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MEHMET BİLİCİ

SALİM BAŞOL TEKİN

MUSTAFA KANDAZ

KERİM ÇAYIR

MUSTAFA VECDİ ERTEKİN

See next page for additional authors

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Authors
MEHMET BİLİCİ, SALİM BAŞOL TEKİN, MUSTAFA KANDAZ, KERİM ÇAYIR, MUSTAFA VECDİ ERTEKİN, and HİLAL KIZILTUNÇ ÖZMEN

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The evaluation of the results of adjuvant chemoradiotherapy in patients with gastric cancer: results from a single center in eastern Anatolia

Mehmet BİLİCİ[1], Salim Başol TEKİN[1], Mustafa KANDAZ[2], Kerim ÇAYIR[1], Mustafa Vecdi ERTEKİN[2], Hilal KIZILTUNÇ ÖZMEN[2]

Aim: To evaluate the results of postoperative chemoradiotherapy in patients with gastric cancer. Gastric cancer is an important public health problem in Turkey, especially in the eastern Anatolia region. Surgery is the primary modality for managing early-stage disease, but most patients who undergo a curative resection develop locoregional or distant recurrence. Therefore, the administration of adjuvant treatment in gastric cancer has great importance.

Materials and methods: Operated patients with stage IB-IV (M0) gastric cancer were enrolled in this study. A total of 148 patients with gastric cancer who had completed adjuvant chemoradiotherapy were evaluated retrospectively. Total overall survival (OS), disease-free survival (DFS), median survival, and 3- and 5-year survival were also determined.

Results: Age, lymph node involvement, clinical stage, and surgical margin are prognostic factors that are significantly correlated with the duration of survival. Sex, smoking status, family history, the localization of the tumor, and the type of surgery were found to have no effects on the duration of survival. Tolerable side effects after administration of adjuvant chemotherapy were observed. The median OS and DFS of the patients were found to be 24.56 and 18.1 months, respectively. OS rates for 3- and 5-year survival were 38.3% and 27.6%, respectively.

Conclusion: These findings suggest that adjuvant chemoradiotherapy is a highly effective and important treatment option in the overall survival of operated patients with gastric cancer.

Key words: Gastric cancer, adjuvant chemoradiotherapy, survival, toxicity

Mide kanserli hastalarda adjuvan kemoradyoterapi sonuçlarının değerlendirilmesi: Doğu Anadolu'dan tek merkez sonuçları

Amaç: Mide kanseri Türkiye'de, özellikle de Doğu Anadolu Bölgesi'nde önemli bir sağlık problemidir. Gastrik kanser tedavisinde cerrahi primer modalitedir, fakat küratif rezeksiyon yapılan çoğu hasta lokal-bölgesel veya uzak rekürrensler geliştirmektedir. Bu nedenle mide kanseri tedavisinde destekleyici uygulamalar önem arz etmektedir. Bu çalışmada, bölgemizde sık görülen mide kanserinin postoperatif kemoradyoterapi sonuçlarının değerlendirilmesi amaçlanmıştır.

Yöntem ve gereç: Çalışmaya opere edilmiş evre IB-IV (M0) mide kanserli hastalar dahil edildi. Destekleyici kemoradyoterapiyi tamamlayan toplam 148 mide kanseri hastası geriye dönük olarak değerlendirildi. Toplam genel sağ kalım, hastalıksız sagkalım, ortanca sağ kalım ile 3 ve 5 yıllık sağ kalımlar hesaplandı.

Bulgular: Sağkalım süresi ile ilişkili anlamlı prognostik faktörler yaş, lenf nodu tutulumu, klinik evre ve cerrahi kenar durumu idi. Cinsiyet, sigara kullanımı, aile hikâyesi, tümör yerleşimi ve ameliyat türünün sağ kalım süresi üzerine bir etkisi yoktu. Opere mide kanseri hastaları için adjuvan kemoradyoterapi uygulamasında tolere edilebilir yan etkiler

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[1] Department of Medical Oncology, Faculty of Medicine, Atatürk University, Erzurum - TURKEY
[2] Department of Radiation Oncology, Faculty of Medicine, Atatürk University, Erzurum - TURKEY
Correspondence: *Mehmet BİLİCİ, Terminal Cad. Akçam Aprt. Kat: 1 No: 5Erzurum - TURKEY*
E-mail: memetbilici@mynet.com

gözlemlendi. Hastaların ortanca tam sağ kalımı 24,56 ay, hastalıksız sağkalımı 18,1 ay olarak saptandı. Üç ve beş yıllık tam sağkalım oranları da sırasıyla % 38,3 ve % 27,6 olarak bulundu.

