Int J Clin Exp Med 2014;7(9):2656-2666
www.ijcem.com /ISSN:1940-5901/IJCEM0001654

Original Article

Evaluation of prognostic factors and survival results in gastric carcinoma: single center experience from Northeast Turkey

Emine Canyilmaz[1], Gulsen Soydemir[1], Lasif Serdar[1], Gonca Hanedan Uslu[2], Asli Sahbaz[1], Fatma Colak[1], Mustafa Kandaz[1], Zumrut Bahat[1], Adnan Yoney[1]

[1]Department of Radiation Oncology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey; [2]Department of Radiation Oncology, Kanuni Research and Education Hospital, Trabzon, Turkey

Received August 1, 2014; Accepted August 26, 2014; Epub September 15, 2014; Published September 30, 2014

Abstract: Objective: To evaluate the prognostic factors affecting overall survival (OS), disease-free survival (DFS), and survival among patients undergoing chemoradiotherapy (CRT) for locally advanced gastric carcinoma. Methods: Between January 2001 and May 2014, 257 patients who presented to our clinic with a diagnosis of stage I-IIIC gastric cancer were evaluated. The male/female ratio of the cases was 2.02:1 and the median age was 55.16±11.8 (20-80) years. Four of the cases (1.6%) were stage IA, 13 (5.1%) were stage 1B, 41 (16%) were stage IIA, 40 (15.6%) were stage IIB, 50 (19.5%) were stage IIIA, 51 (19.8%) were stage IIIB, and 58 (22.6%) were stage IIIC. Results: The mean follow-up time was 22.5 months (3.3-155.0); loco-regional recurrence was noted in 34 (13.2%) patients who underwent postoperative chemoradiotherapy, and metastases were observed in 108 (42%) patients. The median OS duration was 26.7 months (95% confidence interval, 20-33.5) and the 2-, 5-, and 10-year OS was 52.8% (standard error [S.E.] 0.032), 36.1% (S.E. 0.032), and 26.9% (S.E. 0.034) respectively. The median DFS was 53.7 months and the 2-, 5-, and 10-year DFS were 58.9% (S.E. 0.034), 47.4% (S.E. 0.037), and 40.7% (S.E. 0.042), respectively. In multivariate analysis of prognostic factors, advanced T stage ($p<0.0001$), advanced nodal stage ($p=0.001$), and surgical margin status ($p<0.0001$) were related to decreased OS and DFS. Conclusion: R1 resection, advanced T stage, and advanced nodal stage were adverse prognostic factors in gastric cancer patients who had undergone CRT after the operation.

Keywords: Chemoradiotherapy, gastric cancer, stage, surgical margin

Introduction

Gastric cancer is prevalent in many countries around the world [1]. Surgical resection is the only potentially curative treatment for gastric cancer, and 30%-50% of patients can be treated operatively with curative intent [2-4]. However, patient survival remains poor, especially in patients with T3-4 tumors and/or lymph node metastases with surgery alone, and the 5-year survival rate of 20-30% in such cases is disappointing [5-7]. The high rates of relapse or distant metastases after resection make it important to consider adjuvant treatment for patients with resected gastric cancer.

In recent years, many studies have shown that a combination of chemotherapy (CT) and radiotherapy (RT) may reduce locoregional failure and improve survival in patients with gastric cancers [8]. The Intergroup 0116 (INT-0116) trial, which involved 556 patients with gastric cancer, the largest phase III trial comparing chemoradiotherapy versus observation, showed that adjuvant chemoradiotherapy (CRT) prolonged overall survival (OS) and relapse-free survival (RFS). This study established adjuvant CRT as the new standard of care after high-risk surgery for gastric cancer in the United States. The biggest disadvantage of this adjuvant treatment, despite its survival benefits, is its quietly high toxicity rate. The reported non-completion rate reported in this study was 34% [9, 10]. Subsequently, in 2005, Kim et al. [11] published the results of an observational study suggesting clinical benefit for postoperative CRT. This study consisted of 544 patients who

received D2 lymphadenectomy and were treated with postoperative adjuvant CRT. It shows that postoperative adjuvant CRT significantly prolonged OS and RFS.

In this study, patients who received postoperative adjuvant CRT at our clinic between January 2001 and May 2014 with a diagnosis of stage I-IIIC gastric cancer were analyzed. The aim of this study was to retrospectively evaluate the results of this treatment and prognostic factors affecting survival.

Material and methods

In this study, 257 patients who presented at our clinic between January 2001 and May 2014 with a diagnosis of stage I-IIIC gastric cancer were evaluated retrospectively. Patient information was obtained through files, conversations with patients, or their relatives directly and/or by phone calls. We recorded data about demographic information, chemotherapy regimen, radiation therapy information, local recurrence status, and distant metastasis status. Staging of patients was performed in accordance with the staging system of the American Joint Committee on Cancer, 7th edition, 2010 TNM. Performance evaluation was performed according to the Eastern Cooperative Oncology Group (ECOG). The staging system from the Radiation Therapy Oncology Group (RTOG) was used to evaluate treatment toxicity.

