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Original Article

Postoperative chemoradiotherapy results in gastric cancer patients from the middle black sea region of Turkey

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Abstract: Objective: The incidence of gastric cancer shows significant geographical variation. Since publication of the United States Intergroup (INT-0116) trial, postoperative chemoradiotherapy has become standard practice in patients with stage 1B and higher gastric cancer in many centers of Turkey. Here, we report our results in stage 1B and higher gastric cancer patients treated with postoperative chemoradiotherapy from the Middle Black Sea Region of Turkey. Methods: Between March 2002 and October 2011, 69 patients were enrolled. The chemoradiotherapy protocol used in patients was similar to that of the INT-0116 trial, except for the radiotherapy dose for positive margin. Results: Eighty-four percent of all patients completed therapy as planned. The most frequent acute toxicities occurred in the gastrointestinal and hematopoietic systems, and most were grade 2. No late toxicities occurred. Fifty-five percent of failures occurred within 3 years, and 88% of all failures involved distant metastasis. The rates of disease-free and overall survivals after 3 years were 45% and 51%, respectively. In a multivariate analysis, overall survival was affected by pN stage and type of resection. Conclusion: Postoperative chemoradiotherapy is a feasible treatment strategy with acceptable toxicity and survival outcomes in patients with gastric cancer from the Middle Black Sea Region.

Keywords: Adjuvant chemoradiotherapy, gastric cancer, survival, toxicity

Introduction

Gastric cancer (GC) is the fourth most common malignancy and the second leading cause of cancer-related death in both sexes worldwide [1]. The incidence of GC shows significant geographical variation both worldwide and in Turkey [2, 3]. The incidences in East Asia, South America and Eastern Europe are higher than those in the United States (U.S.) and Western Europe [2]. In Turkey, these rates are much higher in the central, northeastern and eastern regions than in other regions [3]. Although GC is the fifth and sixth most common cancer in males and women, respectively, it is the second leading cause of cancer-related death in males after lung cancer and the third leading cause of cancer-related death in females after lung and breast cancers in Turkey [3, 4]. Most GC patients are diagnosed with locally advanced or disseminated disease in the Western world. Only 10-15% of GC patients are diagnosed at an early stage in Western nations, but this figure is over 50% in Japan, where routine screening programs are applied [5]. The rate reported in Turkey is only 5.4% [6].

Surgery is the only potential curative treatment modality [7]. The overall survival rate is dismal because of high recurrence rates after surgery [8]. The loco-regional failure (LRF) rates after surgery with curative intent were reported to be nearly 70% [9]. Poor survival results after curative surgery prompted the idea of adjuvant treatments. The U.S. Intergroup (INT-0116) trial, Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial and Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) reported survival benefits for surgery combined with postoperative chemoradiotherapy (CRT), perioperative chemotherapy (CT) and postoperative CT, respectively, com-

pared with surgery alone [10-12]. According to these trials, when surgery is used as the initial treatment, the adjuvant therapy recommended for non-metastatic (M0) patients is CRT for ≥ stage IB in the U.S., CRT or CT for > T1N0 in Europe and CT for stage II/III in Japan [7, 13, 14].

Despite the survival benefit of postoperative CRT, acute and late toxicities may be seen in a certain number of patients. The most commonly affected systems in both acute and late periods are hematological and gastrointestinal. The reported acute toxicity rates vary between 40-66%. Grade 3 or higher hematological and gastrointestinal toxicities are seen in 29.9-61% and 16.7-33% of patients, respectively. The CRT protocol cannot be completed in 2-46% of patients due to development of acute toxicity. And, reported two most common occurring late toxicities are anemia (39%) and gastritis (18%). In addition, 26% of patients with anemia have associated gastritis [8, 10, 15-19].

Postoperative CRT improves loco-regional control. However, this is invalid for distant failures. The reported rates of loco-regional and distant failure are between 14.9-20% and 37.7-80%, respectively. In addition to the adverse effect of failure patterns to survival, positive resection margin (R1) status, advanced pathological tumor (pT) and nodal (pN) stages are related to decreased survival in patients treated with this protocol [16-20].

The aim of this study was to evaluate acute and late toxicities, patterns of failures, survival outcomes and related prognostic factors in GC patients with stage IB and higher cancer treated with postoperative CRT from the Middle Black Sea Region of Turkey.