Sonuç: Bu sonuçlar, adjuvan kemoradyoterapinin opere edilmiş mide kanserli hastaların tedavisinde önemli bir seçenek olduğuna işaret etmektedir.

Anahtar sözcükler: Mide kanseri, adjuvan kemoradyoterapi, sağkalım, toksisite

Introduction

Gastric cancer is the second leading cause of cancer deaths, with 1 million new cases a year throughout the world (1). The incidence of gastric cancer is highest in eastern Turkey and lowest in the western region. The incidence ranges from 9.6/100,000 in males to 5.7/100,000 in females (2). According to the data of the Ministry of Health, gastric cancer occupies first place among cancer incidence in males and second place in females around Erzurum and Van (3).

Despite improvements in staging methods and operative techniques, 5-year survival rates following curative surgery range between 30% and 40%, and local (lymph node) and systemic (liver, bone) recurrences are common. Thus, the concept of adjuvant treatment in gastric cancer has developed (4). The study of phase III intergroup (INT-0116) by Mac Donald et al., which combined chemotherapy and adjuvant external radiotherapy in 2001, has changed the standards. The median survival was 36 months in the chemotherapy group versus 27 months in the surgery group, and the 3-year survival rate was 52% and 41%, respectively (5,6). However, a consensus has not been reached on the standard treatment in operated gastric cancer over time. Ongoing and future studies will clarify this further.

In the present study, we aimed to evaluate the results of postoperative chemoradiotherapy for gastric cancer, which is common in our region.

Materials and methods

The patients who were enrolled in this study had been operated on for gastric cancer and were referred to the clinics of the departments of Medical Oncology and Radiation Oncology of Atatürk University's Faculty of Medicine between December 2000 and August 2009. Of these patients, those who underwent total gastric resection and received adjuvant chemoradiotherapy (1 cycle of chemotherapy + chemoradiotherapy + 3 cycles of chemotherapy) for pathological stage IB-IV (TNM0) were included, and those patients who exhibited metastases were excluded from this study. Scanning for metastases was performed using computerized tomography before the surgery and patients who had not undergone preoperative staging were evaluated by the same method before treatment.

The TNM Classification of Malignant Tumors of the American Joint Committee on Cancer was used for staging. The patients' data were obtained from the hospital archives. The information for those patients who did not attend follow-up visits was obtained by telephone interview or from the Birth Registration Office. The patients in this study were enrolled sequentially, but cases for which data could not be obtained were excluded from this work.

Patients without distant metastases who were transferred to our clinic for postoperative adjuvant treatment were staged. The patients between stage IB (T1N1M0) and IV (TNM0), or those who underwent inadequate surgery, were included. The following was administered to patients as adjuvant chemotherapy: 1 cycle of FUFA (5-FU at 425 mg/m^2 between days 1 and 5, and FA at 20 mg/m^2 between days 1 and 5) plus 1 cycle of chemotherapy 1 month later (from 1.8 Gy/day to a total of 45 Gy/day, simultaneously with radiotherapy, 5-FU at 420 mg/m^2 and FA at 20 mg/m^2, on the first 4 days and for the last 3 days of the radiotherapy), and 3 cycles of FUFA (5-FU at 425 mg/m^2 between days 1 and 5 and FA at 20 mg/m^2 between days 1 and 5) at 1-month intervals, 1 month after the completion of radiotherapy. FUFA chemotherapy, in the same doses, was administrated once a week and for 5 weeks consecutively to some patients, especially older patients.