Treatment

RT was performed between January 2001 and June 2011 in a two-dimensional planning system via the Co60 and/or linear accelerator (6-10 MV), and after June 2011 via the linear accelerator (6-18 MV) apparatus with a three-dimensional planning system. Until June 2011, RT was applied as parallel opposed fields (anterior-posterior and posterior-anterior) at fractions of 1.8-2 Gy daily, for a total of 45 Gy. After June 2011, three-dimensional conformal RT (3D RT), or the Intensity-Modulated Radiation Therapy (IMRT) technique, was performed at fractions of 1.8-2 Gy daily for a total of 45-50.4 Gy. The RT field included the tumor bed, as well as regional nodes that were perigastric, celiac, local para-aortic, splenic, suprapancreatic, pancreaticoduodenal, and porta hepatic, and extended 2 cm beyond the proximal and distal margins of resection.

CT (fluorouracil, 425 mg/m^2/day, and leucovorin, 20 mg/m^2/day) was initiated on day 1 and was followed by CRT beginning 28 days after the start of the initial cycle of chemotherapy. The second course of CT was given for 4 days with fluorouracil (400 mg/m^2/day) and leucovorin (20 mg/m^2/day) on the first four and the last three days of RT. After the RT course, the first-course CT scheme was repeated as adjuvant therapy for 3 months.

Follow-up

Patient follow-up was performed for the first 2 years at intervals of 3 months and thereafter for every 6 months, and consisted of a clinical examination, a complete blood count, liver function tests, and thoracic and abdominal computed tomography scanning when clinically indicated.

Endpoints

OS was defined as the duration from diagnosis to the last follow-up or date of death. DFS was defined as the duration from surgery to recurrence or metastasis.

Statistical methods

Data evaluation and statistical analyses were performed using SPSS version 13 software. OS and DFS were calculated using the Kaplan-Meier method. To examine the difference in survival between groups, the log-rank test was used, and the Bonferroni correction was used to make comparisons among groups. For multivariate analysis, independent factors predicting survival were analyzed using Cox regression analysis. A type-1 error level of less than 5% was considered significant.

Results

Patient characteristics

During the period from 2001 to 2014, a total of 257 patients were examined and diagnosed as having stage I-IIIC gastric cancer. The median age was 55±11.8 (range, 20-80). There was a strong predominance of males (172 patients, 67%) compared with females. Furthermore, 89.9% (231) of patients had adenocarcinoma and 9.7% (25) had signet ring cell carcinoma (SRC) while only 0.4% (1) of the cases had car-

Table 1. Patient and tumor characteristics

Characteristic	N (%)
Gender	
Male	172 (67%)
Female	85 (33)
Age (y)	
Mean ± SD	55.16±11.8
Range	20-80
Tumor size (cm)	
Mean ± SD	7±4.88
Range	1-20
Tumor histologic	
Adenocarcinoma	231 (89.9%)
Signet ring cell carcinoma	25 (9.7%)
Carcinoid	1 (0.4%)
Histologic grade	
Grade 1	33 (12.8%)
Grade 2	80 (31.1%)
Grade 3	63 (24.5%)
Grade 4	77 (30%)
Unknown	4 (1.6%)
Tumor location	
Linitis plastica	13 (5.1%)
Cardia	41 (15.9%)
Corpus	60 (23.3%)
Antrum	140 (54.5%)
Unknown	3 (1.2%)
T Stage	
T1A	5 (1.9%)
T1B	7 (2.7%)
T2	41 (16%)
T3	72 (28%)
4A	126 (49%)
T4B	5 (1.9%)
Node Status	
N0	50 (19.5%)
N1	65 (25.3%)
N2	59 (23%)
N3A	67 (26.1%)
N3B	16 (6.2%)
Stage	
Stage IA	4 (1.6%)
Stage IB	13 (5.3%)
Stage IIA	41 (16%)
Stage IIB	40 (15.6%)
Stage IIIA	50 (19.5%)
Stage IIIB	51 (19.8%)
Stage IIIC	58 (22.6%)
LVI	

cinoid tumor. Of the tumors, 54.5% (140) were located in the antrum, 23.3% (60) in the corpus, 15.9% (41) in the cardia, and 8.1% (13) in the linitis plastica. The surgical margin was negative in 163 cases (63.4%), positive in 30 (11.7%), and close (defined as <2 mm) in 56 cases (21.8%). Information on the status of surgical margins could not be obtained in 8 cases (3.1%). Thirty-two (12.4%) patients who received curative therapy did not complete their total radiation course due to radiation toxicity. The median RT dose for curative treatment was 45 Gy (range; 21.6-54). Patient characteristics are summarized in **Table 1**.

Local and distant recurrence

The mean follow-up time was 22.5 months (3-155), and loco-regional recurrence was noted in 34 (13.2%) patients who underwent postoperative CRT, while metastases were observed in 108 (42%) patients. Both metastasis and recurrence were noted in 28 (10.9%) patients. Among 34 patients with local recurrence, 12 patients had positive surgical margins, 15 patients had close surgical margins, 7 patients had negative surgical margins, and all local recurrences were observed within the radiation fields. Twenty-four cases had undergone D1 resection, while 10 had D2 resection. Among 34 patients with local recurrence, 16 patients had positive lymphovascular invasion, whereas 18 patients had negative lymphovascular invasion. The distribution of metastatic regions included the liver in 38 (14.9%) patients, lung in 22 patients (8.6%), bone in 18 (7.1%) patients, peritoneal carcinomatosis in 17 patients (6.6%), and others in 13 (5%) patients. A total of 162 (63%) patients died during the follow-up period and 95 (21.7%) patients survived for the duration of the follow-up period (**Table 2**).