Materials and methods

Patient evaluation

In this retrospective study, 69 patients with stage IB and higher GC who underwent surgery and received postoperative CRT between March 2002 and October 2011 were enrolled.

In our clinic, postoperative CRT is planned for patients with histologically confirmed gastric adenocarcinoma; stage IB (M0) or higher GC, according to the American Joint Committee on Cancer (AJCC) TNM staging classification for GC; a performance status of ≤ 2 according to Eastern Cooperative Oncology Group; a caloric intake > 1500 kcal/day; adequate function in the major organs per the INT-0116 study; and R1 resection after surgery with curative intent irrespective of the lymph node dissection type (D0: removal of less than D1; D1: removal of lymph node stations 1-6 (N1); D2: removal of N1 and lymph node stations 7-11) [7, 10, 21]. In this study, all patients were re-staged according to the seventh edition of the AJCC TNM staging classification for GC before analysis.

Treatment

During the postoperative period, CT ((fluorouracil (FU), 425 mg/m^2 body surface area/day, and leucovorin (LV), 20 mg/m^2 body surface area/day, for 5 days)) was initiated on day 1 and was followed by CRT beginning 4 weeks after the start of the initial CT cycle. CRT consisted of 45 Gy radiation for a negative resection margin (R0) status and 50.4 Gy radiation for a R1 resection status at 1.8 Gy/day, 5 days/week for 25-28 days. Concomitant CT comprised FU (400 mg/m^2 body surface area/day) and LV (20 mg/m^2 body surface area/day) on the first four and last three days of radiotherapy (RT). Four weeks after the completion of RT, two 5-day cycles of CT were given 4 weeks apart. As shown, CT and CRT were planned per the INT-0116 study [10].

Before 2005, radiation was delivered via Cobalt-60 (Co^{60}) teletherapy (Theratronics 780-C) using a two-dimensional (conventional) planning system, while in 2005 and after, it was delivered via a linear accelerator machine (Clinac® DHX; Varian Medical Systems, Palo Alto, CA, USA) using a three-dimensional (conformal) planning system (Eclipse™ 8.6; Varian Medical Systems). RT was delivered primarily to the tumor bed, regional lymph nodes (perigastric, celiac, local paraaortic, splenic, porta hepatic, suprapancreatic and pancreaticoduodenal) and 2 cm beyond the proximal and distal margins of resection, per the INT-0116 study [10]. RT fields were customized in each patient according to the suggestions of Tepper and Gunderson [21]. While conventional RT was delivered with two or three fields, conformal RT was delivered with three or four fields. In addition, the International Commission on Radiation Units and Measurements (ICRU) 50 and 62 reports were taken into consideration for RT

Table 1. Postoperative findings

	n	%
Gastrectomy type		
Total	39	56.5
Subtotal	30	43.5
Tumor site		
Antrum	16	23.2
Corpus	48	69.6
Cardia	5	7.2
Histopathology type		
Adenocarcinoma	60	87
Signet-cell ring	9	13
Dissection type		
D0	30	43.5
D1	26	37.7
D2	13	18.8
Resection type		
R0	61	88.4
R1	8	11.6
Tumor grade		
Gx	18	26.0
G1-G2 (low grade)	27	39.1
G3-G4 (high grade)	24	34.9
pT stage		
T2	3	4.3
T3	32	46.4
T4a	32	46.4
T4b	2	2.9
pN stage		
N0	7	10.1
N1	20	29
N2	16	23.2
N3a	14	20.3
N3b	12	17.4
AJCC stage		
1B	1	1.4
2A	4	5.8
2B	12	17.4
3A	21	30.4
3B	16	23.2
3C	15	21.7
ENE		
Yes	16	23.2
No	53	76.8
LVI		
Yes	44	63.8
No	25	36.2
PNI		
Yes	40	58
No	29	42

planning [22]. The spinal cord, kidneys, liver and heart were the organs at risk, and their radiation dose exposures were evaluated by dose volume histograms with tolerance limits (60% of liver < 30 Gy, maximum spinal cord dose < 45 Gy, 30% of heart < 40 Gy, two-thirds of one kidney was spared from the field, and two-thirds of the other kidney < 20 Gy) per the INT-0116 study [10].

Follow up

Patients were followed up at 3-month intervals for the first 2 years, biannually for 2-5 years and annually thereafter. Follow-up evaluation for each patient consisted of a physical examination, complete blood count, and liver function tests. Vitamin B-12, iron and calcium levels were monitored in patients with total gastrectomy and treated as indicated. Radiologic imaging and endoscopy were performed as clinically indicated or at least annually.