Definition of the toxicity profile was done in accordance with the Common Terminology Criteria for Adverse Events Version 4.0 of the National Cancer

Institute (7). Data were expressed as percentages, mean or median values (±), and standard deviations (X ± SD). The analyses of the categorical variables were performed using the chi-square test. The statistical analysis was performed using SPSS 15 for Windows. The Kaplan-Meier test was used for the evaluation of the survival analysis. The effects of variables of potential prognostic importance on survival were compared using the log-rank test in one-variable analysis. Confidence intervals (CIs) of 95% were calculated. $P < 0.05$ was considered significant.

Results

Table 1 illustrates the characteristics of 148 patients enrolled in the present study. The median age was 57 years (range: 28-81 years). When the patients were separated according to age, 11 (7.4%) patients were under 40 years of age, 20 (13.5%) were aged between 40 and 49 years, 54 (36.5%) were between 50 and 59 years, 41 (27.7%) were between 60 and 69 years, and 22 (14.9%) were over 70 years. In accordance with the Eastern Cooperative Oncology Group, the initial performance of all patients in the study was 0 or 1. From the geographic data, 73 (49.3%) patients were from Erzurum, 17 (11.5%) from Erzincan, 17 (11.5%) from Ağrı, 12 (8.1%) from Kars, 8 (5.4%) from Van, 8 (5.4%) from Bayburt, 7 (4.7%) from Iğdır, 2 (1.4%) from Muş, 1 (0.7%) from Artvin, 1 (0.7%) from Gümüşhane, 1 (0.7%) from Rize, and 1 (0.7%) from Tunceli. Distant metastasis sites at the last follow-up were the liver in 32.4% of cases, the liver and peritoneum in 13.5%, the peritoneum in 8.1%, the liver and bone in 4.7%, the lung in 3.4%, and the surrenal gland in 0.7%. No distant metastasis was found in 37.8% of the patients. The rate of smoking was found to be 43.9% (65 patients) among the patients; 4 (6.2%) of the smoking patients were female and 61 (93.8%) were male. There was a statistically significant difference between males and females ($P < 0.001$). According to Lauren's classification, 30 (39.5%) of the patients with intestinal-type gastric cancer were female and 46 (60.5%) were male. Of the patients with diffuse-type gastric cancer, 24 (33.3%) were female and 48 (66.7%) were male. No statistically significant relationship was detected between Lauren's classification and sex ($P = 0.273$).

By the end of the study, 88 (59.5%) of the patients had died. When mortality rates were compared, a statistically significant difference was found between males and females ($P = 0.013$).

Regarding the side effects (Table 1), none of the patients exhibited neutropenic fever. No disease-related mortality was observed in patients who received radiotherapy.

The difference between histopathological type and sex was not statistically significant ($P = 0.503$). When patients ≤60 years of age and those ≥61 years of age were compared, no statistical significance was detected between the histopathology and patient groups ($P = 0.129$). Similarly, histopathology and the localization of the tumor were compared and no statistical significance was detected ($P = 0.353$).

The histopathological type was compared with the stage of lymph node involvement (N0, N1, and N2) and the localization of the tumor, and no statistical significance was seen in either comparison ($P = 0.109$ and $P = 0.353$, respectively). The smoking status and histopathological subtypes were compared and no statistical significance was observed ($P = 0.534$). There was no statistically significant difference between the localization of the tumor and Lauren's classification ($P = 0.127$). However, intestinal-type gastric cancer was found to be more common in proximal tumors (65.9%). Given the comparison between proximal gastric cancers (cardia and fundus) and distally located cancers (antrum and pylorus), it was also found that intestinal-type gastric cancer was statistically significantly more common in proximally located cancers ($P = 0.04$).