No	129 (50.2%)
Yes	115 (44.7%)
Unknown	13 (5.1%)
PNI	
No	168 (65.4%)
Yes	75 (29.2%)
Unknown	14 (5.4%)
Type of surgery	
Total gastrectomy	97 (37.7%)
Subtotal gastrectomy	160 (62.3%)
Type of dissection	
D1	133 (51.8%)
D2	119 (46.3%)
Unknown	5 (1.9%)
The number of lymph nodes removed during operation	
Mean ± SD	16.4±11.1
Range	5-66
Surgical margin	
Negative	163 (63.4%)
Close	56 (21.8%)
Positive	30 (11.7%)
Unknown	8 (3.1%)
RT Technique	
Conventional	204 (79.4%)
Conformal	13 (5.1%)
IMRT	40 (15.6%)
Total RT dose (Gy)	
Mean ± SD	45±4.02
Range	21.6-54
Treatment break	
Yes	110 (42.8%)
No	147 (57.2%)
Treatment break (days)	
Mean ± SD	2±3.2
Range	0-17

Abbreviations: LVI, lymphovascular invasion; PNI, perineural invasion; IMRT, Intensity-Modulated Radiation Therapy.

Table 2. Details of relapse

Site of relapse	n	(%)
Local	34	13.2
Distant	108	42
Local + Distant	28	10.9
Liver	38	14.9
Lung	22	8.6
Bone	18	7.1
Peritoneal carcinomatosis	17	6.6
Other	13	5

Survival

The median OS was 26.7 months (95% CI, 20.12-33.3) and the 2-, 5-, and 10-year OS was 52.8% (S.E. 0.032), 36.1% (S.E. 0.032), and 26.9% (S.E. 0.034), respectively (**Figure 1**). The median DFS was 53.7 months (95% CI, 31.4-76.1), and the 2-, 5-, and 10-year DFS were 58.7% (S.E. 0.034), 47.3% (S.E. 0.037), and 40.5% (S.E. 0.041), respectively (**Figure 2**).

In univariate analysis, age (≤50 and >50), gender, tumor histology, tumor size (≤4 and >4 cm), tumor grade, tumor location (antrum, corpus, cardia, linitis plastica), T stage (1, 2, 3 or 4), nodal involvement (N0, N1, N2, or N3), stage (1, 2, or 3), lymphovascular invasion (LVI), perineural invasion (PNI), type of surgery (total or partial gastrectomy), surgical margin status (positive, close, or negative), the number of lymph nodes taken out during surgery (≤15 vs. >15), dissection type (D1 or D2), interruption of therapy, RT dose (≤45 Gy vs. >45 Gy), and RT technique (conventional, 3D-RT, or IMRT) were investigated as prognostic factors that could affect OS and DFS. Factors such as age (p=0.005), tumor grade (p<0.0001), tumor size (p=0.001), LVİ (p< 0.0001), PNİ (p<0.0001), T stage (p<0.0001), nodal involvement (p< 0.0001), stage (p<0.0001), tumor location (p=0.038), type of surgery (p=0.026), and surgical margin status (p<0.0001) yielded a better statistically significant OS. Among these factors, tumor histology (p<0.0001), tumor grade (p<0.0001), tumor size (p=0.001), LVİ (p<0.0001), PNİ (p<0.0001), T stage (p<0.0001), nodal involvement (p<0.0001), stage (p<0.0001), and surgical margin status (p<0.0001) yielded a better statistically significant DFS. The results of the univariate analysis are summarized in **Table 2**.

Based on multivariate analysis of these prognostic factors, we found that tumor grade (p=0.001), T stage (p<0.0001), nodal involve-

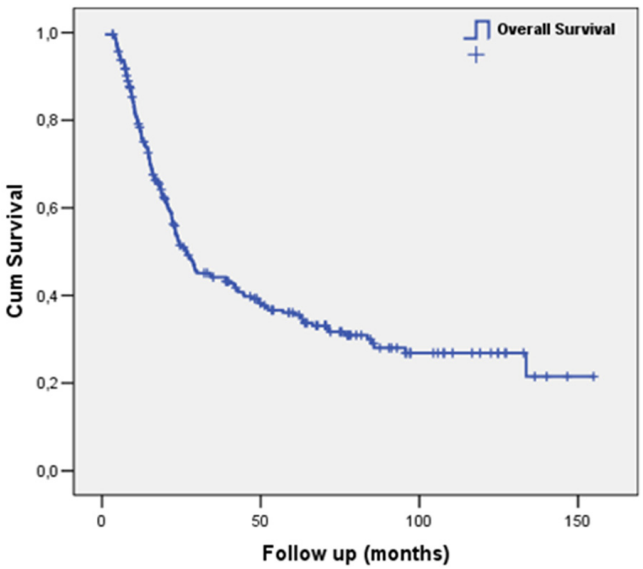

Figure 1. Overall survival.