Toxicity evaluation

Acute and late toxicities were graded from 0 to 5 based upon the Radiation Therapy Oncology Group/European Organization for Research on Treatment of Cancer (RTOG/EORTC) scoring criteria.

End points and statistical analysis

The failure pattern was categorized as loco-regional (gastric bed, regional lymph nodes, gastric remnant, anastomoses and duodenal stump), distant (sites other than the regional lymph nodes, peritoneal seeding, liver and extra peritoneal metastasis) and mixed (loco-regional and distant) types [9]. The failure pattern and dates

The number of lymph nodes removed during operation	
Mean ± SEM	21.6 ± 1.7
Range	5-63
The number of positive lymph nodes	
Mean ± SEM	7.2 ± 0.9
Range	0-38
Tumor size (cm)	
Mean ± SEM	5.8 ± 0.3
Range	1.3-14

Abbreviations: D0 = removal of less than D1 lymph node dissection; D1 = removal of lymph node stations 1-6 (N1); D2 = removal of N1 and lymph node stations 7-11; R0 = negative resection margin; R1 = positive resection margin; AJCC = American Joint Committee on Cancer; ENE = extranodal extension; LVI = lymphovascular invasion; PNI = perineural invasion; SEM = standard error of the mean.

Table 2. Acute toxicities of postoperative chemoradiotherapy

	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Gastrointestinal	36 (52.2)	8 (11.6)	20 (29)	5 (7.2)	0 (0)
Hematologic	55 (79.7)	3 (4.3)	9 (13)	2 (2.9)	0 (0)
Cardiac	67 (97.2)	0 (0)	1 (1.4)	1 (1.4)	0 (0)
Ear	68 (98.6)	0 (0)	0 (0)	1 (1.4)	0 (0)

of the first failure and death (if the patient died) were recorded.

Survival was categorized into four types: locoregional failure-free survival (LRFFS), metastasis-free survival (MFS), disease-free survival (DFS) and overall survival (OS). LRFFS and MFS were defined as the time from the date of surgery to the date of the first confirmed LRF or distant failure (DF), respectively. DFS was defined as the time from the date of surgery to that of the first confirmed LRF or DF, and OS as the time to death or the last follow-up of the patients.

Age, gastrectomy type, lymph node dissection type, tumor site, histopathology type, tumor grade, pT stage, pN stage, AJCC stage, number of dissected lymph nodes, ratio of metastatic lymph nodes to dissected lymph nodes, extranodal extension (ENE), surgical margin status (resection type), tumor size, lymphovascular invasion (LVI) and perineural invasion (PNI), treatment interruption and weight loss were potential factors affecting survival. These potential covariates were evaluated in univariate analysis using the long-rank test, with p values ≤ 0.05 considered to indicate statistical significance. Multivariate Cox regression analysis was performed on the significant determinants identified by univariate analysis. All calculations were performed using SPSS, version 16.0 (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics

All 69 patients were from the Middle Black Sea Region. The most common presenting symptoms were abdominal discomfort in 41 (59.4%) patients, nausea and vomiting in 14 (20.3%), weight loss in 6 (8.7%), loss of appetite in 3 (4.3%), anemia-associated symptoms in 3 (4.3%), hematemesis in 1 (1.4%) and hematochezia in 1 (1.4%). Of these patients, 52 (75.4%) were male and the remaining 17 (24.6%) female. The mean age was 54.3 ± 1.2 years.

Treatment

Table 1 presents the details of the postoperative findings. The mean time from diagnosis to surgery was 24.3 ± 3.4 days. The mean time from surgery to initial CT was 36.4 ± 3.2 days. RT was delivered to 31 (44.9%) patients using a conformal planning system. The RT doses were 45 Gy in 60 (87%) patients and 50.4 Gy in 8 (11.6%) due to R1 resection and 23.4 Gy in 1 (1.4%) due to grade 3 gastrointestinal system (GIS) toxicity. The mean CRT interruption period was 2 ± 0.5 days. In 11 (16%) patients, CRT protocol could not be completed due to acute toxicity.

Toxicity

Table 2 presents the details of the acute toxicities observed. The most frequent acute toxicities occurred in the gastrointestinal and hematopoietic systems, and most were grade 2. Neither grade 4/5 acute toxicities nor late toxicities occurred.