After a median follow-up of 28.46 months (range: 5.60-84), the median overall survival (OS) time of the 148 patients was 24.56 ± 2.9 months (18.76 months minimum and 30.36 months maximum, with 95% CI). The 3- and 5-year survival rates of the patients were 38.3% and 27.6%, respectively (Figure 1). The median disease-free survival (DFS) time of 115 patients (DFS data for 33 patients could not be obtained) was 18.13 ± 2.35 months (13.52 months minimum and 22.74 months maximum, with 95% CI). The 3- and 5-year DFS rates of the patients were 24.5% and 13.9%, respectively (Figure 2). Table 2 illustrates the survival of the patients. Lymph node involvement, clinical stage, and the extent of surgical

Table 1. General features of the patients.

		n	%
Sex	Female	54	36.5
	Male	94	63.5
Age	≤60	89	60.1
	≥61	59	39.9
Smoking status	Yes	65	43.9
	No	83	56.1
Family history	Yes	14	9.5
	No	133	89.9
Localization	Cardia + fundus	44	29.1
	Corpus	32	21.6
	Antrum	49	33.1
	Pylorus	12	8.1
	Whole stomach	11	7.4
Histopathology	Well-differentiated adenocarcinoma	36	24.3
	Moderately differentiated adenocarcinoma	38	25.7
	Poorly differentiated adenocarcinoma	46	31.1
	Mucinous adenocarcinoma	12	8.1
	Signet ring cell adenocarcinoma	16	10.8
Stage	IB	3	2
	II	27	18.1
	IIIA	68	45.9
	IIIB	34	23
	IV	16	10.8
Background	Yes	9	6.1
	No	139	93.9
Hematological toxicity	No	116	78.4
	Grades 1-2	24	16.2
	Grades 3-4	8	5.4
Mucositis	No	108	73
	Grades 1-2	37	25
	Grades 3-4	3	2
Diarrhea	No	132	89.2
	Grades 1-2	16	10.8
	Grades 3-4	0	0
Final status	Alive	60	40.5
	Dead	88	5.9
T stage	T1	1	0.7
	T2	16	10.8
	T3	130	87.8
	T4	1	0.7
Lymph node (N stage)	N0	20	13.5
	N1	75	50.7
	N2	38	25.7
	N3	15	10.1
Lauren's classification	Intestinal	76	51.4
	Diffuse	72	48.6
Type of surgery	Total gastrectomy	93	62.8
	Distal subtotal gastrectomy	55	37.2
Surgical margin	Positive	14	9.5
	Negative	134	90.5
Number of removed lymph nodes	<15	52	35.1
	≥15	96	64.9
Type of dissection	D0	3	2.0
	D1	26	17.6
	D2	119	80.4
Relapses or metastases	No local-regional recurrence or distant metastasis	37	25
	Local-regional recurrence	19	12.8
	Local-regional recurrence + distant metastasis	13	8.8
	Distant metastasis	46	31.1
	Unknown	33	22.3

margin were determined as statistically significant prognostic factors correlated with the OS and DFS times ($P < 0.05$). We also demonstrated that sex, smoking status, family history, the localization of the tumor, and the type of surgery exerted no effect on survival time (Table 2).

Discussion

Surgical approach remains the milestone of the curative treatment for gastric cancer (8). However, the 5-year survival rates of patients who undergo curative surgery for locally advanced gastric cancer are low due to high rates of distant metastasis and

Table 2. Survival analyses according to the patients' features.