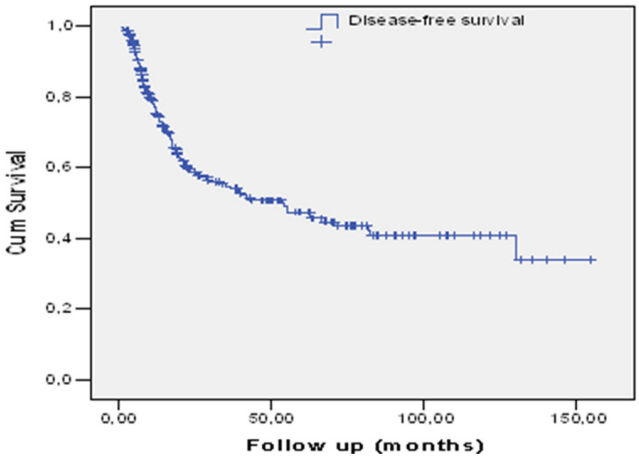

Figure 2. Disease free survival.

ment (p=0.001), and surgical margin status (p<0.0001) were related to OS in a statistically significant manner (**Table 3**). We also found that T stage (p<0.0001), nodal involvement (p=0.048), stage (p=0.019), surgical margin status (p=0.019), and RT dose (p=0.049) were related to DFS in a statistically significant manner (**Table 4**).

Discussion

In Western countries, most patients with gastric cancer present with advanced disease and have poor OS [12]. Surgical resection remains the cornerstone of potentially curative treatment. Five-year survival rates following surgery alone range from 26% to 8%. However, even after microscopically radical (R0) surgical resection, the disease recurs in most patients [13]. In the past decade, neoadjuvant and adjuvant treatment strategies have improved OS and have therefore become the standard of care [9]. Adjuvant combined CRT has become standard of care in the United States following the landmark Intergroup 0116 trial. In a recent update of the INT-0116 study, the benefit of adjuvant CRT after radical (R0) resection for gastric cancer was confirmed [10]. In our study, while the median OS was 26.7 months, the 2-, 2.5- and 10-year OS were found to be 52.8%, 36.1%, and 26.9%, respectively; these rates are consistent with those in the literature (**Figure 1**). The median DFS was 53.7 months and the 2-, 5-, and 10-year DFS were 58.9% (S.E. 0.034), 47.4% (S.E. 0.037), and 40.7% (S.E. 0.042), respectively (**Figure 2**).

Worldwide, gastric cancer is seen more commonly in men than in women, with a male/female ratio ranging from 1.5 to 2. There is a sharp increase in stomach cancer rates in individuals over the age of 50 [14]. Most individuals diagnosed with stomach cancer are between their late 60s and 80s. In our study, the median age of the patients was 55 years (20-80), and the male/female ratio was 2/1; this is consistent with the literature. Some studies report better survival rates for women [15]. Curtis et al. [16] showed that the prognosis was better in women according to age and stage. In our study, sex had no effect on survival rate. Age at diagnosis was a strong and independent prognostic factor, and our findings from univariate and multivariate analyses were not similar to those of previous reports indicating better survival in younger patients.

Tumor size and grade were other significant factors that affected the survival probability in gastric cancer patients in our study. This finding was similar to a study that pointed to a higher hazard ratio of death for patients with larger tumors or worse tumor grade of tumor [17]. Orsenigo et al. [18] also drew similar conclusions with respect to tumor size in a univariate analysis. Our findings in univariate analysis were similar with those of previous reports and indicated better overall survival and disease-

Table 3. Results of log-rank univariate analysis for overall survival and disease-free survival

Variable	n	Median Survival (95% CI)	*p* value	Median disease-free survival (95% CI)	*p* value
Age (year)					
≤50	87	44.5 (15-74)	0.005	55.2 (13.4-97)	0.343
>50	170	22.4 (18.2-26.6)		39.7 (14.3-65.1)	
Gender					
Male	172	26.7 (15-38.5)	0.925	55.2 (25.9-84.6)	0.812
Female	85	26.5 (21.6-31.3)		33.4 (2.3-64.4)	
Tumor diameter (cm)					
≤4 cm	88	60.7 (27-94.4)	0.010	29.7 (13.1-46.2)	0.021
>4 cm	145	23.8 (18.9-28.7)			
Tumor histologic					
Adenocarcinoma	231	28.3 (16.5-40)	0.156	55.2 (33.5-76.9)	<0.0001
Signet ring cell carcinoma	25	21.9 (11.7-32.1)		1.9	
Carcinoid	1	14.5		25.5 (10.9-40.1)	
Histologic grade					
G1-G2	113	63.1 (45.8-80.4)	<0.0001	70.6	<0.0001
G3	63	23 (17-29)		29.7 (0-102.5)	
G4	77	15 (11.2-18.7)		16.2 (12-20.5)	
Tumor location					
Linitis plastica	13	11.1 (3.6-18.7)		25.7 (10.7-40.7)	
Kardia	41	22 (16-28)	0.038		0.236
Korpus	60	41.6 (23.6-59.6)		19.4 (0-54.4)	
Antrum	140	28.3 (12.3-44.3)		-53.7 (23.9-83.5)	
T stage					
T1-2	53	83.6	<0.0001	81.9 (33-130.9)	<0.0001
T3	72	(58.7-108.5)		-	
T4	131	-15.1 (13.3-17)		15.4 (12-18.8)	
Node status					
N0	50	85.7 (62.9-108.6)		-	
N1	65	63.6 (35.8-91.4)	<0.000	66.5	<0.0001
N2	59	22.1 (17.4-26.9)	1	40.7 (6.6-74.8)	
N3	83	12.9 (10.2-15.6)		13 (9.9-16.2)	
Stage					
Stage 1	17	83.6 (42.7-124.5)	<0.0001	66.5 (59.5-73.6)	<0.0001
Stage 2	81	95.6		-	
Stage 3	159	16 (13.2-18.9)		17.6 (14.6-20.7)	
LVI					
No	129	51.6 (35.1-68.1)	<0.0001	-	<0.0001
Yes	115	18.7 (13.3-24.1)		19.8 (15.3-24.2)	
PNI					
No	168	42.4 (25-59.7)	<0.0001	81.9	<0.0001
Yes	75	15.8 (11.2-20.4)		19.1 (13.3-24.8)	
Type of surgery					
Total gastrectomy	97	22.1 (17-27.3)	0.026	28.7 (5.5-51.9)	0.069
Partial gastrectomy	160	34.5 (21-47.9)		66.5 (31.6-101.5)	
Type of dissection					
D1	133	28.3 (19.6-37)	0.963	53.7 (27.8-79.6)	0.944