Failure patterns

Failure occurred in 36 (52.2%) patients, and 55% of failures occurred during the first 3 years. The failure patterns were LRF in 4 (5.8%)

Table 3. Univariate analysis for prognostic factors of survival

	LRFFS		MFS		DFS		OS	
	Month	*P*-value	Month	*P*-value	Month	*P*-value	Month	*P*-value
pT stage		0.01		0.11		0.3		0.8
T2	44.6		45.6		44.6		45.6	
T3	74.5		54.3		49.9		57.7	
T4a	82.7		64.3		59.4		57.8	
T4b	8.5		8.5		8.5		NA	
pN stage		0.01		0.000		0.01		0.000
N0	62.8		48.3		48.1		56.3	
N1	91.7		82.5		83.1		82.4	
N2	81.9		71.6		62.7		65.3	
N3a	74.0		38.2		33.4		49.0	
N3b	17.0		14.1		12.7		16.1	
Gastrectomy type		0.12		0.42		0.35		0.22
Subtotal	75.1		67.4		63.9		70.7	
Total	89.1		55.9		50.5		54.0	
Tumor site		0.2		0.026		0.01		0.01
Antrum	69.8		59.4		59.4		59.6	
Corpus	90.4		66.5		61.6		69.5	
Cardia	32.2		18.2		15.4		23.2	
Dissection type		0.9		0.17		0.2		0.2
D0	85.7		62.8		59.6		68.2	
D1	78.6		70.0		63.0		63.6	
D2	39.5		27.3		25.4		31.0	
Grade		0.04		0.025		0.024		0.006
Low (G1 and G2)	97.7		80.1		73.5		84.5	
High (G3 and G4)	43.9		34.1		31.0		33.4	
ENE		0.008		0.000		0.006		0.000
No	92.4		73.4		68.5		73.8	
Yes	29.5		22.2		18.6		25.2	
Resection type		0.5		0.008		0.026		0.001
R0	86.4		67.7		62.4		69.9	
R1	26.1		20.8		19.9		21.9	
Tumor size		0.10		0.42		0.31		0.06
< 5 cm	96.2		68.8		65.6		79.7	
≥ 5 cm	70.6		54.1		49.5		50.6	
LVI		0.55		0.63		0.48		0.93
No	74.4		58.0		54.6		55.7	
Yes	82.7		61.3		56.1		64.1	
PNI		0.94		0.64		0.55		0.93
No	81.2		68.3		64.4		65.1	
Yes	79.4		55.1		50.2		58.9	
Treatment break		0.17		0.48		0.74		0.64
No	90.0		64.8		58.7		64.9	
Yes	61.4		50		51.9		54.7	
Age		0.28		0.83		0.94		0.64
< 65	87.2		61.8		57.4		62.2	
≥ 65	74.5		65		60.5		68.4	

Weight Loss		0.47		0.69		0.92		0.98
< 3 kg	80.2		59		56.8		62.8	
≥ 3 kg	84.0		63.4		55.3		60.3	
Metastatic node ratio		0.026		0.034		0.008		0.01
≤ 20%	96.2		73.5		71.9		77.3	
> 20%	61.5		46.7		39.5		45.5	
Dissected lymph nodes		0.59		0.85		0.97		0.56
< 15	82.7		63.8		58.2		66.7	
≥ 15	78.9		57.5		54.5		57.0	
Stage		0.2		0.1		0.04		0.046
I-II	81.5		68.8		68.2		73.5	
III	78.1		56.4		50.1		55.4	

Abbreviations: LRFFS = loco-regional failure free survival; MFS = metastasis free survival; DFS = disease free survival; OS = overall survival; NA = not available; D0 = removal of less than D1 lymph node dissection; D1 = removal of lymph node stations 1-6 (N1); D2 = removal of N1 and lymph node stations 7-11; R0 = negative resection margin; R1 = positive resection margin; AJCC = American Joint Committee on Cancer; ENE = extranodal extension; LVI = lymphovascular invasion; PNI = perineural invasion.