	n	Median OS (m)	95% CI		P	3-year OS (%)	5-year OS (%)	n	Median DFS (m)	95% CI		P	3-year DFS (%)	5-year DFS (%)
			Min.	Max.						Min.	Max.			
General	148	24.56	18.76	30.36		38.3	27.6	115	18.13	13.52	22.74		23.4	13.9
Sex					0.276							0.271		
Female	54	26.70	11.54	41.85		45.2	37.3	44	18.13	14.01	22.24		33.9	16.9
Male	94	24.23	17.73	30.73		35.1	23.1	71	15.56	7.93	23.20		19.2	5.3
Age					0.009							0.44		
≤60	89	30.26	21.90	38.62		43.9	30.3	70	18.76	12.96	24.56		24.8	11.6
>61	59	18.80	13.30	24.29		30.4	23.7	45	15.36	11.93	18.80		21.6	17.3
Smoking					0.16							0.33		
Yes	65	21.80	17.42	26.17		32.5	24.5	49	14.90	6.85	22.94		18.1	14.5
No	83	28.06	20.61	35.51		43.3	29.7	66	18.43	14.31	22.55		27.5	13
Localization					0.54							0.14		
Cardia + fundus	44	24.23	22,11	26.34		35.4	26.2	35	16.93	11.64	22.22		25.7	12.8
Corpus	32	22.10	18.50	25.69		39.1	11.2	24	18.43	1.06	35.80		12	-
Antrum	49	34.56	20.91	48.22		46.8	36.7	39	23.23	13.10	22.36		33.6	23
Pylorus	12	20.76	11.60	29.93		37.5	28.4	8	9.3	0.00	19.54		16.7	-
Whole stomach	11	22.66	10.65	34.67		24.2	12.1	9	15.33	0.43	30.23		11.1	-
Lymph node involvement					<0.001							<0.001		
N0	20	72.73	12.36	133.09		60.3	54.1	15	-	-	-		73.1	73.1
N1	75	37.53	28.07	46.99		50.1	38.5	57	23.23	15.07	31.39		27.5	15.1
N2	38	23.10	15.25	30.94		19.9	5.3	32	12.96	7.80	18.13		7.9	-
N3	15	10.43	5.80	15.06		6.7	-	11	6.93	5.42	8.44		-	-
Stage					<0.001							<0.001		
IB	3	12.56	-	-		50	-	-	-	-	-		-	-
II	27	72.73	51.75	93.71		80	64	21	-	-	-		71.6	71.6
IIIA	68	30.26	19.84	40.68		40.7	29.1	51	18.72	15.49	22.03		19.3	5.1
IIIB	34	20.93	12.93	28.93		19.1	5.1	28	12.80	8.18	17.41		8.4	-
IV	16	10.43	4.16	16.70		12.5	-	12	6.93	4.89	8.97		-	-
Type of surgery					0.21							0.48		
Total gastrectomy	93	24.23	20.44	28.02		35.1	25.1	72	16.13	9.96	22.30		21.1	12.5
Distal subtotal gastrectomy	55	33.20	19.55	46.84		43.8	31.8	43	18.76	15.23	22.29		27.7	17.3
Type of dissection					0.23							0.05		
D0	3	16.96	1.87	32.06		-	-	3	10.26	3.33	17.20		-	-
D1	26	22.10	18.79	25.40		24.1	19.3	20	16.13	11.87	20.39		11.4	-
D2	119	28.06	18.37	37.76		43.9	31.2	92	24.46	14.89	34.04		27.2	17.3
Surgery margin					0.01							0.003		
Positive	14	14.73	11.56	17.89		39.9	27.8	11	8.10	6.23	9.97		-	-
Negative	134	26.26	18.54	33.98		23.6	11.8	104	18.76	13.72	23.80		26.2	15.5

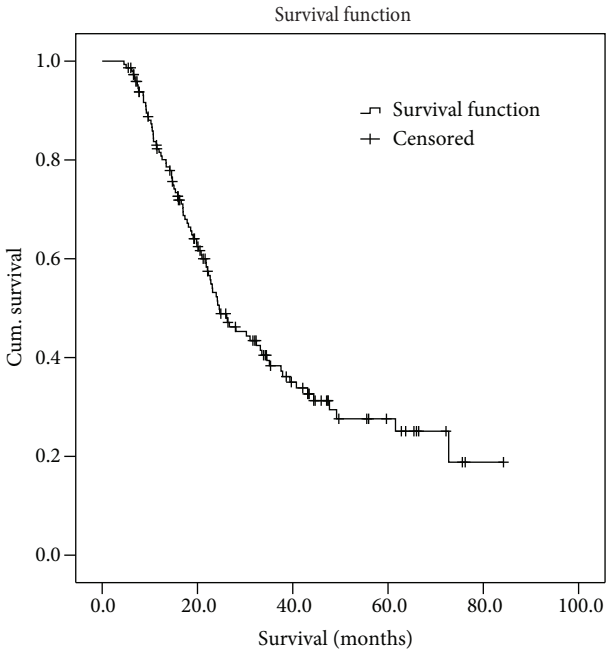

Figure 1. Overall survival time.