D2	119	24.5 (18.2-30.8)		55.2 (10.3-100.2)	
Surgical margin					
Negative	163	47.1 (22.6-71.6)	<0.0001	-	<0.0001
Close	56	20.7 (8.1-33.2)		35.3 (22.3-48.3)	
Positive	30	14.7 (9.5-19.8)		11.5 (2.9-20.1)	
RT technique					
Conventional	204	26.7 (17-36.5)	0.318	53.7 (30.4-77)	0.556
Conformal	13	29.9		130.2	
IMRT	40	22.1 (13.7-30.6)		21.7	
RT dose					
≤45	225	27.4 (17.2-37.6)	0.222	53.7 (32-75.3)	0.842
>45	32	19.3 (6.9-31.6)		130.2 (4.3-256.1)	
Interruption of therapy					
No	110	29.9 (13.7-46.1)	0.578	63 (22.3-103.6)	0.675
Yes	147	24 (18.9-29.2)		53.7 (36.1-71.3)	

Abbreviations: LVI, lymphovascular invasion; PNI, perineural invasion; IMRT, Intensity-Modulated Radiation Therapy.

Table 4. Results of multivariate analysis for overall survival and disease-freesurvival by the Cox proportional hazard model

	Overall survival		Disease-free survival	
Variable	Hazard Ratio (95% CI)	*p* value	Hazard Ratio (95% CI)	*p* value
Age (year)				
≤50 vs. >50	1.5 (1-2.4)	0.057	1.1 (0.7-1.8)	0.678
Gender				
Female vs. Male	0.9 (0.6-1.4)	0.666	0.9 (0.6-1.4)	0.606
Tumor diameter (cm)				
≤4 cm vs. >4 cm	1.1 (0.7-1.6)	0.842	1.1 (07-1.9)	0.660
Tumor histology				
Adenocarcinoma & Signet ring cell carcinoma	1.6 (0.9-3.1)	0.147	1.7 (0.8-3.5)	0.178
Histologic grade		0.038		0.422
G1-G2 vs. G3	1.1 (0.7-1.9)	0.715	1 (0.6-1.9)	0.942
G1-G2 vs. G4	1.9 (1.1-3.2)	0.014	1.5 (0.8-2.8	0.225
T Stage		<0.0001		<0.0001
T1-2 vs. T3	0.5 (0.3-1.1)	0.069	0.3 (0.1-0.8)	0.011
T1-2 vs. T4	1.8 (0.9-3.6)	0.085	1.3 (0.6-2.9)	0.517
Node Status		0.002		0.048
N0-1 vs. N2	1.1 (0.5-2.1)	0.859	0.8 (0.4-1.8)	0.583
N0-1 vs. N3	2.3 (1.2-4.4)	0.011	1.7 (0.8-3.6)	0.180
Stage		0.071		0.019
Stage 1 vs. Stage 2	1 (0.3-3.1)	0.937	(0.3-4.5)	0.851
Stage 1 vs. Stage 3	2.3 (0.6-9.2)	0.235	4 (0.8-19.4)	0.085
LVI				
No vs. Yes	1.1 (0.7-1.7)	0.801	1.3 (0.7-2.2)	0.368
PNI				
No vs. Yes	1.4 (0.8-2.2)	0.212	1.4 (0.8-2.5)	0.241
Type of surgery				
Total gastrectomy & Partial gastrectomy	0.9 (0.6-1.3)	0.545	1 (0.6-1.6)	0.967

Type of dissection				
D1 vs. D2	0.9 (0.6-1.3)	0.594	0.2 (0-3)	0.977
Surgical margin		0.034		0.032
Negative vs. Close	1.6 (1.1-2.4)	0.018	1.3 (0.8-2)	0.341
Negative vs. Positive	1.6 (0.9-2.6)	0.096	2.1 (1.2-3.8)	0.009
RT technique		0.283		0.097
Conformal vs. conventional	1.3 (0.5-3.6)	0.640	2.5 (0.7-9)	0.164
Conformal vs. IMRT	2.1 (0.7-6)	0.175	4.1 (1.1-15.3)	0.034
RT dose (Gy)				
≤45 vs. >45	1.1 (0.6-2.2)	0.763	0.4 (0.2-1)	0.049
Interruption of therapy				
No vs. Yes	1 (0.6-1.5)	0.846	0.7 (0.5-1.2)	0.224

Abbreviations: LVI, lymphovascular invasion; PNI, perineural invasion; IMRT, Intensity-Modulated Radiation Therapy.

free survival for small tumor size and grade I or II tumors in gastric cancer.