Table 4. Multivariate analysis for survivals

	LRFFS		MFS		DFS		OS	
	Odds Ratio (Range) (95% CI)	*P*-value	Odds Ratio (Range) (95% CI)	*P*-value	Odds Ratio (Range) (95% CI)	*P*-value	Odds Ratio (Range) (95% CI)	*P*-value
pN stage	NA	0.10	1.66 4 (1.13-2.48)	0.009	1.76 (1.23-2.50)	0.002	1.80 (1.21-2.68)	0.003
ENE	NA	0.12	2.65 (1.10-6.36)	0.02	NA	0.06	NA	0.07
Resection type	NA	0.53	3.33 (1.22-9.11)	0.02	2.63 (0.99-6.98)	0.052	3.72 (1.40-9.81)	0.008

Abbreviations: LRFFS = loco-regional failure free survival; MFS = metastasis free survival; DFS = disease free survival; OS = overall survival; ENE = extranodal extension; NA = not available.

patients, DF in 19 (27.6%) and mixed in 13 (18.8%). DF occurred in 32 (46.4%) patients during the follow-up period. The most common sites of DF were the isolated peritoneum in 10 (14.5%) patients, isolated liver in 9 (13%), lung and liver in 4 (5.8%), bone in 3 (4.3%), lung, liver and peritoneum in 2 (2.8%), lung in 1 (1.4%), liver and peritoneum in 1 (1.4), inguinal lymph nodes in 1 (1.4%) and seminal vesicles in 1 (1.4%). Distant metastases were seen in 88% of all failures.

Prognostic factors

In the univariate analysis, statistically significant prognostic factors for LRFFS were pT stage (P=0.01), pN stage (P=0.01), tumor grade (P=0.04), ENE (P=0.008) and metastatic node ratio (P=0.026). Significant prognostic factors for MFS were pN stage ($P < 0.001$), tumor site (P=0.026), tumor grade (P=0.025), ENE ($P < 0.001$), resection type (P=0.008) and metastatic node ratio (P=0.034). Significant prognostic factors for DFS were pN stage (P=0.01), tumor site (P=0.01), tumor grade (P=0.024), ENE (P=0.006), resection type (P=0.026), metastatic node ratio (P=0.008) and AJCC stage (P=0.04). Significant prognostic factors for OS were pN stage ($P < 0.001$), tumor site (P=0.01), tumor grade (P=0.006), ENE ($P < 0.001$), resection type (P=0.001), metastatic node ratio (P=0.01) and AJCC stage (P=0.046) (**Table 3**).

In the multivariate analysis, significant prognostic factors for MFS were pN stage (P=0.009), resection type (P=0.02), and ENE (P=0.02). Significant prognostic factors for both DFS and OS were pN stage (P=0.002 and P=0.003) and resection type (P=0.052 and P=0.008) (**Table 4**).

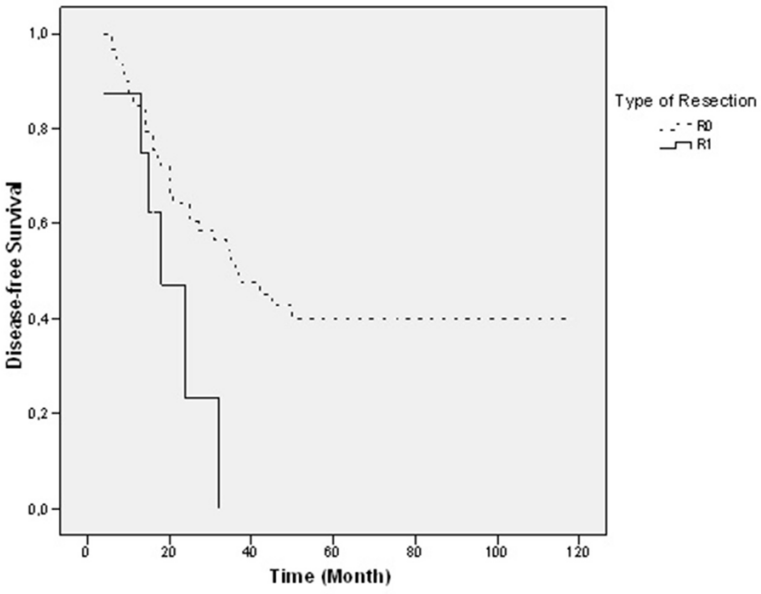

Figure 1. Disease-free survival according to type of resection. Abbreviations: R0 = negative resection margin; R1 = positive resection margin.