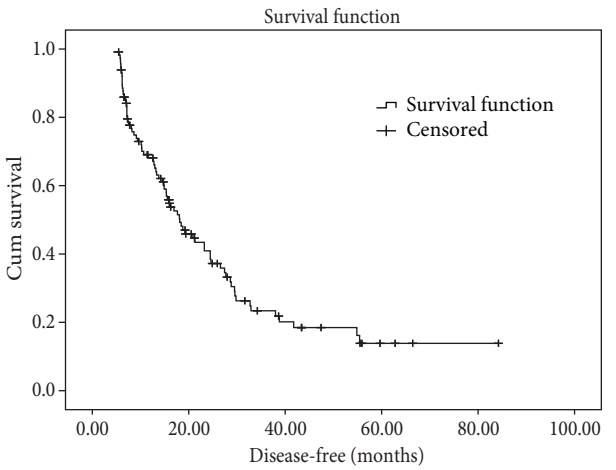

Figure 2. Disease-free survival time.

local recurrence (9). Long-term survival was poor with surgery alone in T3-4 tumors and lymph node-positive tumors (10). Once relapse has occurred, curative interventions generally fail. Therefore, the primary aim of ongoing studies is to prevent relapse (11,12).

Gastric cancer is generally relatively resistant to radiotherapy, which has been shown to have limited benefits in palliation of symptoms in the advanced-stage disease (13). In a randomized study conducted for this purpose, external beam radiation therapy was evaluated. The British Stomach Cancer Group randomized 4336 therapy-naive patients (no adjuvant radiotherapy or chemotherapy) with stage II and III disease, who underwent gastric resection. The 5-year survival rates were found to be 20% in the adjuvant radiotherapy group and 12% in the surgery group ($P > 0.2$). Local-regional recurrence was found to be statistically significantly lower in the adjuvant chemotherapy group (10% versus 27%) (14). The exact benefits of adjuvant radiotherapy alone have not been elucidated yet.

In a study conducted in 1984, Moertel et al. (15) found benefits in adjuvant chemotherapy plus radiotherapy. Statistically significant improvements were obtained in both relapse-free survival and overall survival in the adjuvant treatment group (5-year survival was 23% versus 4%, $P < 0.05$). Rates of local-regional relapse were found to decrease with adjuvant therapy (54% with the surgery alone, 39% with chemoradiotherapy). Since 10 patients in the experimental arm rejected the treatment, a probable bias is considered to have influenced the results of the study.

In a phase III intergroup (INT-0116) study by MacDonald et al., patients with postoperative stage IB-IVM0 gastric and gastroesophageal junction adenocarcinoma were randomized into groups. Surgery alone or surgery plus combination chemotherapy (FUFA: 5-FU and leucovorin) with simultaneous radiotherapy (45 Gy) were performed in the groups (5). Our study was similar to the study protocol by MacDonald et al. The administration of chemotherapy in 3 cycles rather than 2 cycles, following the chemoradiotherapy, was the only difference in our study. The patient characteristics of the intergroup (INT-0116) study were similar to those of our study. In both studies, although the rates varied, the most common tumor (T) stage was T3. Regarding toxic effects, 17% of the patients discontinued the treatment due to the toxic effects of the chemoradiotherapy. Due to toxicity, 3 (1%) patients died. Hematologic and gastrointestinal toxicities were the most commonly observed side effects (5). The toxic effects were less common in our study compared to the study mentioned above. In our patients, there was no treatment related mortality.

In parallel with the intergroup (INT-0116) study, hematologic (leucopenia-neutropenia) and gastrointestinal toxicities were observed to be more common in our study. In our study, the most common toxicities were of the hematological and gastrointestinal types, as was seen in the intergroup study. However, our toxicity rates were lower than in that trial. Our low toxicity rates can be explained by the administration of the FUFA regimen once a week for 5 weeks, instead of 5 days consecutively. Furthermore, the lower incidence of toxic effects was probably caused by preventive measures, new developments in radiotherapy, and a short patient follow-up period. Because of the retrospective nature of our study, the assessment of toxicity may be problematic and unhealthy, and this condition should be taken into consideration.