About 90% to 95% of cancers of the stomach are adenocarcinomas. In our study, the histopathological diagnosis was adenocarcinoma in 89.9% of patients; this is consistent with the literature. The prevalence of SRC in the stomach has been reported to vary from 3.4 to 39% [19]. Maehara et al. [20] reported that patients with SRC are likely to survive longer than those with other types of gastric cancer. This was supported by Otsuji et al. [21], who reported that the survival of patients with early stage SRC carcinoma was improved, whereas patients in advanced stages had poor prognoses, similar to that of other types of gastric cancer. In contrast, Kim et al. [22] and Kwon et al. [23] reported that there was no significant difference in overall survival rates between patients with early stage SRC and those with other types of gastric cancer. These studies demonstrated that the prognosis for patients with advanced stage SRC carcinoma was significantly worse than that for patients with other types of advanced stage cancer. In our study, the histopathological diagnosis was SRC carcinoma in 9.7% of patients and the overall survival rate did not differ between SRC and other cell types, consistent with the literature. Multivariate analysis indicated that patients with signet ring cell histology had a significantly increased risk of dying (relative risk, 1.027; $p>0.10$) in comparison with patients without SRC histology.

Chae et al. [24] showed that the 5-year survival rates of 295 cases of gastric cancer patients after D2 lymph node dissection (N0, N1, N2, N3a, and N3b) were 89.7%, 73.6%, 54.9%, 23.1%, and 5.4%, respectively. Other studies have also found that lymph node metastasis was a prognostic factor for gastric cancer [25-27]. Zhu et al. [28] reported that TNM stage and lymph node metastasis were related to prognosis. In our study, univariate analysis of the entire group of 257 patients with gastric cancer also showed that TNM stage and lymph node metastasis were related to prognosis. The Cox regression model for multivariate analysis showed that positive lymph nodes and TNM stage were both independent prognostic factors.

Lymphovascular invasion (LVI) predicts poor outcome in several malignancies, including gastric cancer [29-31]. In a review by Dicken et al. [32], LVI emerged as a prognostically promising factor, which independently predicted survival and was associated with advanced T stage, prompting some authors to suggest that LVI should be included in risk stratification and selection of patients for entry into clinical trials. Dicken et al. [33] reported that LVI was an independent predictor of survival in gastric cancer. Demir et al. [34] showed that the prognostic significance of lymphovascular invasion was noteworthy in both univariate and multivariate analyses. In our study, with univariate analysis, a statistically significant relationship ($p<0.001$) was found between OS and DFS and LVI.

Perineural invasion (PNI) is found to be related to a more aggressive tumor phenotype and poor prognosis in several malignancies, most notably head and neck and prostate cancers [35]. Bilici et al. [36] showed that the median survival of PNI-positive patients is much short-

er than that of PNI-negative ones and demonstrated that PNI is a useful prognostic factor for curative gastric cancer. In a recent review, PNI was an independent prognostic factor affecting OS and DFS of gastric cancer patients who had undergone curative resection [35]. In our study, univariate analysis revealed a statistically significant relationship ($p<0.05$) between OS and DFS, and PNI.

A tumor-positive resection margin, defined as an R1 resection, occurs in 2-22 % of patients and has often been documented as a poor prognostic factor. In non-randomized studies using adjuvant CRT, outcomes in patients with residual disease are significantly worse [37-39]. For example, in one study, median survival was 19.3, 16.7, and 9.2 months respectively for patients with no residual, microscopic residual, and gross residual disease [38]. In the current study, 86 (33.5%) patients had gross total resections with pathologically confirmed microscopic residual or sharp dissection of a primary tumor adherent to adjacent structures. In this study, upon univariate and multivariate analyses, a statistically significant relationship ($p<0.05$) was found between OS and DFS and the surgical margin.

In an analysis of prognostic factors that predict OS, RT technique, RT dose, and interruption of therapy were not found to be statistically significant in univariate and multivariate analyses. In an analysis of prognostic factors that predict DFS, RT technique, RT dose, and interruption of therapy were not found to be statistically significant in univariate analysis. Multivariate analysis of prognostic factors that were effective for DFS revealed that RT dose (Gy) was considered significant. Zhu et al. [28] reported that postoperative IMRT did not improve OS in patients with resected gastric cancer. Minn et al. [40] and Liu et al. [41] showed that disease outcome is not significantly different between patients treated with IMRT versus those treated with 3D-CRT. Yoney et al. [42] reported that interruption of therapy was not found to be associated with more statistically significant DFS and OS curves. According to a study by Henning et al. [39], patients treated with 50.4 to 54 Gy had improved locoregional control when compared to those treated with 44.8-50.3 Gy. However, this has not been clearly shown in this specific population.

Conclusion

Postoperative CRT can prolong survival and decrease recurrence in patients with resected gastric cancer. R1 resection, advanced T stage, and advanced nodal stage were adverse prognostic factors in gastric cancer patients who had undergone CRT after surgery. The use of new cytotoxic and biological agents can improve the results of CRT; thus, randomized studies on these therapeutic modalities are clearly needed.