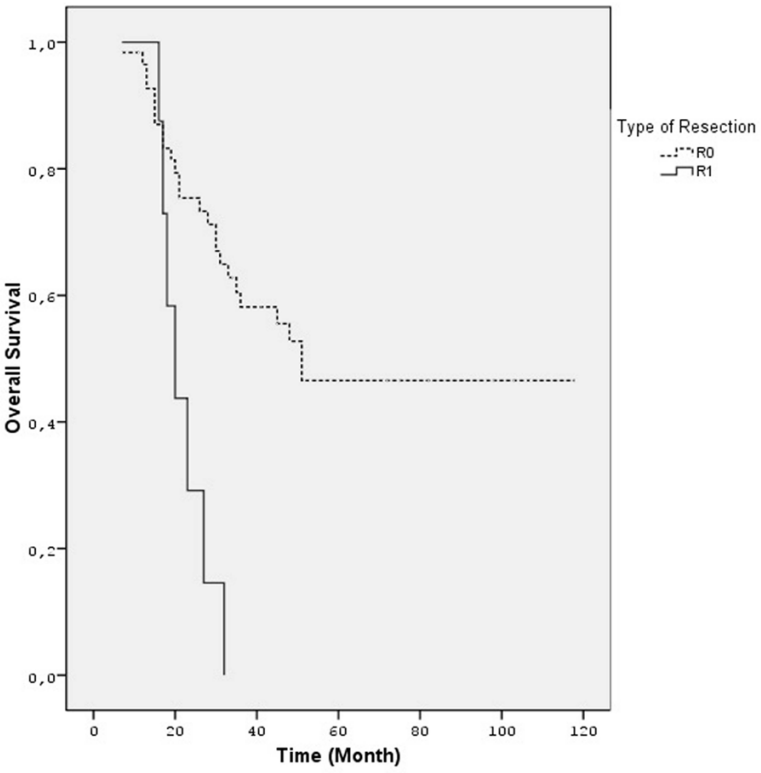

Figure 2. Overall survival according to type of resection. Abbreviations: R0 = negative resection margin; R1 = positive resection margin.

Survival

After a mean follow-up period of 38.3 ± 3.6 months, 37 (53.6%) patients were alive. The mean LRFFS was 85 ± 6.6 months, and the 1-, 2- and 3-year LRFFS were 94%, 74% and 69%, respectively. The mean MFS was 36 ± 8.7 months, and the 1-, 2- and 3-year MFS were 90%, 69% and 49%, respectively. The mean DFS was 34 ± 5.5 months, and the 1-, 2- and 3-year DFS were 85%, 60% and 45%, respectively. The mean OS was 45 ± 8.5 months, and the 1-, 2- and 3-year OS were 97%, 70% and 51%, respectively.

It was observed that the mean survival times decreased with increasing pN-stage between pN1 and pN3b. However, the mean survival times were worse in pN0 patients than pN2 patients (**Table 3**). The 1- and 3-year DFS were 100% vs. 46% in pN0, 89% vs. 70% in pN1, 93% vs. 60% in pN2, 77% vs.18% in pN3a, and 58% vs. 0% in pN3b patients, respectively. The 1- and 3-year OS were 100% vs. 68% in pN0, 100% vs. 68% in pN1, 100% vs. 59% in pN2, 100% vs. 50% in pN3a, and 80% vs. 0% in pN3b patients, respectively. Additionally, the mean survival times were three times better in patients with R0 than R1 resection (**Table 3**). **Figures 1** and **2** present the DFS and OS curves according to resection margin status.

Discussion

In GC patients, complete tumor removal with a sufficient resection margin (R0) plus extended (D2) lymph node dissection is considered to be the most important factor for reduced loco-regional recurrence and improved survival [23]. D2 lymph node dissection is performed routinely in Japan [14]. A Dutch trial reported fewer cases of LRF and GC-related

deaths after D2 versus D1 lymph node dissection [24]. Both U.S. and European guidelines recommend D2 lymph node dissection in GC patients [7, 13].

Because of high LRF and poor survival rates after surgery with curative intent, the adjuvant treatment strategies such as postoperative CRT were suggested. The INT-0116 study by Macdonald et al. and the Korean study by Kim et al. both reported a significant improvement in survival with the use of postoperative CRT [8, 10]. In the INT-0116 study, 566 stage IB-IV (M0) patients were randomized to receive surgery alone (n=275) or postoperative CRT (n=281). Only R0 patients were included in the study, and only 54 (10%) patients underwent D2 lymph node dissection. In the CRT arm, 181 (64%) patients completed the treatment as planned. The reason for cessation was acute toxicity in 49 (17%) patients. Acute grade 3 or higher hematologic and gastrointestinal toxicities occurred in 148 (54%) and 89 (33%) patients, respectively, and 3 (1%) patients died due to CRT toxicity [10]. This study was criticized for its surgical inadequacies.

