymph nodes was a poor prognostic factor for survival among patients receiving neoadjuvant therapy.

Table 3: Univariate and multivariate analyses of prognostic factors for survival among patients receiving neoadjuvant therapy

	Univariate analysis		Multivariate analysis	
	OR (95.0% CI)	*P*-value	OR (95.0% CI)	*P*-value
Gender	0.879 (0.299-2.586)	0.814	2.930 (0.486-17.662)	0.241
Age	1.016 (0.966-1.068)	0.541	1.045 (0.959-1.138)	0.315
Location				
Upper		0.822		0.137
Middle	0.817 (0.296-2.250)	0.695	0.202 (0.035-1.181)	0.076
Lower	1.157 (0.439-3.045)	0.768	1.169 (0.185-7.373)	0.868
Borrmann Classification				
Type I		0.905		0.828
Type II	1.306 (0.380-4.487)	0.672	1.134 (0.142-9.044)	0.905
Type III	1.260 (0.298-3.985)	0.694	0.708 (0.145-3.451)	0.669
Lauren classification	3.225 (0.959-10.912)	0.058	0.615 (0.081-4.643)	0.637
Tumor size	1.082 (0.951-1.231)	0.230	1.305 (0.981-1.736)	0.068
Depth of invasion		0.900		0.988
N Stage				
N0		<0.001**		0.001*
N1	3.683 (0.672-20.180)	0.133	13.560 (1.049-175.315)	0.046
N2	2.073 (0.379-11.336)	0.400	1.380 (0.127-14.964)	0.791
N3a	3.770 (0.782-18.191)	0.098	4.068 (0.402-41.201)	0.235
N3b	39.254 (6.465-238.344)	<0.001	153.897 (8.396-282.031)	0.001
Total number of lymph nodes	0.982 (0.945-1.021)	0.362	0.963 (0.916-1.013)	0.149
Vascular invasion	4.019 (0.940-17.178)	0.061	2.245 (0.148-34.179)	0.560
Perineural invasion	2.186 (0.810-5.899)	0.122	2.039 (0.432-9.624)	0.368

OR: odds ratio, CI: confidence interval, *P<0.05, **P<0.001

Discussion

In Western countries, neoadjuvant chemotherapy is administered as a standard treatment approach in resectable gastric cancer patients with a tumor depth of wall invasion beyond the muscularis propria (T2 and higher) and/or with significant perigastric lymph node involvement [5,6]. In Japan, in contrast, the standard treatment approach to locally advanced gastric cancer is neoadjuvant therapy with S-1 chemotherapy after gastrectomy with D2 lymph node dissection, although there are ongoing studies into the neoadjuvant therapy approach [4]. The aim in neoadjuvant chemotherapy in locally advanced gastric cancer is to diminish the tumor size, and thereby increasing the radical resection rate, and to benefit from its positive effects on survival without increasing postoperative complication rates. Despite the specified benefits, neoadjuvant chemotherapy may rarely lead resectable gastric cancer patients to become unresectable during or after treatment [11]. As such, studies into the optimal treatment approach are ongoing [7].

In the present study, we compared the clinicopathological characteristics of patients receiving and not receiving neoadjuvant therapy, and identified differences in tumor depth of wall invasion, tumor localization and type of surgery between the two groups. The tumors of the patients receiving neoadjuvant therapy had generally a proximal localization, which concurs with the findings of a French study in which the majority of patients were reported to have proximally located gastric tumors, and differences were noted only in R0 resection between the two groups [12].

Several meta-analyses have reported significant improvements in disease-free survival and overall survival in those receiving neoadjuvant chemotherapy, along with no increase in complications or postoperative mortality [3,13,14]. These studies suggest that prolonged survival can be attributed to the neoadjuvant chemotherapy, although no other prognostic factors for survival were noted among patients receiving neoadjuvant therapy. The meta-analysis by Liao et al. [15] reported that neoadjuvant chemotherapy did not increase postoperative morbidity and mortality, and had no effect on overall survival. Likewise, the study by Hashemzadeh et al. [11] reported neoadjuvant chemotherapy to increased resectability in locally advanced gastric cancer, but suggested that more randomized controlled trials were required to establish its effect on survival. In the CRITICS trial, postoperative radiotherapy was administered after perioperative chemotherapy with the same chemotherapy protocol, however no effect on overall survival was seen in those with gastric cancer [16]. No preoperative or postoperative radiotherapy was administered to any of the patients in the present study, and no difference in survival could be identified between the two groups. In the examination of the prognostic factors for survival in the neoadjuvant chemotherapy group, both the univariate and multivariate analyses identified greater postoperative lymph node involvement as the most significant prognostic factor.

Our study is limited by its retrospective and singe-center design, and the low number of patients receiving neoadjuvant therapy.

Conclusion

Gastric cancer is usually identified only once it has reached an advanced stage in countries without a gastric cancer-screening program, and various treatment methods are applied to decrease cancer-related mortality. Neoadjuvant chemotherapy is a treatment method that is used to prolong the disease-specific survival by increasing R0 resectability. In the present study, the most significant prognostic factor for survival was the number of positive lymph nodes among patients receiving neoadjuvant chemotherapy. In the event of postoperative multiple positive lymph nodes being identified in this patient group, postoperative chemotherapy protocol can be changed or other methods can be applied together with chemotherapy. More prospective randomized controlled studies are required in this regard.

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