Acknowledgements

The aim of this study was to retrospectively evaluate the results of this treatment and prognostic factors affecting survival.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Emine Canyilmaz, Department of Radiation Oncology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey. Tel: +90 462 377 51 32; Fax: +90 462 32 5 22 70; E-mail: dremocan@yahoo.com

References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 1: 69-90.

[2] Macdonald JS. Role of post-operative chemoradiation in resected gastric cancer. J Surg Oncol 2005; 90: 166-170.

[3] Theuer CP, Kurosaki T, Ziogas A, Butler J, Anton-Culver H. Asian patients with gastric carcinoma in the United States exhibit unique clinical features and superior overall and cancer specific survival rates. Cancer 2000; 89: 1883-1892.

[4] Noguchi Y, Yoshikawa T, Tsuburaya A, Motohashi H, Karpeh MS, Brennan MF. Is gastric carcinoma different between Japan and the United States. Cancer 2000; 89: 2237-2246.

[5] Cady B, Rossi RL, Silverman ML, Piccione W, Heck TA. Gastric adenocarcinoma: a disease in transition. Arch Surg 1989; 124: 303-8.

[6] Meyers WC, Damiano RJ, Rotolo FS, Postlethwait RW. Adenocarcinoma of the stomach: changing patterns over the last four decades. Ann Surg 1987; 205: 1-8.

[7] Noguchi Y, Imada T, Matsumoto A, Coit DG, Brennan MF. Radical surgery for gastric cancer. A review of the Japanese experience. Cancer 1989; 64: 2053-62.

[8] Taketa T, Sudo K, Wadhawa R, Blum MM, Ajani JA. Adjuvant therapy in gastric cancer: what is the optimal approach? Curr Oncol Rep 2013; 15: 146-51.
[9] Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001; 345: 725-730.
[10] Smalley SR, Benedetti JK, Haller DG, Hundahl SA, Estes NC, Ajani JA, Gunderson LL, Goldman B, Martenson JA, Jessup JM, Stemmermann GN, Blanke CD, Macdonald JS. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol 2012; 30: 2327-2333.
[11] Kim S, Lim DH, Lee J, Kang WK, MacDonald JS, Park CH, Park SH, Lee SH, Kim K, Park JO, Kim WS, Jung CW, Park YS, Im YH, Sohn TS, Noh JH, Heo JS,Kim YI, Park CK, Park K. An observational study suggesting clinical benefit for adjuvant postoperative chemoradiation in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. Int J Radiat Oncol Biol Phys 2005; 63: 1279-85.
[12] Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R. EUROCARE-4: survival of cancer patients diagnosed in 1995-1999. Results and commentary. Eur J Cancer 2009; 45: 931-91.
[13] D'Angelica M, Gonen M, Brennan MF, Turnbull AD, Bains M, Karpeh MS. Patterns of initial recurrence in completely resected gastric adenocarcinoma. Ann Surg 2004; 240: 808-16.
[14] Hartgrink HH, Jansen EP, van Grieken NC, van de Velde CJ. Gastric cancer. Lancet 2009; 374: 477-90.
[15] Roviello F, Marrelli D, de Manzoni G, Morgagni P, Di Leo A, Saragoni L, De Stefano A; Italian Research Group for Gastric Cancer. Prospective study of peritoneal recurrence after curative surgery for gastric cancer. Br J Surg 2003; 90: 1113-9.
[16] Curtis RE, Kennedy BJ, Myers MH, Hankey BF. Evaluation of AJC stomach cancer staging using the SEER population. Semin Oncol 1985; 12: 21-31.
[17] Coburn NG, Swallow CJ, Kiss A, Law C. Significant regional variation in adequacy of lymph node assessment and survival in gastric cancer. Cancer 2006; 107: 2143-51.
[18] Orsenigo E, Carlucci M, Braga M, Tomajer V, Di Palo S, Tamburini A, Di Carlo V, Staudacher C. Prognostic factors of gastric neoplasms: experience with 1,074 cases undergoing surgical treatment at a single center. Suppl Tumori 2005; 4: 86-7.
[19] Theuer CP, Nastanski F, Brewster WR, Butler JA, Anton-Culver H. Signet ring cell histology is associated with unique clinical features but does not affect gastric cancer survival. Am Surgeon 1999; 65: 915-21.
[20] Maehara Y, Sakaguchi Y, Moriguchi S, Orita H, Korenaga D, Kohnoe S, Sugimachi K. Signet ring cell carcinoma of the stomach. Cancer 1992; 69: 1645-50.
[21] Otsuji E, Yamaguchi T, Sawai K, Takahashi T. Characterization of signet ring cell carcinoma of the stomach. J Surg Oncol 1998; 67: 216-20.
[22] Kim JP, Kim SC, Yang HK. Prognostic significance of signet ring cell carcinoma of the stomach. Surg Oncol 1994; 3: 221-7.
[23] Kwon KJ, Shim KN, Song EM, Choi JY, Kim SE, Jung HK, Jung SA. Clinicopathological characteristics and prognosis of signet ring cell carcinoma of the stomach. Gastric Cancer 2014; 17: 43-53.
[24] Chae S, Lee A, Lee JH. The effectiveness of the new 7th UICC N classification in the prognosis evaluation of gastric cancer patients: a comparative study between the 5th/6th and 7th UICC N classification. Gastric Cancer 2011; 14: 166-71.
[25] Wang W, Sun XW, Li CF, Lv L, Li YF, Chen YB, Xu DZ, Kesari R, Huang CY, Li W, Zhan YQ, Zhou ZW. Comparison of the 6th and 7th editions of UICC TNM staging for gastric cancer: results of a Chinese single-institution study of1503 patients. Ann Surg Oncol 2011; 18: 1060-7.
[26] Ahn HS, Lee HJ, Hahn S, Kim WH, Lee KU, Sano T, Edge SB, Yang HK. Evaluation of the seventh American Joint Committee on Cancer/International Union Against Cancer classification of gastric adenocarcinoma in comparison with the sixth classification. Cancer 2010; 116: 5592-8.
[27] Qiu MZ, Wang ZQ, Zhang DS, Liu Q, Luo HY, Zhou ZW, Li YH, Jiang WQ, Xu RH. Comparison of 6th and 7th AJCC TNM staging classification for carcinoma of the stomach in China. Ann Surg Oncol 2011; 18: 1869-76.
[28] Zhu WG, Xua DF, Pu J, Zong CD, Li T, Tao GZ, Ji FZ, Zhou XL, Han JH, Wang CS, Yu CH, Yi JG, Su XL, Ding JX. A randomized, controlled, multicenter study comparing intensity modulated radiotherapy plus concurrent chemotherapy with chemotherapy alone in gastric cancer patients with D2 resection. Radiother Oncol 2012; 104: 361-6.
[29] Talamonti MS, Kim SP, Yao KA, Wayne JD, Feinglass J, Bennett CL, Rao S. Surgical outcomes of patients with gastric carcinoma: the importance of primary tumor location and microvessel invasion. Surgery 2003; 134: 720-727.