Since, Kim et al. reported in their Korean study results with postoperative CRT per the INT-0116 study in GC patients with D2 lymph node dissection [8]. In this study, 990 stage II-IV (M0) patients were randomized to surgery alone (n=446) or postoperative CRT (n=544). Only R0 patients were included in the study, and all patients underwent D2 lymph node dissection. In the CRT arm, 409 (75.2%) patients completed the treatment as planned. The reason for cessation was acute toxicity in 54 (9%) patients. Acute grade 3 or higher hematologic and gastrointestinal toxicities occurred in 163 (29.9%) and 81 (14.9%) patients, respectively, and 1 (0.2%) patient died due to pneumonia [8].

In our study, 8 (11.6%) patients underwent R1 resection. Only 13 (18.8%) underwent D2 lymph node dissection, which is not performed routinely in Turkey [25]. Fifty-eight (84%) patients completed treatment as planned.

In 2012 as an update to the INT-0116 study, Smalley et al. reported no excess treatment-related toxicities over a median follow-up period of 10.3 years [26]. After a median follow-up period of 33 (6-125) months, Chang et al. reported the following late complications associated with postoperative CRT: anemia, renal impairment, deranged liver function, gastritis, intestinal obstruction, anastomotic stricture, malabsorption, hypertension and secondary malignancy [17]. In our study, we did not observe any late complications over a mean follow-up period of 38.3 ± 3.6 (7-118) months.

As mentioned above, the INT-0116 study reported OS and DFS advantages in the postoperative CRT group compared with the surgery-only group. In that study, the 3-year OS rate was 50% in the CRT group versus 41% in the surgery-only group, while the DFS rates were 48% and 31%, respectively [10]. In our study, the 3-year OS and DFS rates after postoperative CRT were 51% and 45%, respectively.

A direct comparison of failure patterns between the INT-0116 and present study was not possible, because the former classified peritoneal metastasis as a regional failure. Relapse rates after CRT reported in the INT-0116 and Korean studies were 42% and 42.5%, respectively [8, 10]. In our study, the rate of the mixed (LRF and DF) failure pattern was 52.1%. The Korean study reported significantly different LRF rates between the CRT and surgery-only groups (14.9% vs. 21.7%, P=0.005) but no difference in DF rates (37.7% vs. 37.7%, P=0.9) [8], implying that CRT controlled LRF but failed to prevent DF. In our study, LRF and DF occurred in 5.8% and 46.3% of patients, respectively. In the Korean study, 71% of the relapses first presented as DF, and this figure was 88% in our study. According to these findings, DF is a serious problem associated with postoperative CRT that needs to be prevented. Such would be possible with knowledge of the risk factors for DF, which in turn could be prevented themselves, or with the development of new treatment strategies. In our study, advanced pN stage, R1 resection and the presence of ENE were independent negative prognostic factors for MFS. Of these factors, pN stage and R1 resection were found to affect OS.

Nodal status (pN stage) is the most independent prognostic factor in GC patients with confirmed R0 status [27]. The incidence and distribution of lymph node metastasis are affected by the tumor depth of invasion (pT stage), site, size, LVI, and macroscopic and histologic type [28]. According to the seventh (2010) AJCC