The adjuvant therapy was observed to result in an increase in DFS and 3-year OS after a 5-year follow-up period. The median survival was found to be 36 months in the chemotherapy arm and 27 months in the surgery-alone arm, and the 3-year survival rates were 52% in the chemotherapy arm and 41% in the surgery-alone arm. The hazard ratio was 1.35 (95% CI, 1.09 minimum, 1.66 maximum; P = 0.005) in the surgery-alone group compared to the chemoradiotherapy arm. In the present study, the median OS was 24.56 months (95% CI, 18.76 minimum, 30.36 maximum), and the 3- and 5-year OS was 38.3% and 27.6%, respectively. This difference in survival is likely associated with higher rates of T3 (87.8%) in the T staging, and higher rates of stage IIIA (45.9%), stage IIIB (23%), and stage IV (10.8%) in the clinical staging. Additionally, the surgical margin was negative in treated patients in the intergroup study, whereas we detected 9.5% surgical margin positivity in our study. While some concerns were raised regarding the surgery performed in the intergroup (INT-0116) study and high rates of D0 (54%) lymphadenectomy, the primary benefit of this regimen was suggested by some researchers to remove the deficiencies of the suboptimal surgery (16). In our study, in parallel with the intergroup study, the differences among dissection groups did not show statistical significance (P = 0.237). However, although there was no significant difference between the dissection groups for DFS (P = 0.05), the value for D2 dissection was 24.46 months. Despite continuing debate about D2 dissection, due to the high rate of bad prognostic factors such as histopathology (poorly differentiated + mucinous + signet ring cell adenocarcinoma rate, 50%), clinical stage (stage III + IV rate, 78.7%), and T stage (stage T3 + T4 rate, 88.5%), adjuvant radiotherapy was used. In a study by Wanebo et al. (17), the results from 18,346 gastric cancer patients were evaluated. No increase was reported in the median survival rate (D2: 19.7 months, D1: 24.8 months) and the 5-year survival rate (D2: 26.3%, D1: 30%) in patients who underwent D2 nodal dissection compared to those who underwent D1 dissection. In 1987, Shiu et al. (18) examined 200 gastric cancer patients and demonstrated that there was no difference in morbidity between D1 and D2 lymphadenectomies. Several studies evaluating the limits of lymphadenectomy in gastric cancer have been conducted. In 2009, Ha et al. (19) retrospectively investigated 1760 patients from a single center who had been operated on by the same surgeon. The aim was to demonstrate the effects of adjuvant chemotherapy on survival in stage IV (M0) gastric cancer patients who had been operated on previously. Patient characteristics were similar in the groups with and without adjuvant chemotherapy. The age was lower in the adjuvant treatment group (P < 0.001). There was no statistical significance between lymph node metastases and T stage (P = 0.65 and P = 0.20, respectively). Time to progression was 17 months on average (between 1 and 120 months). The 3- and 5-year DFS rates were longer in the chemotherapy group compared to the nonchemotherapy group (38.4% and 32% in the chemotherapy arm and 17.86% and 8.9% in the nonchemotherapy arm, respectively; P = 0.015). Similarly, the 3- and 5-year disease-specific survival rates were statistically significantly higher in the chemotherapy group (52.3% and 39.6% in the chemotherapy arm and 30.6% and 24.5% in the nonchemotherapy group, respectively; P = 0.001). In our study, we also had 16 (10.8%) patients without distant metastases who had been operated on previously and received adjuvant treatment subsequently. Although adjuvant treatment regimens were highly heterogeneous in the study by Ha et al., all of the patients received the same treatment in our study. The median OS of stage IV patients was found to be 10.43 months (CI: 4.16 minimum, 16.70 maximum), and the 3- and 5-year survival rates were

12.5% and 0%, respectively, in our study. The stage-related survival time was found to be statistically significant (P = 0.001).

In conclusion, age, lymph node involvement, clinical stage, and the extent of surgical margin are prognostic factors associated with survival time (P < 0.05). Sex, smoking status, family history, the localization of the tumor, and the type of surgery had no effects on survival time. Tolerable side effects were generally observed in adjuvant chemotherapy administered in gastric cancer patients who had been operated on previously. Our retrospective study concluded that adjuvant chemoradiotherapy in gastric cancer patients is a crucial adjuvant treatment option that prevents relapses and increases survival time.

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