[30] Chambers WM, Khan U, Gagliano A, Smith RD, Sheffield J, Nicholls RJ. Tumour morphology as a predictor of outcome after local excision of rectal cancer. Br J Surg 2004; 91: 457-459.
[31] Maehara Y, Kabashima A, Koga T, Tokunaga E, Takeuchi H, Kakeji Y, Sugimachi K. Vascular invasion and potential for tumor angiogenesis and metastasis in gastric carcinoma. Surgery 2000; 128: 408-416.
[32] Dicken BJ, Bigam DL, Cass C, Mackey JR, Joy AA, Hamilton SM. Gastric adenocarcinoma: review and considerations for future directions. Ann Surg 2005; 241: 27-39.
[33] Dicken BJ, Graham K, Hamilton SM, Andrews S, Lai R, Listgarten J, Jhangri GS, Saunders LD, Damaraju S, Cass C. Lymphovascular invasion is associated with poor survival gastric cancer:an application of gene-expressional tissue array techniques. Ann Surg 2006; 243: 64-73.
[34] Demir G, Unsal D, Zengin N, Er O, Dane F, Yalçin S; Turkish Oncology Group. Analysis of resected gastric cancer in Turkish population. Hepatogastroenterology 2014; 61: 259-66.
[35] Deng J, You Q, Gao Y, Yu Q, Zhao P, Zheng Y, Fang W, Xu N, Teng L. Prognostic value of perineural invasion in gastric cancer: a systematic review and meta-analysis. PLoS One 2014; 9: e88907.
[36] Bilici A, Seker M, Ustaalioglu BB, Kefeli U, Yildirim E, Yavuzer D, Aydin FM, Salepci T, Oncel M, Gumus M. Prognostic significance of perineural invasion in patients with gastric cancer who underwent curative resection. Ann Surg Oncol 2010; 17: 2037-44.
[37] Bora H, Unsal D, Akmansu M. Results of chemoirradiation after curative resection of locally advanced gastric cancer. Int J Clin Pract 2004; 58: 451-456.
[38] Henning GT, Schild SE, Stafford SL, Donohue JH, Burch PA, Haddock MG, Trastek VF, Gunderson LL. Results of irradiation or chemoirradiation following resection of gastric adenocarcinoma. Int J Radiat Oncol Biol Phys 2000; 46: 589-98.
[39] Henning GT, Schild SE, Stafford SL, Donohue JH, Burch PA, Haddock MG, Gunderson LL. Results of irradiation or chemoirradiation for primary unresectable, locally recurrent, or grossly incomplete resection of gastric adenocarcinoma. Int J Radiat Oncol Biol Phys 2000; 46: 109-18.
[40] Minn AY, Hsu A, La T, Kunz P, Fisher GA, Ford JM, Norton JA, Visser B, Goodman KA, Koong AC, Chang DT. Comparison of intensity-modulated radiotherapy and 3-dimensional conformal radiotherapy as adjuvant therapyfor gastric cancer. Cancer 2010; 116: 3943-52.
[41] Liu GF, Bair RJ, Bair E, Liauw SL, Koshy M. Clinical outcomes for gastric cancer following adjuvant chemoradiation utilizing intensity modulated versus three-dimensional conformal radiotherapy. PLoS One 2014; 9: e82642.
[42] Yoney A, Bati Y, Isikli L, Unsal M. Postoperative chemoradiation in patients with localized gastric adenocarcinoma: Single center experience. Indian J Cancer 2011; 48: 24-30.