TNM staging system for GC, the pN stage can be determined accurately by dissection of at least 16 lymph nodes. At the same time, pN0 disease is defined as the presence of any metastatic GC cells in the examined lymph nodes regardless of the total number of dissected lymph nodes. Dissection of less than 16 lymph nodes leads to incorrect staging or stage migration in pN0-N3a patients [29, 30]. In our study, as shown in **Table 3**, the mean survival times were worse in pN0 patients than in pN2 patients. This was attributed to inadequate dissection, because although 85% of patients were pT3 stage or higher, inadequate dissection was performed in 70%. Furthermore, it should be kept in mind that, after pN stage, pT stage is the most important prognostic factor [27]. The incidences of lymph node metastasis of GC with invasion to the mucosa, submucosa, muscularis propria, subserosa, serosa and beyond the serosa are 5%, 23%, 52%, 70%, 74% and 82%, respectively [29]. Because of incorrect staging, inadequately dissected patients should be considered at high risk for relapse and should be followed up closely. According to the AJCC TNM staging system, within the same N stage, the 5-year OS was worse in patients with dissection of < 16 compared with ≥ 16 lymph nodes [29, 30]. This problem is essentially resolved by dissection of ≥ 16 lymph nodes. Another option is use of the metastatic lymph node ratio (mLNR), defined as the ratio of the number of metastatic lymph nodes to the total number of nodes examined during pathologic examination, independent of the number of dissected lymph nodes [29, 30]. Use of the mLNR significantly decreases stage migration and is less affected by the number of dissected and examined lymph nodes [29-31]. However, Kulig et al. advocated using mLNR staging only in patients with inadequate dissection [32]. Cut-off values for the mLNR have not been standardized, but it is a good prognostic indicator despite differences in values [29-32].

R1 resection was reported to be a poor prognostic factor, with rates of 2-22% [33]. Its prognostic effect is independent of lymph node involvement [34]. It is associated with a larger tumor size, deeper wall penetration, more extensive gastric involvement, greater nodal involvement, higher stage, diffuse histology, a more advanced Bormann type, lymphatic vessel involvement, and total gastrectomy [35]. Stiekema et al. reported their results in R1-resected GC patients after postoperative CRT [33]. In that study, 110 patients (80 (73%) with R0 and 30 (27%) with R1 resection) were enrolled. The rates of relapse after the first cancer were the same between the R0 and R1 resection groups (P=0.7). The 3-year DFS and OS rates were reported to be 45% and 47% for the R0 resection group and 38% and 48% for the R1 resection group, respectively (P=0.3 for DFS; P=0.5 for OS). Consequently, they suggested that R1 resection was not an adverse prognostic factor for GC patients who had undergone postoperative CRT [33]. In another study, Kundel et al. reported postoperative CRT results from 166 patients with GC (129 (78%) with R0 and 37 (22%) with R1 resection) [18]. They did not assess the significance of differences in the localization of the first relapse between the R0 and R1 resection groups. The 3-year DFS and OS rates were reported to be 60% and 61% with R0 resection and 29% and 33% with R1 resection, respectively (P=0.001 for DFS; P=0.01 for OS). As a consequence, they suggested that R1 resection was a poor prognostic factor, even after postoperative CRT [18]. In our study, R1 resection was performed in eight (11.6%) patients, of whom six (75%) exhibited DF, one was alive after a follow-up period of 16 months, and one died of a heart attack after 18 months of treatment with no occurrence of failure. LRF did not occur in any of the R1-resected patients after postoperative CRT. In the present study, postoperative CRT achieved loco-regional control but failed to prevent DF in R1-resected patients. This suggests that tumor cells within positive surgical margins can be controlled by CRT. It is likely that such cells are very aggressive and may enter the circulation during surgery. This may explain the high rate of metastasis in the R1-resected patients. The risk of R1 resection should be avoided, which may be possible with preoperative therapies used to induce tumor shrinkage.

Oppedijk et al. reported their results in a study known as the CROSS trial [36]. They investigated the role of preoperative CRT in patients with esophageal and gastroesophageal cancer. In that study, preoperative CRT (weekly carboplatin plus paclitaxel with 1.8/41.4 Gy RT) followed by surgery was compared with surgery alone in 366 patients. Adenocarcinoma was found in 75% of the patients. Preoperative CRT, compared with surgery alone, reduced the rates of LRF (34% vs. 14%, P < 0.001), peritoneal carci-

nomatosis (14% vs. 4%, $P < 0.001$), hematogeneous dissemination (35% vs. 29%, $P=0.025$) and R1 resection (32% vs. 7%, $P < 0.001$) [36]. This strategy can be used prior to surgery in patients with defined risk factors for R1 resection.

In summary, first, postoperative CRT in patients with GC is a feasible treatment strategy with acceptable toxicities and survival outcomes, which were comparable with those from previous U.S. and Korean studies on this Middle Black Sea Region population. Second, pN stage and resection type are the most important independent prognostic factors for OS in patients with GC. Finally, preoperative CRT may be more successful than postoperative CRT in high-risk patients with locally advanced GC, especially when a risk of R1 resection exists.

Disclosure of conflict of interest

None.

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